Cognitive Recovery: The Power of Treatment in the Opioid Crisis

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Disclosures & Conflicts of Interest

- No disclosures
- No conflicts of interest
Learning Objectives

1) Demonstrate knowledge of the history & current status of the opioid crisis

2) List the ways opioid use affects brain & cognitive function

3) Discuss the impact of two commonly used opiate agonist treatments (methadone & buprenorphine) on cognitive function
Opioids

Fentanyl

Lethal Dose

Opioid Use Disorder (OUD) – DSM-V

Change in terms and diagnostic criteria:
1) Taking more or for longer than intended
2) Unsuccessful efforts to stop or cut down
3) Spending a great deal of time obtaining, using, or recovering
4) Craving
5) Failure to fulfill major role obligations due to use
6) Continued use despite resulting social or interpersonal problems
7) Important activities reduced because of use
8) Recurrent use in hazardous situations
9) Continued use despite resulting physical or psychological problems
10) Tolerance*
11) Withdrawal symptoms*

Criteria: 2-3=mild, 4-5=moderate, >5=severe OUD
*Those prescribed opioids may exhibit tolerance and withdrawal, but would not be considered to have an opioid use disorder.

Increase in Opioid Prescriptions

Pain = 5th vital sign
Increases in Opioid Deaths Parallel Opioid Sales and Treatment Admissions

Soaring Drug Overdose Death

Overdose Deaths Primarily from Opioids: Prescription Drugs, Heroin and Synthetics (i.e. Fentanyl and similar)
Leveling Off of Opioid Prescribing

Annual prescribing rates by overall and high-dosage prescriptions

Costs of Opioid Epidemic & Benefits of Addressing the Epidemic

1) Personal Costs: Individuals + Families + Communities

2) Public Health Costs

3) Benefits: Advance Science & Treatment + Reduce Suffering + Improve Public Health

OUD: Part 1 Take Home Highlights

- Opioid Epidemic = Major public health crisis
- Evolution of an epidemic
- Neuropsychology has a critical role to play
Learning Objectives

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2) List the ways opioid use affects brain & cognitive function

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Biopsychosociocultural Framework of Brain Health

Biological  
Cognition  
Emotion  
Behavior  
Cultural  
Social

Rivera Mindt et al., 2008

Development of OUD Involves Multiple Factors

Biology  
Genes/Development  
Environment  
OPIOID USE  
Brain Mechanisms  
OUD
Effects of Opioids on the CNS

Reward Pathway & Dependence

- Localization of opiate binding sites within the brain and spinal cord
- Opiate binding within the reward pathway
Opiates binding to opiate receptors in the nucleus accumbens: increased dopamine release

The fine balance in connections that normally exists becomes severely disrupted in OUD

Effects of OUD on the Brain

- OUD is related to dysfunction in:¹⁻⁷
  - Neurovascular disorders
  - Leukoencephalopathy*
  - Atrophy
  - Specific Regions:
    - Frontal lobes
    - Basal ganglia
    - Hippocampal region

*Inhaled heroin

¹. Eisch et al., 2006; ². Goldstein et al., 2012; ³. Kosten et al., 2002; ⁴. Lyoo et al., 2006; ⁵. Ma et al., 2010; ⁶. Pezwas et al., 2002; ⁷. Goldstein et al., 2010
Acute areas of ischemia in both the anterior and middle cerebral artery territories involving predominantly the gray matter as a result of a diffuse vasculitis with a "bird-in-wing" sign along the anterior cerebral artery, with an acute occlusion of the left of the pericallosal artery (arrows) and turbulent irregularities in multiple different vessels in a patient with intravenous heroin abuse.

