Opiate Addiction: 
*Treatment Perspectives*

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Stages of Addiction  |  Predominant Neurocircuitry  |  Biomarker Opportunities
---|---|---
**Binge/Intoxication**  |  |  • Acute drug exposure  
• Acute drug effects  
• Genetics of intoxication

**Withdrawal/Negative Affect**  |  |  • Physical dependence  
• Pathophysiology of withdrawal  
• Genetics of mood responses  
• Genetics of withdrawal

**Preoccupation/Anticipation ("Craving")**  |  |  • Neurocognitive markers  
• Neurofunctional imaging  
• Endophenotypic markers (e.g., inhibitory control)  
• Vulnerability to relapse
Opioid Overdose

• Miosis, Respiratory Depression, coma, pulmonary edema

• Treatment:
  – Naloxone-mu opioid antagonist 0.4mg-2mg IV or IM q2-3 min up to 10 mg
  – Mechanical ventilation
Opioid Withdrawal

**TABLE 7**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Scores</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting pulse rate</td>
<td>0-4</td>
<td>0=80 or less; 1=81-100; 2=101-120; 4=120 or greater</td>
</tr>
<tr>
<td>Sweating</td>
<td>0-4</td>
<td>0=none; 4=sweat streaming from face</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0-5</td>
<td>0=sits still; 5=unable to sit still (even for a few seconds)</td>
</tr>
<tr>
<td>Pupil size</td>
<td>0-5</td>
<td>0=normal; 5=dilated (only iris rim visible)</td>
</tr>
<tr>
<td>Bone or joint aches</td>
<td>0-4</td>
<td>0=none; 4=severe discomfort</td>
</tr>
<tr>
<td>Runny nose or tearing</td>
<td>0-4</td>
<td>0=none; 4=constant</td>
</tr>
<tr>
<td>GI upset</td>
<td>0-5</td>
<td>0=none; 5=multiple episodes of vomiting or diarrhea</td>
</tr>
<tr>
<td>Tremor</td>
<td>0-4</td>
<td>0=none; 4=severe</td>
</tr>
<tr>
<td>Yawning</td>
<td>0-4</td>
<td>0=none; 4=yawning several times/minute</td>
</tr>
<tr>
<td>Anxiety &amp; Irritability</td>
<td>0-4</td>
<td>0=none; 4=severe, precluding participation</td>
</tr>
<tr>
<td>Gooseflesh skin</td>
<td>0-5</td>
<td>0=smooth; 5=prominent piloerection</td>
</tr>
</tbody>
</table>

COWS = Clinical Opiate Withdrawal Scale; GI = gastrointestinal.
Score: 5-12 mild; 13-24 = moderate; 25-36 = severe.

Kosten, NEJM
Medication Assisted Treatment (MAT)

Receptor Activation:
Full Agonist, Partial Agonist, Antagonist

- Full Agonist (methadone)
- Partial Agonist (buprenorphine)
- Antagonist (naloxone)

Log Dose of Opioid
MAT: Methadone

• Methadone
  – Full mu opioid agonist
  – Withdrawal maintenance
  – Outpt
    • initial: 20mg, observe 2hrs
    • max day 1 dose: 40 mg
    • maint: 20-120 mg/day
  – Inpt
    • initial: 20mg up to max 40mg
    • taper: 10mg per day to 20mg then decrease by 5mg
  – Adverse Effects: Constipation, respiratory depression, sedation, diaphoresis, QTc prolongation
MAT: Buprenorphine

• Buprenorphine
  – Partial mu opioid agonist
  – withdrawal maintenance
  – Outpt: COWS>8
    • initial: 2mg max: 8 mg, observe 2h
    • maint: 8-24mg/day
  – Inpt:
    • initial: 2-4 mg max: 8mg,
    • day 2: 8-12 mg
    • day 3 three: 6 mg, day4: 0-4 mg, day 5 0-2 mg
  – Adverse Effects: Respiratory depression (difficult unless benzos on board), constipation, pregnancy, precipitate withdrawal

• Buprenorphine/Naloxone
  – partial mu/ opioid ant
  – withdrawal maintenance
  – 2/0.5mg-24/6mg
  – less risk of diversion
MAT: Naltrexone

