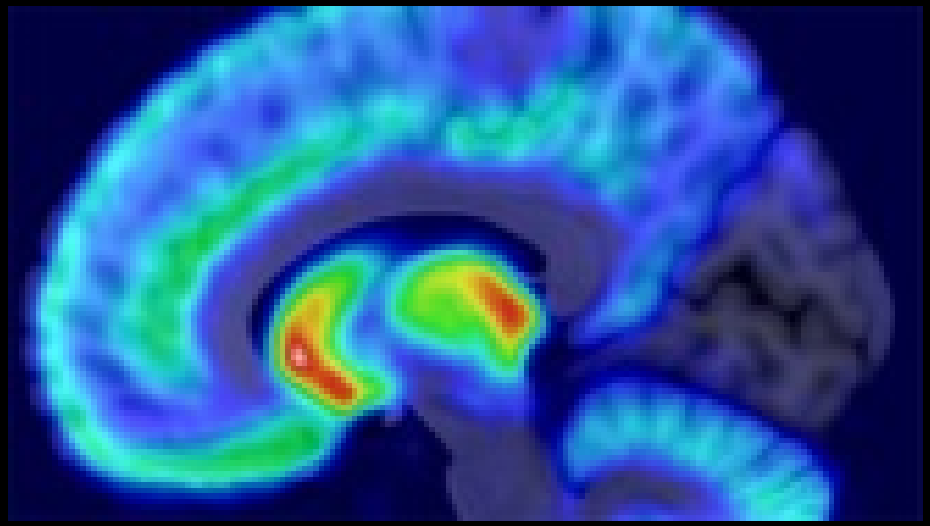
Depression Effects On Long-Term Prescription Opioid Use, Abuse and Addiction



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  - Purdue (effectiveness of primary care taper plans)
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    - National Institute on Drug Abuse (NIDA)
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- Consulting
  - Aetna (pharmacy benefits)
  - Chrono Therapeutics (opioid taper device testing)
  - State of Washington (opioid policies)

Introduction: chronic pain and depression

- >50% prevalence major depression in patients seeking chronic pain specialty care
- >50% prevalence chronic pain in patients seeking care for depression
  - Mutually reinforcing, each causes the other (Gureje, 2001)
  - Depression increases likelihood of opioid Rx, but decreases responsiveness to opioids (Wasan 2005, 2015)
  - Pain decreases responsiveness to antidepressants and combined depression therapy (Bair 2004, Thielke, 2007)
- Chronic pain + depression similar neuroscience
  - Similar patterns neural activation on fMRI scans (Zubieta)
  - Respond to many of the same medications (Hooten, 2016)

Introduction: chronic pain and substance use disorders (SUD)

- Chronic pain is common in patients with SUD
  - 27% to 87% prevalence of chronic pain (Bair, 2003)
- Patients with chronic pain are 2-3x more likely to develop SUD (Rosenblum 2003, Tegethoff 2015)
- Reward deficiency may link pain to SUD
  - Low dopamine, anhedonia, anti-reward adapt.
  - High salience pain relief, low salience other rewards
  - (Baliki 2015, Borsook 2016)

Opioid therapy for chronic pain and depression

- No treatment guidelines recommend long-term opioid therapy for pain and depression
  - No RCTs of opioid therapy for pain in depressed
- Opioid therapy for depressed pts. is common
  - 3x more common in HMO pts. recent depression
    - Higher daily doses, more days' supplied, (Braden 2009)
  - Also commercial, Medicaid, Veteran populations
    - MH esp. common in high-dose, long-term opioid pts.
    - Suggests adverse selection rather than careful selection

"Adverse selection" defined

- Selection of high-risk patients with substance abuse (SA) and mental health (MH) disorders for high-risk opioid regimens:
  - Higher rates of opioid use, especially long-term
  - high daily doses
  - long duration of therapy
  - multiple opioids
  - concurrent sedatives
- Results in reverse treatment disparity with vulnerable patients over-treated with opioids
  - (Sullivan 2015, 2016, 2017)