Acute (upper row) and chronic (after 6 months) effects following heroin inhalation (chasing the dragon)

Chronic Effects of Heroin Inhalation (typical form)
### Meta-Analysis on the Cognitive Effects of Chronic OUD*

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex Psychomotor</td>
<td>Large</td>
</tr>
<tr>
<td>Attention</td>
<td>Medium</td>
</tr>
<tr>
<td>Working memory</td>
<td>Medium</td>
</tr>
<tr>
<td>Memory</td>
<td>Medium</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>Medium</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>Medium-to-Medium</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>Small</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>Smallest, non-significant</td>
</tr>
<tr>
<td>Motor</td>
<td>Small</td>
</tr>
</tbody>
</table>

Note: N = 61 studies; 2,580 patients with OUD and 2,102 healthy control participants (15.9% female); Exclusions: Comorbid medical, neurological, psychiatric, and substance use disorders

Wollman et al., 2018

### Pilot Study 1

- **Aim:** To describe cognitive function among opioid-dependent adults seeking buprenorphine treatment and to explore the impact of lifetime psychiatric conditions on cognitive function.

- **Design:** Cross-sectional assessment of cognitive function, substance use, and psychiatric characteristics of adults seeking buprenorphine treatment within substance use treatment centers in NYC.

Arias et al., 2016

Grant: NIH P20DA026149

### Methods: Participants & Recruitment

- **Participants**
  - Adults with OUD initiating BUP/NLX within next 30 days

- **Recruitment sites**
  - Community health center with primary care-based BUP/NLX
  - Opioid treatment program offering BUP/NLX

- **Inclusion criteria**
  - English speaking; 18-65 y; >6 years education; current OUD
  - No BUP/NLX for 15 consecutive days prior to enrollment

- **Exclusion criteria**
  - Serious mental illness (e.g., schizophrenia, psychosis, bipolar)
  - Serious medical conditions known to impact cognitive function (e.g., stroke, traumatic brain injury w/LOC>12 hours, seizure disorder)
Methods: Cognitive Domains & Tests

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency</td>
<td>Controlled Word Association Test (FAS)</td>
</tr>
<tr>
<td></td>
<td>Semantic (Animal) Fluency</td>
</tr>
<tr>
<td>Speed of Information Processing</td>
<td>Wechsler Intelligence Scale (WIS) Digit Symbol</td>
</tr>
<tr>
<td></td>
<td>WIS-III Symbol Search</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>WIS-III Letter Number Sequencing</td>
</tr>
<tr>
<td></td>
<td>Paced Auditory Serial Addition</td>
</tr>
<tr>
<td>Learning</td>
<td>Hopkins Verbal Learning Test-Revised</td>
</tr>
<tr>
<td></td>
<td>Brief Visual Memory Test-Revised</td>
</tr>
<tr>
<td>Memory</td>
<td>Hopkins Verbal Learning Test-Revised</td>
</tr>
<tr>
<td></td>
<td>Brief Visual Memory Test-Revised</td>
</tr>
<tr>
<td>Motor</td>
<td>Grooved Pegboard Time</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Wisconsin Card Sorting Task: 64 Card Version</td>
</tr>
<tr>
<td></td>
<td>Trail Making Test (Part B)</td>
</tr>
</tbody>
</table>

Results: Participant Characteristics

(N = 39)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>32%</td>
</tr>
<tr>
<td>Latinx</td>
<td>60%</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>21%</td>
</tr>
<tr>
<td>Age, years ± SD</td>
<td>46.4 ± 9.6</td>
</tr>
<tr>
<td>Education, years ± SD</td>
<td>11.6 ± 2.5</td>
</tr>
<tr>
<td>Depression (Baseline CIDI MDD diagnosis)</td>
<td>34%</td>
</tr>
<tr>
<td>Substance Use (CIDI, DSM-IV)</td>
<td></td>
</tr>
<tr>
<td>Lifetime alcohol dependence</td>
<td>34%</td>
</tr>
<tr>
<td>Lifetime alcohol abuse</td>
<td>50%</td>
</tr>
<tr>
<td>Lifetime cocaine abuse</td>
<td>61%</td>
</tr>
</tbody>
</table>

Neurocognitive (NC) Characteristics Based on Average T-scores and Rates of Impairment

