Opioid Crisis Overview: History, Current Trends, Pharmacology and Developments in treatment
Indiana Association for Addiction Professionals Virtual Conference 2020
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Addictions Recovery Center & CNS Productions, Inc.

Part I: Current Epidemic and Trends - Opiate/Opioids - The Drugs and Causes

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Issues: Effective Pain Relief Vs. Increase Opioid Addiction Problems
Accelerating Abuse of Opiates and Opioids: Illicit and Diversion of Prescription Pain Medications

Past Eras of Opiate Abuse in U.S.
- 1860s-1880s: Soldier's Illness, Conscribed Asian Workers, Patent Medicine Era (The Opium Problem: Suggestions as to Remedies, Horace B. Day 1869)
- Mid 1960s-Mid 1980s: Consequence of Viet Nam War, SW Asian and Latin American Heroin
- Mid 2005-?: Diversion of Rx Opioids – Vicodin, Oxycontin; Methadone Overdoses; Bumper crops of Heroin = Epidemic of Opioid abuse and addiction: U.S. 4.6% of World Population, consumes 80% of its opioids and 99% of it hydrocodone

Opioids: Understanding the Current Epidemic and the Evolving Science of Pain and Addiction Co-Morbidity Consists of 3 Parts:
Part I: Current Epidemic and Trends – The Opioids and Causes
Part III: Brain’s Addiction Pathway and Developments in Opiate Use Disorder Treatment

Disclosures

Growing Roots: Related Articles: Evidence Based Practices

JOURNAL OF PSYCHOACTIVE DRUGS
A Multidisciplinary Forum

CNS PRODUCTIONS, INC.
Current Epidemic of Iatrogenic Rx Opioid Pain Medication Addiction and OD Deaths

2010 - 2018 U.S. Prescription Drug Deaths (primarily opioid pain medications) were Greater than Auto Accident Deaths!

Methadone represented 30% of these deaths in 2010 yet only amounted to only 2% of all pain medications prescribed.

Age-adjusted rate of drug overdose deaths and drug overdose deaths involving opioids — United States, 2000–2014

Opioid ODs ↑ 200%

ODs ↑ 137%

OD Deaths by type of Opioid – US, 2000-2014

Opioid OD Deaths hit record levels in 2014 with an increase of 14 percent in the year alone. Nearly half a million Americans died from drug overdoses between the years 2000 and 2014.
Annual U.S. Costs due to excessive drinking was $249 Billion in 2017

CDC Vital Signs 2018

- Each Drink results in $1.90 economic costs to U.S.
- Excessive Drinking results in $746 annual costs for every U.S. Man, Woman and Child

Est. U.S. Annual Costs 2017: Alcohol Abuse - $249 Billion; Opioid Crisis $504 – Billion*; Drug Abuse - $193 Billion


Increased Heroin Addiction Link to Increased Rx Opioid Painkiller Misuse/Addiction

Heroin use is part of a larger substance abuse problem.

People who are addicted to...

- Alcohol
- Marijuana
- Cocaine
- Rx Opioid/Painkiller

Most used at least 3 other drugs.

Heroin use is highly addictive opioid drug with a high risk of overdose and death for users.

Note: CDC 2015; Bonner L 2015

2018 Past-Year Use of Illicit Drugs other than Pot by US Teens remains steady over past 3 years

In 2014: After Pot, Rx and OTC medications are the most likely drugs abused by 12th graders

Past-Year Use of Illicit Drugs and Pharmaceuticals among 12th Graders

Current Use (past 30 days):

- Opioid Use beginning to Dip
- Binge Drinking (5 or more drinks/episode)
- Other Illicit Drugs remaining ~level But
- Vaping Nicotine nearly Doubled

Note: 2018 Monitoring The Future (MTF) High School Seniors

K2/Spice (“synthetic marijuana”) used by ~6% of HS seniors:

Note: MTF 2014
2018 Misuse of Rx Opioids by 12th graders dropped significantly over the last 5 years

Increase in New Starts of Prescription Opioid Abuse Among Teenagers

Drug-Related Emergency Department (ED) Visits Involving Nonmedical Use of Opioid Analgesics
The Under – Over Medication Pendulum

