Introduction to Medication-Assisted Treatment

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Reward Pathway

- Neurons start in the midbrain → release dopamine in the nucleus accumbens
- Baseline: steady dopamine
- Drugs: burst of dopamine (pleasure/salience/motivation)
- Responsible for “hedonic tone”
What is Hedonic Tone?

- Sense of well-being, happiness, pleasure, contentment
- “Set” in the reward pathway
- Range: Euphoria $\leftrightarrow$ Dysphoria
- Altered by psychoactive activities/substances
- Reward Deficiency Syndrome?
  - Kenneth Blum: DRD2 allele $\rightarrow$ lower D2

Slide courtesy of Dr. Ed Salsitz
Natural Rewards and Dopamine Levels

Adapted from: Di Chiara et al, *Neuroscience*, 1999
Effects of Drugs on Dopamine Levels

Adapted from: Di Chiara and Imperato, *Proceedings of the National Academy of Sciences USA*, 1988; courtesy of Nora D Volkow, MD
Effects of Drugs on Dopamine Levels

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Acute drug effects

- Extra dopamine release $\rightarrow$ changes in cell signaling
  - D1 DA receptor stimulation $\rightarrow$
cAMP-dependent protein kinase (PKA) $\rightarrow$
  phosphorylation of CREB $\rightarrow$
  immediate early gene products such as cFos $\rightarrow$
  short-term neuroplastic changes for a few hrs/days

... but none of this explains long-lasting behavioral changes
How to explain end-stage addiction?

- Overwhelming desire to obtain drug
- Diminished ability to control drug seeking
- Reduced pleasure from biological rewards

End-stage addiction is mostly about waiting for the police, or someone, to come and bury you in your shame.

David Carr
meetville.com
Transition to addiction

- Repeated use $\rightarrow$ brain changes that last for days-weeks

  - Long-acting proteins involved
    - $\Delta$FosB = transcriptional regulator,
      increases AMPA glutamate receptor subunits

Create new circuits based on glutamate, not dopamine
New circuits created from prefrontal cortex (glutamate)
All of these brain regions must be considered in developing strategies to effectively treat addiction.
And to make matters worse...

Dopamine D2 Receptors are Decreased by Addiction
Blue = mature state
What environmental factors make us vulnerable to addiction?

dopamine D2 receptor — the DRD2 gene). Concomitantly, environmental factors such as stress (high stress combined with polymorphisms in dopaminergic genes, as well as other neurotransmitter genetic variants), and social defeat also alter brain-reward mechanisms in such a manner as to impart vulnerability to addiction [7]. Thus, elevated stress levels, stress & social defeat (interacting with our genes)

Transformative Spiritual Experience
“We’ve been doing this for over 40 years since Nixon... The drugs are more available, purer quality, and cheaper than they’ve ever been before... and we’ve destroyed more lives than drugs have by incarcerating people, hanging felony convictions on them, denying them education, denying them jobs... And we don’t even have one drug-free prison in America.”

- Retired police captain Peter Christ
InSite in Vancouver: An overdose prevention center (i.e., a safe injection site)
BEFORE DCR

Make money.
Buy street heroin.
Hide from the police.
Find or share needle.
Use puddle water.
Rush to inject while keeping a look out.
Throw drug paraphernalia on the ground.
Repeat.

AFTER DCR

Make money.
Buy street heroin.
Visit DCR.
Receive hygienic paraphernalia (syringe, cookers, filter, alcohol pad).
Use under supervision of trained professional first aid.
Properly dispose of drug paraphernalia in biohazard containers.
Relax, take a shower, change clothes, talk to a social worker & organise the rest of my day.

Life of people who use drugs before and after the opening of DCR’s
Opioids
Endogenous vs. Exogenous Opioids
# Classification of Opioids

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Origin</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td>Naturally occurring</td>
<td>Pure agonists</td>
</tr>
<tr>
<td>morphine</td>
<td>morphine, codeine, thebaine</td>
<td>morphine, fentanyl,</td>
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<tr>
<td>fentanyl</td>
<td></td>
<td>remifentanil</td>
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<tr>
<td>remifentanil</td>
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<tr>
<td><strong>Intermediate</strong></td>
<td>Semisynthetic</td>
<td>Partial agonist</td>
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<tr>
<td>buprenorphine</td>
<td>oxycodone, hydrocodone,</td>
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<td>pentazocine</td>
<td>hydromorphone,</td>
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<td>butorphanol</td>
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<tr>
<td><strong>Weak</strong></td>
<td>Synthetic</td>
<td>Agonists-antagonists</td>
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<tr>
<td>codeine</td>
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<td></td>
<td>tramadol</td>
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<td>Pure antagonists</td>
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<td>naloxone</td>
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<td>naltrexone</td>
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Opiate Receptors In The CNS

- Thalamus
- Hypothalamus
- Pituitary glands
- Periventricular nuclei
- Periaqueductal grey
- RAPHE MAGNUS: Enkephalin (δ)