<table>
<thead>
<tr>
<th>Domain</th>
<th>M (SD)</th>
<th>NC impaired (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRAT-3 Standard Score</td>
<td>86.2 (13.6)*</td>
<td>-</td>
</tr>
<tr>
<td>Global NC Function</td>
<td>41.2 (6.5)</td>
<td>42%</td>
</tr>
<tr>
<td>Learning</td>
<td>33.9 (10.2)</td>
<td>74%</td>
</tr>
<tr>
<td>Memory</td>
<td>34.8 (11.1)</td>
<td>68%</td>
</tr>
<tr>
<td>Executive Function</td>
<td>42.7 (9.4)</td>
<td>45%</td>
</tr>
<tr>
<td>Motor Function</td>
<td>40.2 (9.3)</td>
<td>45%</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>42.8 (8.1)</td>
<td>37%</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>44.9 (9.5)</td>
<td>32%</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>48.1 (8.5)</td>
<td>16%</td>
</tr>
</tbody>
</table>

Note: Scores for the WRAT-3, used to ascertain premorbid functioning is presented in Standard Score (M=100, SD=15). T-Scores <40 = NC impairment.
Co-Morbid Alcohol & Cocaine Dependence Related to Worse Cognitive Impairment but Not Major Depressive Disorder

F. Atos et al. / Addict Behav. 60 (2016) 327–342

Table 5
Neuropsychological domains and their differences between all groups

<table>
<thead>
<tr>
<th>Diagnosis of alcohol dependence</th>
<th>Diagnosis of cocaine dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent (n = 11)</td>
<td>Non-dependent (n = 25)</td>
</tr>
<tr>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Attention/working memory</td>
<td>30.9 (8.6)</td>
</tr>
<tr>
<td>Learning</td>
<td>34.3 (12.9)</td>
</tr>
<tr>
<td>Memory</td>
<td>33.1 (16.2)</td>
</tr>
<tr>
<td>Vigilance</td>
<td>17.5 (13.9)</td>
</tr>
<tr>
<td>Attentional switching</td>
<td>9.6 (6.3)</td>
</tr>
</tbody>
</table>

Note: Means and standard deviations (NC/ID) based on average T Scores. * p<0.05; ** p<0.001.

OUD: Part 2 Take Home Highlights

- **OUD** = Complex disorder of brain & behavior
  - Chronic OUD = ▼
  - Brain integrity
  - Cognitive function
    - Comorbid alcohol & cocaine use = ▼

Learning Objectives

1) Demonstrate knowledge of the history & current status of the opioid crisis

2) List the ways opioid use affects brain & cognitive function

3) Discuss the impact of two commonly used opiate agonist treatments (methadone & buprenorphine) on cognitive function
Opioid Dependence is a Chronic Medical Illness

Relapse Rates Are Similar for SUD & Other Chronic Conditions

Receipt of SUD Services Lags Behind Other Chronic Disorders
**Gap in Treatment for OUD**

National Survey on Drug Use and Health (NDUHS) 2013; TEDS 2003-2013

**OUD is Like Many Other Chronic Conditions**

OUD is preventable

OUD is treatable

Recovery is possible

**Treating a Neurobehavioral Disorder Must Go Beyond Just Fixing the Chemistry**

We Need to Treat the Whole Person!

- Pharmacological (medications)
- Behavioral Therapies
- Medical + Social
- Psychological Services

In a Socio-Cultural Context
What is Harm Reduction?

- ↓ harms for ppl not seeking or unable to access treatment
- Practical Strategies: ↓ SU consequences
- Interventions guided by risk-benefit analysis
- Abstinence is NOT a prerequisite to care

Slide courtesy Dr. J. Weiss

Harm Reduction Interventions

- Opiate Agonist (OAT) ↓ HIV, HCV, & mortality
- Naloxone for overdose mortality
- Treatment continuity after incarceration
- Syringe exchange programs: ↓ HIV & injection risk
- Supervised injection facilities (SIF):
  * ↓ overdose mortality and injection risks

Slide courtesy Dr. J. Weiss

Treatment Options for OUD

- Non-pharmacologic
- Medication-Assisted Treatment (MAT):
  - Opioid agonist treatment (OAT):
    * Methadone
    * Buprenorphine
  - Opioid antagonists: Naltrexone
  - Detoxification vs. maintenance treatment