Anxiolytics – benzodiazepines
Treatment of ADD/ ADHD – analeptics
Especially Analgesics – opiate and opioids morphine, methadone, Oxycontin, Vicodan and now Zohydro advocacy
Even OTC Medications – DxM, antihistamines, anti-diarrheals

Current Epidemic of Iatrogenic Rx Opioid Pain Medication Addiction and OD Deaths

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Methadone represented 30% of these deaths in 2010 yet only amounted to only 2% of all pain medications prescribed

Center for Disease Control Evaluation of Rx Drug Abuse Problem

*Unintended Rx drug OD death every 19 minutes in 2007
*Each Rx opioid OD death = 9 detox admissions, 35 ER visits, 161 abusers/addicts, & 461 reports of nonmedical use of Rx opioids
*9 million U.S. long-term medical Rx opioids users and 5 million annually report nonmedical use
*Pharmacy U.S. distribution of Rx opioids rose 600% from morphine equivalent of 96 mg. in 1997 to 700 mg. per capita in 2007

Opioid Abuse & ODs including Iatrogenic Rx. Meds Epidemic in US – Nat. Inst. Health

- U.S. 4.6% of world population yet consumes 80% of global opioid supply, 99% of global hydrocodone supply, 81% oxycodone supply & 2/3 of the world’s illicit drugs
- Rx opioid dependence rose from 1.5 to 2.1 million Americans from 2002 to 2012
- Heroin dependence ↑ from 214,000 to 467,000 2007 to 2012
- 75% of Rx medication OD deaths involved opioid analgesics

Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)

Age-adjusted rate of drug overdose deaths and drug overdose deaths involving opioids — United States, 2000–2014
Amount of prescription painkillers sold by state per 10,000 people (2010)

Drug overdose death rates by state per 100,000 people (2008)

2015 U.S. Heroin Epidemic
OD deaths quadrupled 2002-13

1996 High Dose ER reformulation of oxycodone pain pill helps spark current Opioid Epidemic

Opioid Epidemic Oxycontin® Link
- Purdue Pharma MS Contin® 15 to 200mg Success
- Percodan = 5mg oxycodone + apap, Schedule II
- 1996 Oxycontin® up to 160mg ER, no apap, Sch. III
- JCAHO/CARF et al.: Pain is 5th vital sign, “pseudo addiction”, Press Ganey Patient Satisfaction
- Oxycontin’s 12-hour extended release problem – “break through pain”, opioid withdrawal syndrome
- Addict subculture quickly find ways to undermine abuse deterrent technologies
- Over prescribing crackdown, addicts seek other Rx. and street opioids (More validation in Albert et al., Rand Publications Working Paper, January 2017, now several hundreds lawsuits)
By May 2018 - 22 States are part of ~440 states, territories, counties, cities, American Indian nations (inc. Nebraska’ Ponca Tribe), and individuals suing Purdue Pharma LLP for deceptive marketing and ignoring addictive nature of Oxycontin by falsely denying or downplaying addiction while overstating the benefits of opioids.


Two Main Unquestionable Facts about the Current Opiate Epidemic

• Widespread Diversion and Improper Use of Opioid Pain Medications has resulted in epidemic OD deaths and Addiction (37% of drug OD deaths in 2013 due to Rx opioids and 19% to heroin with parallel increase in opioid addiction.

• Major source of diverted opioids is physician prescriptions made available to friends, family members or for illicit sales

Volkow & McLellan NEJM 2016

Some Unethical, Unwise, and Over-Prescribing of Opioids

Many horror stories and tabloid reports especially when a public figure is involved or overdoses (e.g. This dog X-ray used in a sting to get pain meds)

But, Most diverted opioid and other prescription drugs are obtained from friends or family members

June 2012 US Senate Caucus on International Narcotics Control

• Rx drugs now second most common form of drug abuse in the U.S.

• Now responsible for most OD deaths, greater than heroin and cocaine combined

• Violent pharmacy robberies increased 82% between 2006 and 2011

• NSDUH data indicates 70% or Rx drugs were supplied by friends or relatives

July 2013 CDC Report: More Rx med death than car crash death in U.S.

• 1999-2010 Rx Opioid OD death increased 400%, in women, 265% in men. 18 women deaths every day!