Adverse selection confirmed

- Among 141,000 Iraq/Afghanistan veterans with chronic pain diagnosis opioids were received by: [Seal, 2012]
  - 6% of those without MH disorders
  - 12% of those with non-PTSD MH disorders (depression)
  - 18% of those with PTSD
    - Also: higher dose opioids, multiple opioids, sedatives, early refills, adverse outcomes
- The 16% of Americans w MH disorders receive over half of all opioids prescribed in the US: OR= 2.1 [Davis, 2017]
- Among 10M commercially insured patients, MH and SUD were associated with opioid Rx: [Quinn, 2017]
  - 2x for anxiety or mood disorder
  - 3x for non-opioid SUD, 9x for opioid SUD

Adverse selection is self-selection

- Adverse selection of patients with depression into long-term high-dose opioid therapy appears to be a process of self-selection:
  - Depressed patients initiate opioid therapy slightly more often than non-depressed patients, but are twice as likely to transition to long-term use (Halbert et al, *2017)*
  - Depressed patients appear to continue opioid use at lower pain intensity levels and higher levels of physical function than do non-depressed patients. (Goesling, 2016)
  - Depressed patients tend to overuse opioids because they use them to treat insomnia and stress. (Grattan, 2012)

Opioids are not effective treatment for depression or anxiety

- Opioids long used to treat mania/melancholia
  - Hippocrates, Galen
  - 19th and 20th Century psychiatric textbooks
- No controlled studies showing lasting relief
  - May provide partial relief of anxiety and insomnia, but deepen avoidance and deactivation
  - *Buprenorphine may be an exception (κ antagonism: Falcon 2016, Kosten 2016, Carlezon 2016)*

Opioids may cause depression

- Opioid therapy >90 days and >50mg MED may increase risk of depression according to retrospective cohort studies
  - Rapid dose increase has highest depression risk
  - Also recurrent and treatment-resistant depression (Scherrer 2014, 2015, 2016, 2017)
  - Most vulnerable: low pain self-efficacy, poor social support, younger opioid onset (Smith 2016)

Depression effects on long-term prescription opioid use, abuse, addiction

- Depression (and catastrophizing) increases risk of misuse, non-medical use and abuse of Rx opioids among adults and adolescents.
- Among adolescents with non-medical use, depression doubles risk of opioid use disorder (OUD). (Swendsen 2010)
- This may be the path by which depression increases the risk of OUD among patients with chronic pain.

Adverse selection is most marked in opioid-benzodiazepine co-prescribing

- Opioid prescribing has declined since 2012, but not opioid-benzo prescribing (Lembke 2018)
- 2001-13, concurrent opioid-benzo use doubled among privately insured patients and increased risk of opioid overdose 2-10x
- 10% antidepressant initiators also initiate BZ; 12% of these become long-term users
- Increasing rates of simultaneous AD + BZ starts: 6% in 2001, 12% in 2012 (Bushnell 2017)

Evidence of opioid dysregulation in major depression (MDD)

- Reduced opioid receptor availability in MDD
  - after sadness induction (Kennedy 2006, Hsu 2015)
  - assoc. w reduced response to SSRI, incr. ACTH
- Greater opioid release after social rejection associated w resiliency, lower negative affect
- Opioid receptor gene (OPRM1) G-allele
  - higher neuroticism, depression
  - greater reactivity to social rejection: ACC, insula
  - (Peciña, 2018)

Non-pain functions of exogenous opioids

- Exogenous opioid medication (mu opioids)
  - Suppresses separation distress in mammals (rodents, primates, humans) (Panksepp, 1978)
  - Reduces aversive/affective aspect of pain more than sensory aspect (Porreca, 2002)
  - Provides more relief of stress-anxiety-insomnia than mood problems, which may worsen
  - Impairs human capacity for emotion perception and social inferences (McDonald, 2013)

Conclusion: depression and opioids

- Relationship between opioids and depression is close, complex and multifaceted
  - Depression is associated with endogenous opioid dysfunction
  - Depression associated with opioid misuse, non-medical use, abuse, OUD
  - Exogenous mu opioids prescribed long-term may increase risk of depression, social cognition deficits
- (Sullivan MD, Depression Effects on Long-term Prescription Opioid Use, Abuse, and Addiction, *Clin J Pain*, 2018)