Slide courtesy Dr. J. Weiss
### Key Differences in OAT Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>FULL opioid agonist</td>
<td>PARTIAL opioid agonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ kappa antagonist</td>
</tr>
<tr>
<td><strong>Receptors</strong></td>
<td>µ opioid receptor</td>
<td>µ + κ opioid receptors</td>
</tr>
<tr>
<td><strong>Receptor affinity</strong></td>
<td>Moderate</td>
<td>VERY HIGH</td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
<td>Oral</td>
<td>Sublingual</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Liquid</td>
<td>Tablet/film</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>24-36 hrs</td>
<td>24-36 hrs</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Liver, P450 system</td>
<td>Liver, P450 system</td>
</tr>
</tbody>
</table>

### OAT Pharmacology

- "Bupe": Partial mu opioid agonist
- Ceiling effect
- Low risk of overdose
- Can be prescribed w/ refill
- Schedule III

### OAT Treatment Delivery

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulations</strong></td>
<td>Highly regulated</td>
<td>Minimally regulated</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Licensed MMTP</td>
<td>Anywhere</td>
</tr>
<tr>
<td><strong>Provider</strong></td>
<td>MD at MMTP</td>
<td>MD or DO</td>
</tr>
<tr>
<td></td>
<td>8 hour training</td>
<td>DEA &quot;X&quot; number</td>
</tr>
<tr>
<td><strong>Counseling</strong></td>
<td>Regulated</td>
<td>Ability to refer</td>
</tr>
<tr>
<td><strong>Visits</strong></td>
<td>Regulated</td>
<td>--</td>
</tr>
<tr>
<td><strong>Urine toxicology tests</strong></td>
<td>Regulated</td>
<td>--</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Regulated</td>
<td>--</td>
</tr>
<tr>
<td><strong>Dispensing</strong></td>
<td>At MMTP</td>
<td>Community pharmacy</td>
</tr>
<tr>
<td><strong>Prescriptions</strong></td>
<td>Regulated</td>
<td>30-day supply w/ refills</td>
</tr>
<tr>
<td><strong>Treatment slots</strong></td>
<td>Regulated</td>
<td>30-100 pts/MD</td>
</tr>
</tbody>
</table>
OAT Efficacy

- Both → opioid abstinence
- Buprenorphine vs. methadone
  - Bupe > low dose methadone
  - Bupe = mod dose methadone
  - Bupe < high dose methadone
- Methadone well established improvements in many other treatment outcomes

Other Treatment Outcomes Associated with OAT

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>↓</td>
<td>--</td>
</tr>
<tr>
<td>High-risk behaviors</td>
<td>↓</td>
<td>--</td>
</tr>
<tr>
<td>HIV transmission</td>
<td>↓</td>
<td>--</td>
</tr>
<tr>
<td>HCV infection</td>
<td>↓</td>
<td>--</td>
</tr>
<tr>
<td>Physical/mental health</td>
<td>↑</td>
<td>--</td>
</tr>
<tr>
<td>Pregnancy outcomes</td>
<td>↑</td>
<td>--</td>
</tr>
<tr>
<td>Social outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criminal activity</td>
<td>↓</td>
<td>--</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>↑</td>
<td>--</td>
</tr>
<tr>
<td>Social functioning</td>
<td>↑</td>
<td>↑ 53</td>
</tr>
</tbody>
</table>

Systematic Review of Cognitive Effects of OAT

Rivera Mindt et al., submitted
OAT Systematic Review Overview

- Observational Studies: 28 of 29
- Cross-sectional Studies: 21 of 29

OAT Studied:
- Methadone = 19
- Buprenorphine = 3
- Methadone vs. Buprenorphine = 7

Study Populations:
- Mostly international: EU: 14, US: 7, Asia: 4, Australia/NZ: 3, Mid. East: 1
- OAT Length: Newly initiated – 6 years
- Sample Sizes: 8 - 225
- Recruitment Sites: Outpatient substance use treatment clinics