• Rx meds (esp. Oxycontin & Vicodin) comprised 34% of suicide deaths in women and 8% in men

• >200,000 women ER visits were due to misuse or abuse of these drugs, -one every three minutes

• Rx Opioid OD deaths were greater than 4 times as many cocaine and heroin deaths in women

• Dr. Thomas Frieden, CDC Director now estimates 42 women deaths each day from Rx Opioid ODs
Opioid Epidemic or are we really in an Addiction Epidemic

Increase Opioid Use Disorder and OD Deaths

Also Increase in Stimulant (cocaine & Methamphetamine Abuse and OD Deaths

Increased Benzo/Opioid OD Deaths during "Opioid Epidemic"

2007 to 2017 35% increased alcohol deaths in US With 85% increase alcohol deaths in women!

Increase Benzodiazepine-Involved OD Deaths especially in combo with Opioids

NIH/NIDA 2018

1996-2013 Benzo filled Rx increased 67% And amount filled increased 140%

Combined use of Benzo and Opioid increase OD death risk 10 fold! 75% Benzo OD deaths Involved Opioids and 23% of Opioid OD deaths also tested Positive for Benzos in 2015

In the Midst of Opioid Epidemic, Increase in Cocaine and Stimulant Abuse and OD deaths 2015 - 2017

U.S. Alcohol-Related Deaths on the rise 35% especially dramatic increase in women 85% 2007-2017

"Speedballing?": Increased Cocaine–Opioid OD Deaths

1.35/100,000 pop. Cocaine deaths; 0.57 Cocaine/Op.-related deaths in 2010

1.36/100,000 pop. Cocaine; 1.36 Cocaine/Op.-related deaths in 2015

Jones-McCall et al. (2017) Am. J. of Public Health

Overdosed on Downers (Esp. Opiates)

ABC as of 2010 CAB:

✓ Call 911
✓ Establish and maintain Airway, oropharyngeal insert, prevent aspiration
✓ Ensure and support Breathing
✓ Assess and secure adequate Circulation Naloxone (Narcan®) parenteral or intra-nasal administration for severely obtunded, Abrupt emergence Reactions and shorter duration of action
Naloxone (Narcan) Nasal and Parenteral

First Responders: Police, Fire, EMTs now being trained and supplied with Naloxone

BH workers and Street Outreach Workers as well

Medical Detox and Addiction Treatment Centers also providing naloxone on discharge


Increasing Naloxone Availability

OTC at CVS Pharmacies: Arkansas, California, Minnesota, Mississippi, Montana, New Jersey, North Dakota, Pennsylvania, South Carolina, Tennessee, Utah, & Wisconsin

OTC at Walgreens: Alabama, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Texas, Utah, Vermont, Virginia, Washington DC, & Wisconsin

Naloxone Coprescribing: Prescribing Naloxone OD kit with opioid Prescriptions

Naloxone Standing Orders: State Medical Director providing Order for Health care professional to provide/administer naloxone

Fentanyl Test Strips

Opioid Pain Medications (downers)

In 2010 U.S. Prescription Drug Deaths (primarily opioid pain medications) were Greater than Auto Accident Deaths!

Methadone represented 30% of these deaths in 2010 yet only amounted to only 2% of all pain medications prescribed

6 Americans Die Daily from Alcohol Poisoning, 1 every 4 hours

2017: 6-7 Americans will die from opioid overdose every hour! US life expectancy drops 3 years in a row 2015-2018
2016 U.S. Life Expectancy ↓ 78.8yrs yet annual medical expenditure ↑ $9,892/person (Japan ↑ 83.98yrs, $4,519)

Opioid Abuse & ODs including Iatrogenic Rx. Meds Epidemic in US – Nat. Inst. Health
- U.S. 4.6% of world population yet consumes 80% of global opioid supply
- Rx opioid dependence rose from 1.5 to 2.1 million Americans from 2002 to 2012
- Heroin dependence ↑ from 214,000 to 467,000 2007 to 2012
- 75% of Rx medication OD deaths involved opioid analgesics

Endogenous Opioid Peptides
- Endorphins, β-Endorphin, Gamma-Endorphin
- Enkephalins
- Dynorphins
- Adrenorphin, amidorphin
- Opiorphin
- et al.
Methadone (Dolophine, Methadose)
Leading Cause of Rx OD Deaths 2010-2011

Buprenorphine Abuse

“Chiclets” = Frozen Fentanyl Patches
OTC Imodium® (Loperamide)

Heroin: making a big comeback in 2010 on!