β - endorphin (μ & δ)
Morphine
Dynorphin (μ)

SPINAL CORD: Dymorphinergic neuron with κ receptors

Presynaptic inhibition of both III and IV fibres by enkephalins

Pain inhibitory complex: enkephalin (δ)
Distress and Pain: Dorsal Anterior Cingulate Cortex

- Pain
- Social rejection
- Hunger
- Thirst
- Breathlessness
Opioid Intoxication

- **Euphoria** experienced as a “rush” of intensely pleasurable feelings

- Reduced psychological pain:
  - Anxiety, depression, anger, paranoid ideation/psychosis

- GI: nausea, vomiting, constipation
- Miosis (pinpoint pupils)
- Respiratory suppression
Opioid Withdrawal

- Dysphoric mood
- Nausea/vomiting
- Muscle aches
- Lacrimation
- Rhinorrhea
- Pupil dilation
- Pilorection
- Sweating
- Diarrhea
- Yawning
- Fever
- Insomnia
3 Waves of the Rise in Opioid Overdose Deaths

- **Wave 1**: Rise in Prescription Opioid Overdose Deaths
- **Wave 2**: Rise in Heroin Overdose Deaths
- **Wave 3**: Rise in Synthetic Opioid Overdose Deaths

**Other Synthetic Opioids**
e.g., Tramadol and Fentanyl, prescribed or illicitly manufactured

**Commonly Prescribed Opioids**
Natural & Semi-Synthetic Opioids and Methadone

**Heroin**

Treatment
Acute withdrawal

- 7 days for heroin
- Up to 25 days for methadone

Post-Acute Withdrawal Syndrome (PAWS)

- Can be up to 1 year
Post-Acute Withdrawal Syndrome (PAWS)

- Alcohol or drug cravings
- Irritability
- Anxiety
- Presence of a dysphoria state or depression
- Trouble sleeping
- Decreased ability to feel pleasure (anhedonia)
- Decreased libido (interest in sex)
- A reduction in short-term memory
- Chronic and lasting fatigue
- Struggling to concentrate
- Difficulty focusing on tasks
- Impaired decision-making skills
- Reduced control of executive functions
- Physical problems, especially pain, that may not be attributed to a specific cause
Death by Detoxification

By Adam Bisaga, M.D., Maria A. Sullivan, M.D., Ph.D.

Hardly a day passes when we do not hear reports from many different areas of the country about young people dying from overdoses of narcotics. The recent death of the actor Cory Monteith was a stark public reminder of this recurring tragedy. Many of these incidents are even more tragic since they happen not too long after discharge from a treatment program. These headlines are a wake-up call: What more can be done to save the lives of young people with drug addictions, especially those who come to us seeking help?

Monteith was taking heroin, but we know that taking opioid painkillers — such as Vicodin or Oxycontin — affect the brain similarly to heroin and could have resulted in the same tragic outcome. He died of an overdose, a leading cause of death in individuals who use heroin or misuse painkillers. Overdoses, which are most often unintentional, are too common among people who regularly use heroin or misuse painkillers. Drug overdose death rates in the U.S. have more than tripled since 1990. In the past decade, deaths from opioids have surpassed motor vehicles as a cause of death in some states.
Benefits of MAT: Decreased Mortality

Death rates:

- General population
- Medication-assisted treatment
- No treatment

Standardized Mortality Ratio

Dupouy et al., 2017
Evans et al., 2015
Sordo et al., 2017
129 times the overdose death risk as compared to gen. pop.

other state residents, with a markedly elevated relative risk of death from drug overdose (129; 95% CI, 89 to 186). The leading causes of death among former inmates

RESULTS

Of 30,237 released inmates, 443 died during a mean follow-up period of 1.9 years. The overall mortality rate was 777 deaths per 100,000 person-years. The adjusted risk of death among former inmates was 3.5 times that among other state residents (95% confidence interval [CI], 3.2 to 3.8). During the first 2 weeks after release, the risk of death among former inmates was 12.7 (95% CI, 9.2 to 17.4) times that among other state residents, with a markedly elevated relative risk of death from drug overdose (129; 95% CI, 89 to 186). The leading causes of death among former inmates were drug overdose, cardiovascular disease, homicide, and suicide.
MEDICATION-ASSISTED TREATMENT (MAT)

- Methadone
- Buprenorphine
- Naltrexone
Why do methadone and buprenorphine work?
When you're dope sick AF and your plug finally calls back after you've already taken your sub.
Methadone
Buprenorphine
XR-Naltrexone
380mg IM every 4 weeks
Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies

Luis Sordo,1,2,3 Gregorio Barrio,4 Maria J Bravo,1,2 B Icier Indave,1,2 Louisa Degenhardt,5,6 Lucas Wiessing,7 Marica Ferri,7 Roberto Pastor-Barriuso1,2

ABSTRACT

OBJECTIVE
To compare the risk for all cause and overdose mortality in people with opioid dependence during and after substitution treatment with methadone or buprenorphine and to characterise trends in risk of mortality after initiation and cessation of treatment.

