ADDICTION 101

OHIO OPIATE CONFERENCE

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Disclosures: none

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PAIN AS THE 5\textsuperscript{TH} VITAL SIGN? DOCTORS UNDERTREATING PAIN. LONG ACTING OXYCONTIN IS LESS ADDICTIVE… WHAT COULD GO WRONG?
With the introduction of pain as the “fifth vital sign,” accompanied by pharmaceutical company efforts to market directly to prescribers, there has been a dramatic increase in prescription opioid sales.

Studies have documented a strong and consistent linear relationship between opioid sales volume and morbidity and mortality associated with these products.

Oxycontin Poster Children – 12/14 dead, two living...
Risk of continued opioid use increases at 4-5 days.

Likelihood of continuing to use opioids:
- 1 year
- 3 years

Number of days for initial opioid prescription:
- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 40

Source: Centers for Disease Control and Prevention
Credit: Sarah Frostenson
How did this happen???

- More than 100,000 people in the United States have died — directly or indirectly — from prescribed opioids since prescribing policies changed in the late 1990’s.
- BERGMAN VS CHIN – California Case first MALPRACTICE Suit for undertreatment of Pain….
- Based on a study of just 38 patients in 1986, Dr. Russell Portenoy …observational 1-2% addicted

- Now we know more like 30% people
- Medical boards, JCAHO mandated…on NO STUDIES
**DEFINITIONS**

- **Drug Misuse**
  - Taking a psychoactive substance for non-medical purposes, out of curiosity

- **Drug Abuse**
  - Drug use that leads to problems (e.g. loss of effectiveness in society; behavioral psychopathology, criminal acts)
## Classic Models of Addiction

<table>
<thead>
<tr>
<th>Model</th>
<th>Emphasized Causes</th>
<th>Example Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moral</td>
<td>Personal responsibility; self-control</td>
<td>Moral suasion; social/legal sanctions</td>
</tr>
<tr>
<td>Spiritual</td>
<td>Spiritual defect</td>
<td>Prayer; 12-step faith-based treatment (e.g. AA)</td>
</tr>
<tr>
<td>Temperance</td>
<td>Drugs</td>
<td>Control of supply; calls for abstinence</td>
</tr>
<tr>
<td>Educational</td>
<td>Ignorance</td>
<td>Education</td>
</tr>
<tr>
<td>Conditioning</td>
<td>Classical/operant conditioning</td>
<td>Counterconditioning; extinction</td>
</tr>
</tbody>
</table>
• Addiction is a Primary
• Chronic disease of brain
• Reward Pathway
• Motivation Pathway
• Memory Network and related circuitry.
Activation of the reward pathway by addictive drugs

- Morphine
- Opium
- Nicotine
- Benzo’s Barbs
- Alcohol
- THC
- Chocolate
- THC
- LSD
- Ritalin
- Amphetamines
- PCP
- Ketamine
- MDMA
- DXM
- Exercise
- Food
- Gambling
- Sex
- Opium
- Nicotine
- Benzo’s Barbs
- Alcohol
- THC
Stimulants, such as nicotine and caffeine (via adenosine), are involved in the direct pathway to release Dopamine (DA)

Opioids, Benzodiazepines, and Alcohol function indirectly by inhibiting GABAergic neurons which will cause the disinhibition of VTA dopaminergic neurons, thereby increasing dopamine transmission in the NAc
AMERICAN SOCIETY OF ADDICTION MEDICINE

- Addiction is a Primary
- Chronic disease of brain
- Reward Pathway
- Motivation Pathway
- Memory Network and related circuitry.
Addiction is characterized by inability to consistently abstain

- impairment in behavioral control
- craving
- diminished recognition of significant problems with one’s behaviors and interpersonal relationships
- and a dysfunctional emotional response.
Natural Rewards Elevate Dopamine Levels

**FOOD**
- NAc shell

**SEX**
- Source: Fiorino and Phillips

**ETHANOL**
- Accumbens

Source: Di Chiara et al.
Effects of Drugs on Dopamine Levels

Source: Di Chiara and Imperato
The only food that our brain is hard wired for is SUGAR.