OAT Systematic Review: Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Early Memory/Spatial</th>
<th>Language</th>
<th>Executive Function</th>
<th>Processing Speed</th>
<th>Learning &amp; Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coding</td>
<td>Numerical Change Detection</td>
<td>Single Word</td>
<td>Stroop Task</td>
<td>Flanker Task</td>
<td>Matching to Sample</td>
</tr>
<tr>
<td>Coding</td>
<td>Two Number Change Detection</td>
<td>Single Word</td>
<td>Stroop Task</td>
<td>Flanker Task</td>
<td>Matching to Sample</td>
</tr>
<tr>
<td>Coding</td>
<td>One Number Change Detection</td>
<td>Single Word</td>
<td>Stroop Task</td>
<td>Flanker Task</td>
<td>Matching to Sample</td>
</tr>
<tr>
<td>Coding</td>
<td>Zero Number Change Detection</td>
<td>Single Word</td>
<td>Stroop Task</td>
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<td>Flanker Task</td>
<td>Matching to Sample</td>
</tr>
</tbody>
</table>

OAT Systematic Review Findings

- Across cognitive domains:
  - Healthy controls > OAT-treated persons > Active OUD persons

- Longitudinal findings:
  - Both OAT groups demonstrated improvement over time overall.

- Methadone (MMT) findings:
  - Cross-sectional: MMT ≈ Abstinent OUD
  - Longitudinal improvements (2 of 4 studies):
    - Processing Speed (large effect size; 2 mo.)
    - Learning & Memory (small-to-medium effect sizes; 2 mo.)
    - Executive Function (large effect size; 5–12 mo.)
Limitations of OAT & Cognition Literature

- Most studies:
  - Focus on methadone
  - Cross-sectional
  - Conducted abroad – external validity?

- Wide methodological heterogeneity between studies

- What’s Needed:
  - Longitudinal & randomized trials
  - Focus on buprenorphine
Pilot Study 2

Aim: To understand the longitudinal cognitive effects of buprenorphine/naloxone (BUP/NLX) among adults with OUD.

Hypothesis: BUP/NLX would be associated with improvement over time.

Study Design:
- Longitudinal observational study (72% retention)
- Baseline (N = 39), 3 mo. (N = 28), and 6 mo. (N = 28)
- Comprehensive cognitive battery (see Pilot Study 1)

Rivera Mindt et al., submitted
NIH R01DA032552

Cognitive Impairment Rates at Baseline and Follow-up

Note. Average T-scores < 40 = Impaired; BL N = 39 & 3 mo. + 6 mo. N's = 28; *p< .05
How Brain Dysfunction Affects Everyday Functioning

- Opioid-exposed Brain
- Cognitive Impairment
- Neurocognitive Evaluation
- Symptoms
- Medication Adherence
- Risky Behaviors
- Poor Functioning in the Real World

Limitations

- Small sample size
- No comparison group
- Adherence measured by self-report
- High prevalence of comorbid alcohol and cocaine use, but limited power to incorporate covariates into analyses
Discussion

- BUP/NLX associated with significantly improved executive functioning (EF)
- Better BUP/NLX adherence related to improved NC function in learning and memory
- Important treatment implications as:
  - EF related to risky behaviors, planning, and problem-solving
  - Learning and memory related to adherence and treatment engagement
- First study to examine longitudinal NC effects of BUP/NLX using a comprehensive NC battery in U.S. with an urban sample of primarily Latinx and African-American participants

OUD: Part 3 Take Home Highlights

- OUD is a chronic condition amenable to treatment
- MAT with OAT is related to improved clinical and cognitive outcomes
- OUD-related cognitive dysfunction has important real-world outcomes

MAT = Medically Assisted Treatment
Conclusions

- Prescription opioid use and opioid use disorder continue to be growing and challenging clinical issues to address.
- Buprenorphine has important properties that are different than other opioids, and can potentially improve cognitive and other outcomes.
- Developing innovative treatment programs is one strategy to address challenges with pain management and treatment of opioid use disorder.

¡Muchas Gracias!
Questions & Follow Up?

@DrRiveraMindt

Dr Monica Rivera Mindt

Email: riveramindt@fordham.edu

Additional Resources

Harm Reduction Skills

- Use non-stigmatizing, person-first, clinically accurate language
- Minimize harms of ongoing drug use
- Risk reduction plan
- Screen for HIV, hepatitis B/C, STI
- Provide naloxone (get trained! Stop OD NYC App)
- Teach safe injection techniques

Slide courtesy Dr. J. Weiss