DESIGN
Systematic review and meta-analysis.

DATA SOURCES
Medline, Embase, PsycINFO, and HILAC in September 2016.

out of buprenorphine treatment (2.20, 1.34 to 3.61). In pooled trend analysis, all cause mortality dropped sharply over the first four weeks of methadone treatment and decreased gradually two weeks after leaving treatment. All cause mortality remained stable during induction and remaining time on buprenorphine treatment. Overdose mortality evolved similarly, with pooled overdose mortality rates of 2.6 and 12.7 per 1000 person years in and out of methadone treatment (unadjusted out-to-in rate ratio 4.80, 2.90 to 7.96) and 1.4 and 4.6 in and out of buprenorphine treatment.
WHAT IS ALREADY KNOWN ON THIS TOPIC
Opioid substitution treatment is effective in suppressing illicit opioid use and reducing all cause and overdose mortality.
Growing evidence suggests that mortality during and after opioid substitution treatment is time varying and differs by type of drug.

WHAT THIS STUDY ADDS
In patients using methadone maintenance treatment there are, on average, 25 fewer deaths/1000 person years than in patients who discontinue it. Mortality risk among opioid users during treatment is less than a third of that expected in the absence of opioid substitution treatment.
Buprenorphine maintenance treatment is probably also effective in reducing mortality in opioid users, but quantification of averted deaths requires further studies.

The mortality risk in the induction phase of methadone (first four weeks) is high but seems to decreases substantially during this period, with a further stabilisation at around six deaths/1000 person years in the remaining time in treatment. This did not occur with buprenorphine. The mortality risk in the four weeks immediately after cessation of either treatment is high and could exceed 30 deaths/1000 person years.
Mortality:

4/20 in placebo group

0/20 in buprenorphine group

Kakko et al, 2003
If you do detox...
When prescribing MAT...

1. Continue despite opioid relapses
2. Continue despite other substance use
3. Can start even if just cravings and no relapse
MAT: A Summary

1) Methadone
   • Federally-regulated methadone maintenance programs (1970s)
   • Decreases overdose deaths, improves psychosocial adjustment, reduces criminal activity, decreases rates of HIV/HCV

2) Buprenorphine
   • Similar outcomes as for methadone
   • Used since 2002
   • DATA 2000 waiver allows office-based prescriptions

3) XR- Naltrexone (Vivitrol® injection)
   • Opioid antagonist (blocks receptor)
   • Much less evidence
Opioids Are Different

- **Post-acute withdrawal syndrome** → high relapse rates
  
  *(we need our endogenous opiates)*

- Detoxification doesn’t work

- **Overdose death** most likely after period of abstinence
  
  - Inpatient rehab
  - Incarceration

- **MAT** is the gold standard of treatment
BUPRENORPHINE TRAINING COURSE

This conference is designed to meet the requirement for a buprenorphine waiver certification under the DATA 2000 federal law. Participants will learn about opioid use disorder and how to prescribe buprenorphine for their patients.

Training is FREE and includes complimentary breakfast, lunch and CMEs.

Registration

CLICK below to Register
All Courses are 8:30 am to 5:00 pm

Friday, April 19, 2019
Newark, NJ
Rutgers New Jersey Medical School

Friday, May 10, 2019
Park Ridge, NJ
Park Ridge Marriott

Friday, July 12, 2019
Somerset, NJ
Kean University
Hospital Somerset

Friday, July 19, 2019
Union, NJ
Clubhouse at Galloping Hill Golf Course

Friday, August 2, 2019
Ringoes, NJ
Huron Glen Golf Club and Restaurant

Friday, August 9, 2019
Old Bridge, NJ
Grand Merquis

Friday, Sept 27, 2019
Whippany, NJ
Hanover Marriott

* This training is for Physicians, Physician Assistants and Advanced Practice Nurses. Eligible providers who complete this full day training and attain the DA 2000 waiver may be eligible to receive financial reimbursement of $750.

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NJMS.Rutgers.edu/Psychiatry

Friday, September 27, 2019

NJMS.Rutgers.edu/Psychiatry
The New Jersey MATrx

OBAT Providers

Premier Providers

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In an emergency, always call 911. For 24/7 help finding treatment, please contact 1-844-REACHNJ (1-844-732-2465).

What type of treatment are you interested in?
- Medication-Assisted Treatment (MAT)
- Inpatient Services
- Outpatient Services
- Withdrawal Management

Near
Zipcode / City
10 Miles

County
All

Provider Name
Agency / Provider name

Show only Intoxicated Driver Resource Center (IDRC)-affiliated agencies

Search  Reset
Northern COE Counties
Please reach out to us!

Northern: COE@njms.rutgers.edu

Southern: SouthernNJCOE@rowan.edu

MAT Provider Hotline
866-221-2611
(Monday - Friday, 8am - 8pm)