Early man was wired for finding sources of sugar, such as honey or ripe fruit.

Glucose for energy.

Fructose to help us store fat.

Storing fat was life saving during times of famine or drought.
WHY NOT BROCCOLI?

• If you eat ice cream for the first time, some dopamine is released in your brain and you like it.
WHY NOT BROCCOLI? ANSWER: INCENTIVE SALIENCE

• Salience is a deep and even unconscious wanting, rooted in our biological and genetic need for food, water, reproduction and connection to others.

• One group of researchers puts it this way: “Core ‘wanting’ does not require conscious awareness, perhaps because it is chiefly a product of subcortical structures involving… dopamine systems (Robinson, Robinson & Berridge, 2013).

• This kind of wanting is deep, and creates a magnetic and attention-commanding aspect to certain activities or substances.
WHY NOT BROCCOLI?

- This transformation is incentive salience. Incentive salience is guided by the neurotransmitter **dopamine** and is more than simply liking something.
- Now, most of us have had ice cream and the dopamine reward we from eating it is familiar.
- If you try heroin the amount of dopamine reward is about 100 times greater than ice cream.
- If you are addicted to heroin, ice cream is no longer salient (important)
- Unfortunately, nothing in real life will be as rewarding to your brain.
- “When I used Percocet, it felt like a warm blanket, like I was ok for the first time in my life” Sense of well being….there is pain and the anxiety from the pain, not caring about being in pain....
• Drug-use initially motivated by positive reinforcement
• Over time, tolerance develops to rewarding effects
• Abstinence leads to withdrawal
• Drug use ultimately maintained by negative reinforcement
• Using “just to feel normal” -- no longer using to get high
• Brain has been reset with tolerance
• Using to avoid withdrawal symptoms

ACE ADVERSE CHILDHOOD EVENTS STUDY
Drug Addiction involves 4 circuits

1. Reward – nucleus accumbens (NAc)  
   ventral pallidum
3. Motivation/drive- orbitalfrontal cortex (OFC)  
   subcallosal cortex
5. Memory and learning- amygdala  
   hippocampus
7. Control- prefrontal cortex  
   anterior cingulate gyrus

Circuits Involved In Drug Abuse and Addiction

All of these brain regions must be considered in developing strategies to effectively treat addiction.
Addictive drugs produce long-lasting changes in brain organization.

The brain systems that are changed include those normally involved in the process of incentive motivation and reward.

Addiction renders these systems hypersensitive ("sensitized") to drugs and drug-associated stimuli.

These sensitized systems mediate a component of reward termed incentive salience or "wanting" (not pleasure or "liking").

Shaking pill bottle, relaxation
Why Can’t Addicts Just Quit?

Non-Addicted Brain

Control

Saliency

Drive

Memory

Addicted Brain

Control

Saliency

Drive

Memory

Because Addiction Changes Brain Circuits

Adapted from Volkow et al., Neuropharmacology, 2004.

NIDA
DRUG DEPENDENCE AMONG EVER-USERS

- Tobacco: 30%
- Heroin: 22%
- Cocaine: 18%
- Alcohol: 13%
- Stimulants: 10%
- Marihuana: 5%
RELAPSE RATES ARE THE SAME AS IN OTHER CHRONIC ILLNESSES

COMPARISON OF RELAPSE RATES BETWEEN DRUG ADDICTION AND OTHER CHRONIC ILLNESSES

- Drug Addiction: 40 to 60%
- Type 1 Diabetes: 30 to 50%
- Hypertension: 50 to 70%
- Asthma: 50 to 70%
<table>
<thead>
<tr>
<th>Drug</th>
<th>Ever Used</th>
<th>Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>75.6%</td>
<td>24.1%</td>
</tr>
<tr>
<td>Cannabis</td>
<td>46.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Cocaine</td>
<td>16.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Stimulants</td>
<td>35.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>12.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>15.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Analgesics</td>
<td>13.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Inhalants</td>
<td>8.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Heroin</td>
<td>1.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>
OPIOID HISTORY