2018 “Designer fentanyl” now the most lethal illicit drug

- Modifications of existing molecules of abuse (isomers, analogs, isosteres, et al.), drugs laws specifically name a molecule and not the modifications of such

- Finding molecules with entirely different chemical structures that produce similar effects to illegal recreational molecules (Structure-Activity Relationship; Pharmacophore)

Example: prescription amyl nitrite and designer “poppers”

For Example: Designer Volatile Nitrites
Illicit “Designer” fentanyl
Sold as: “China White”, Oxycontin or added to heroin to ↑ potency
- Fentanyl = up to 100 x stronger than morphine, heroin is twice as strong as morphine
- Various Illicit “designer” isomers:
  - α-methylfentanyl (AMF) & β-methylfentanyl
  - 3-methylfentanyl
  - acetylfentanyl
  - sufentanly
  - α-methyldithiofentanyl & 3-methylthiofentanyl
- Sufentanly is 5 to 10 x stronger than fentanyl and thiofentanyls are even much stronger

- OD deaths/million: North America 164.5, W. & Cent. Europe 28.9, Latin America 15.6, Asia 29.6, Africa 61.9
- U.S. has highest drug overdose death rate in the world!
- Growing incidence of illicit fentanyl analogs laced heroin overdoses (W-18 a fentanyl analog that is 10,000 times stronger than morphine)

Illicit Designer Fentanyls
- Fentanyl
- Acetyl Fentanyl
- Sufentanly
- 3-Methyl Fentanyl
- W-18
- Carfentanly
- Parafluorofentanly

The equivalent of one grain of salt of Carfentanly is enough to kill a human being

Mexican Drug Cartels Ramping Up Production Of Deadly Drug
Fentanyl, the extremely potent opioid that Prince overdosed on, has now become a favorite of drug cartels across Mexico due to its extreme profitability, The New York Times reports.
The United States has an insatiable demand for opioids in the 21st century, including heroin, oxycotin and other prescription drugs, with unintentional overdose deaths quadrupling since 1999.
Buy kg Heroin - $6,000  Sell - $80,000

Buy kg Fentanyl - $5,000  Sell - $1.6 million (can be cut and stretched to 16-24 kg)

“Gunpowder” Heroin? Said to be more potent then “Tar” but less than “China White”

Claims that Gunpowder Heroin is really Fentanyl mixed with Tar Heroin or some dark powder

Counterfeit Xanax® laced with fentanyl

Fake Xanax®

Real Xanax®

alprazolam

Also fake Vicodin®, Lortab®, Norco® tablets found to contain fentanyl

Acetyl Fentanyl aka “China White, Apache, Goodfella, Jackpot, TNT, Murder 8 and Tango and Cash”

W-18 1-(4-nitrophenylethyl)piperidylidine-2-(4-chlorophenyl)sulfonamide

W18 Drug Is 10,000 Times Stronger Than Morphine: Calgary Police Warning

There’s only been a single release of a powerful new drug called W-18 in Calgary, but police say with as high that much more is available in the streets.

Lately, we’ve seen a drug called W-18, which has been linked to a drug called fentanyl, which has been traced to fentanyl-related deaths in 2017 and only six deaths reported in 2013.
"Pink, Pinky, U4" = U47700
Mixtures of heroin, fentanyl, carfentanyl and U-47700 (Furanyl Fentanyl)

"Grey Death"
Gulf Coast 2017, ~eight times more potent than heroin

“U-47700”
OPIOID ANALGESIC
7.5x morphine.

AH-7921

Developed in the 1970’s as a pain reliever
Never developed commercially
80% the strength of morphine
Used as an active ingredient in ‘synthetic cannabis’ products created in Japan
Isotonitazene a non-fentanyl opioid is non-scheduled as of 6/2020

Slightly more potent than fentanyl, about 2.5 X more potent than hydromorphone (Dilaudid)

Bucinnazine (2-methyl or 2,6 dimethyl AP-237, 1-butyryl-4-cinnamyldipiprazine)

“Krokodil” & “Baker’s Brew”

Krokodil
Desomorphine is made from codeine with iodine, lighter fluid, oils or gasoline, et al.