• Naltrexone
• mu opioid antagonist
  – maintenance oral: 50mg/day or 100mg q 2days
  – Maintenance IM: 380 mg IM monthly
• precipitate withdrawal, monitor LFTs
• Good option for professionals
Reward Pathway

prefrontal cortex

nucleus accumbens

VTA
Reward and Anti-Reward Systems

• As disease progresses there is a physiologically based inability (dopamine desensitization) to experience normal healthy non-drug behaviors as motivating

• Over time “reward” is blunted (reward threshold), stress reactivity is high and drive is for relief

• This means that addicts are driven to escape intolerable stress even more than “reward”

• Addicts trying to stay sober, confront a landscape of “cues and triggers”, including stressors

• Dopamine desensitization also effects pre-frontal circuits involved with decision making creating relapse vulnerability
Psychosocial Treatment

• Dialectical Behavioral Therapy
• Mindfulness
• 12 step meetings
• Group Therapy
• Cognitive Behavioral Therapy (relapse prevention)
Psychosocial Treatment

• Self Medication Hypothesis (Khantzian)
  – Opiates- counter effects of rage and anger
• Continued Use =dysfunction in the PFC
The Minnesota Model
Medically Integrated, 12-Step Oriented (some recovering staff), Therapeutic Community Based Treatment Model emphasizing:

Total Abstinence
Self-awareness
Spiritual Growth
Bonding w Community
Healthy Lifestyle
Psychological and Social Growth
Neuronal Repair
Addressing Anhedonia

Endogenous Opioid System Dysregulation
(Responsible for mood regulation/hedonic tone)

- OPRM1 low expressor (A118g allele) may be more rejection sensitive (social pain)
- Psychosocial RX (including 12 Step Recovery, mindfulness and self awareness/transcendence)
- Buprenorphine/Samidorphan (kappa antagonist) combination (experimental) for depression (and post-acute withdrawal and anhedonia?)
- Low Dose (LD) buprenorphine and LD naltrexone
- TMS-helps reduce cue induced cravings
OPRM1

• Genetic variations in the A1 allele of the D2 receptor gene (OPRMI) may result in reduced dopamine signaling leading to greater need for artificial means for dopamine enhancement (Parsian, Cloninger & Zhang, 2000).

• These genetic variations may also predict responses to certain medications. For example, naltrexone may work much better in this A1 variation group, even possibly stimulating ‘hidden opiate receptors’ thereby producing a paradoxical sense of well being (Kosten, et.al. 2002).
OPRM1

• OPRM1 low expressor (A118g allele) may be more rejection sensitive (social pain)

• Psychosocial RX (including 12 Step Recovery, mindfulness and self awareness/transcendence)
Internal Opiate System and Depression

- Buprenorphine/Samidorphan (kappa antagonist) combination (experimental) for depression (and post-acute withdrawal and anhedonia?)
Dosing (LD)

(LD) Buprenorphine

(LD) Naltrexone

Low
Neuromodulation

Directly Influencing the Electrical Activity of the Brain

Deep Brain Stimulation (DBS)

Transcranial Magnetic Stimulation (TMS)

Brain Wave Entrainment (BWE)
Changes in Glutamatergic Synapses in the Nucleus Accumbens During Relapse After Long-term Use of Cocaine, Heroin, or Nicotine. The upper drawing is the control situation where glial glutamate uptake via glial glutamate transporter 1 (GLT1) is normal, thereby limiting access of synaptically released glutamate to extrasynaptic glutamate receptors, including metabotropic glutamate receptors (mGluRs) and N-methyl-d-aspartate (NMDA) receptors expressing the GluN2B subunit. After long-term drug use, glutamate uptake via GLT1 is downregulated. Thus, when an addict experiences drug-associated stimuli that can precipitate relapse, the corresponding release of glutamate more readily overflows the synaptic cleft to stimulate postsynaptic mGluR5 and NMDA receptors, which in turn increases AMPA signaling (elevated number of AMPA receptors) and synapse size, thereby potentiating synaptic activity. Supporting excessive presynaptic glutamate release, signaling via inhibitory presynaptic mGluR2 autoreceptors is reduced after long-term drug use. N-acetylcysteine restores GLT1, thereby normalizing synaptic potentiation by drug-associated stimuli and inhibiting relapse. Increases and decreases in signaling and glutamate uptake are indicated by larger or smaller arrowheads, respectively.
• Thanks!
• http://www.samhsa.gov/medication-assisted-treatment
• http://www.buppractice.com
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ACS Chem. Neurosci. XXXX, XXX, XXX–XXX