• Hippocrates ancient Greece Morphine
• 15th century China- first officially recorded use of opium as a recreational drug.
• 1874- heroin developed – put an acetyl group on Morphine – developed by Bayer
• 1898- heroin marketed by Bayer as safe pediatric cough suppressant – Mrs Winslows Syrup....
OPIATES & OPIOIDS

**Opiates** = naturally present in opium
- e.g. morphine, codeine, thebaine

**Opioids** = manufactured
- Semi-synthetics are derived from an opiate
  - heroin from morphine
  - buprenorphine from thebaine
- Synthetics are completely man-made to work like opiates
  - methadone
NARCOTIC REGULATION IN US

• 1914- Harrison Narcotics Tax Act
• 1964- Methadone introduced as experimental treatment for opioid addiction
• 1968- Bureau of Narcotic and Dangerous Drugs formed (changed to DEA in 1973)
• 1995 – Pain as the 5th Vital Sign (what was runner up? For the 5th vital sign? )
• 2000 DATA 200 WAIVER (from what?)
• 2010 – OD surpass MVA as #1 cause accidental death
FDA APPROVED TREATMENTS FOR OPIOID USE DISORDER – MU RECEPTORS

- **Buprenorphine/Naloxone** (Suboxone/Zubsolv/Bunavail) – since 1990s – office based treatment
- **Buprenorphine monopродuct** -- PARTIAL AGONIST/ANTAGONIST
- **Methadone** (Dolophine®) – since 1960’s highly regulated FULL AGONIST
- Antagonist Therapy – **Vivitrol** – can start in prisons – no abuse potential – 1 MONTH!
- New – **Probuphene** – implant (like Norplant) for Buprenorphine 6 MONTHS!!!
ROLE OF MAT

- Detox was dominant model, until 2012 – data show 90% relapse without MAT
- Detox w/o subsequent pharmacologic support
  - Decades of evidence show lack of effectiveness….
  - (What’s the definition of insanity?)
- Rx to prevent relapse not offered s/p detox
- Treatment goal
  - emphasis on becoming “drug-free” – is this misplaced?
  - risk reduction? Ambivalence about recovery…
  - Brain has been reset….normalizing brain
HALF LIVES – AFTER 5 HALF LIVES GONE

- Heroin 6 minutes  Di Acetyl Morhine
- 6 MAM  Mono Acetyl Morphine 30 minutes
- Methadone 12-24 hours
- Buprenorphine 24-36 hours
- REPLACING A SHORT HALF LIFE WITH LONG HALF LIFE
- REPLACING AN ILLEGAL DRUG WITH LEGAL ONE
- (what if we called heroin, “hero-morph” – we are giving you a heroid instead of opioid……)
RED FLAGS IN TREATMENT

“My” Medicine – My Subs, Oxys, Percs, 30’s – focusing only on the prescription (no one ever names…or loses their Lipitor)

“I don’t need counselling….” THIS IS MANDATORY

Getting more than 16 mg

Getting Subutex – AND NOTHING ELSE WORKS…..but not pregnant

“allergy “ is very rare….crash cart?

Getting benzodiazepines, soma, gabapentin, tramadol, adderal

Using marijuana

Won’t sign a consent for pain doc, PO etc. safety issue….

Medication NOT IN UDS!!!! (But I ran out EARLY doc…I need more….)

****should I call the police? Usually NO CFR 42 confidentiality applies…

***discharging patients (stopping the Medication vs terminating patient – we can treat – offer counselling but won’t involve controlled substance
PREGNANT WOMEN AND TREATMENT

• Buprenorphine monoprodut versus methadone
  Incidence of withdrawal the same

• Neonates had better outcomes than moms not on methadone or bup
  Duration of withdrawal LESS for bup group
  Less days in ICU monitoring
  Important for in-laws…..family dynamics

BOTH BUP AND BUP/NAL OFF LABEL
METHADONE ONLY FDA APPROVED TX

Unless Hep C, HIV, can breastfeed
“PEOPLE SELL THEIR DESSERT, THEY DON’T SELL THEIR LUNCH” – TED PARREN, MD CLEVELAND CLINIC

Longer you are on Buprenorphine/Naloxone, the less and less you should need

IS PARTIAL ANTAGONIST

“Doc, I’m still in withdrawal”

(NO, POST ACUTE WITHDRAWAL SYNDROME, YOU NEED MORE COUNSELLING – BUP DOESN’T DO IT ALL)

“DIVERSION” VS “TRAFFICKING”

COMMUNITY FAMILY ILLNESS/SHARING/STILL ILLEGAL....
METHADONE

- Methadone liquid only for MAT
- Restricted access – Methadone Clinics only
- Less easily diverted – **DAILY DOSE EXCEPT SUNDAY TO START**
- For severe use or pt wanting more structure
- Initially daily
  - Can progress to 2 week month supply in 2 years
- At higher doses can ‘blockade’ other opioids
- **QTc prolongation at high doses** – over 50, baseline EKG
- Is methadone from clinic on OARRS? VA on OARRS?
METHADONE

- Methadone highest efficacy relieving withdrawal
- Risk of overdose during and if dc’d VERY LONG HALF LIFE – can overdose; risk od most in first week of adjusting to medication
- MOST OD FROM PAIN PRESCRIPTIONS NOT ADDICITON TX PROGRAMS
- Like Brave New World but HAS NO SENSE OF HUMOR….no Benzos, no alcohol, no sedatives
WHAT IS VIVITROL?  
(BILLBOARDS AROUND TOWN)

- Monthly injection – Naltrexone full agonist – stops opioid effects; alcohol effects (remember Revia)
- No pills/films to take – prisons really love this – no diversion
- More compatible with holding down a job/raising family
- Counselling is required (in reputable program) not mandated
- More compatible with travel
- Disadvantage: forced abstinence – higher risk of overdoses when stop; not required to have counselling in place; depression risk (endogenous opioids for mood), probably over rated
- Get liver functions before starting
- MUST HAVE NEGATIVE UDS BEFORE STARTING, DO ORAL CHALLENGE FIRST – NECROSIS, PPT WITHDRAWL
NALOXONE INJECTION

- Available without prescription $25 Kroger
- Narcan nasal spray -- $200, can put into nasal mucosa; no needles around/ kids around
- Evzio – like epi pen – auto injector ….. manufacturer has raised price from around $400 to $6000 over past 6 months…..
- Dealers should buy this for their patients….but not thinking long term…..
PROBUPHENE

- New implant of Suboxone -- 8 mg time released equivalent
- REMS COURSE demonstrate competence on implanting – Norplant tubes in a fan
- No significant diversion people could remove it…tattoo body piercing
- FDA indicated if patient weaned to 8 mg….
SUCCESS STORIES—SO DOC, WHO REALLY GETS CURED?

- No one “cures” other diseases but life improved
- We don’t hear about them/Shame/stigma
- Shatterproof.org – patients cannot speak up for themselves due to stigma fear of consequences
  - such pts practically

  **INDISTINGUASHABLE** from general population

For every $1 we spend on addiction treatment, save $2 in social costs, incarceration
CONCLUSIONS

• Opioid use disorder is a brain disease – MAT works – we don’t know how long should be on it – lowest effective dose – risk/benefit decision

• MAT must include counselling/UDS, monitoring or diversion – regulations by Ohio Medical Board, DEA, effects on Community..

• There are advantages/disadvantages to all the treatments
GOOD NEWS/BAD NEWS

- Decreased admissions for prescription opioids
- Decreased deaths due to prescription opioids
- More doctors educated in proper prescribing
- More doctors using PDMP
- More patients following safe storage and disposal of old/no longer needed medications

- Increase in addiction to Heroin
- Increase in deaths from Heroin and Fentanyl (illicit)
- Too few addiction treatment centers
- Too few pain doctors trained in the use of Buprenorphine
BEST NEWS

• Addiction is a treatable disease
• Patients with addiction are able to learn to manage their chronic illness
• Families can heal
• Addiction treatment saves lives and families.

THANK YOU 😊