Poppy Seed Tea
Seeds are crushed or blended, steeped in boiling water, strained and then mixed with grapefruit extract

Concern over Kratom: “Legal Phyto-Vicodin?”
FDA Deems Kratom an Opioid 2/6/18

Alleged 15X Concentrated mitragynine and 7-hydroxymitragynine extracted from Kratom leaves
Captain Kratom
“Synthetic Vicodin”

Kratom, Ithang, kakuam, thom

Mitragyna speciosa
Thailand, Indonesia, et al.

7-hydroxymitragynine, speciogy-nine, paynantheine, mitraphyl-line, & about 2 dozen others

Various commercial concentrated 15X to 250x extracts

Kratom Pharmacology
• Low Dose = Yohimbe-like stimulant
• Higher doses = Mu-opioid receptor agonist
• Effects (4 gms = 4 hours of euphoria)
  – Analgesia, cough suppression
  – CNS depressant, ↓ blood pressure
  – Quick onset and lasts ~ 1 – 4 hours
• Acute side effects: dry mouth, ↓ appetite
  – Constipation
  – No n/v, ↓ blood sugar
• Opioid-like full physical addiction

Rx Opioids (Downers)

Continued Rise in Prescription Opioid Abuse
New Oxycontin® Formulation to Mitigate Abuse April 2010

So, by 2012:
1. Freeze Oxy or
2. Opana®

Or, 3. Heroin

2016 Xtampza ER approved with DETERx
Tech. = Oxycodone 10 – 40mg

Note: Narco, Lortabs, Lorcet, Hycodan, Vicoprofen, Anexia, Anolor, Hycomine, Xodol, Zydone and many others pain or cough meds contain hydrocodone

2014 Zohydro gets FDA approval: 50 mg of hydroco-done to be released over 12 hours with no acetoamino-phen as 63% of US liver deaths due to acetoaminophen toxicity. On 10/6/14 all became Fed. Schedule II.

2015 Hysingla ER: 20, 30, 40, 60, 80, 100, 120 mg. approved for 2015

Methadone (Dolophine, Methadose)
Leading Cause of Rx OD Deaths 2010-2011

Note: Methadone pre-eminent in Rx OD deaths.
Chiclets = Frozen Fentanyl Patches

Dsuvia (sufentanil) SL tabs 30 mcg
FDA approved in Nov. 2018

“Chiclets” = Frozen Fentanyl Patches

Centers for Disease Control and Prevention (CDC) 7/3/12
Steep Rise in Methadone OD deaths in 2000s Peaked out in 2007 and now falling
Still, methadone currently accounts for almost 1/3 of U.S. Rx medication deaths
In 2011 methadone was only 2% of all pain prescriptions yet responsible for more than 30% of Rx pain medication deaths

Expanding Diversion and Abuse of Prescription Medications Especially Opioids by Youth

OTC Immodium® (Loperamide)

Rx. & OTC medication abuse by High School Seniors

Prescription/Over-the-Counter Drugs Account for 8 out of 10 of the Most Frequently Abused Drugs
Prevalence of Past Year Drug Use Among 12th Graders

Johnson, L. et al. annual Monitoring the Future, U. of Michigan
The Under – Over Medication Pendulum

**Anxiolytics – benzodiazepines**
Treatment of ADD/ ADHD – analeptics
Especially Analgesics – opiate and opioids
morphine, methadone, Oxycontin, Vicodan
and now Zohydro advocacy
Even OTC Medications – DxM, antihistamines

In 2014: After Pot, Rx and OTC
medications are the most likely drugs
abused by 12th graders

Center for Disease Control Evaluation
of Rx Drug Abuse Problem
*Unintended Rx drug OD death every 19 minutes in 2007*
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35 ER visits, 161 abusers/addicts, & 461 reports
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600% from morphine equivalent of 96 mg. in
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Rates of prescription painkiller sales,
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* Major source of diverted opioids is
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- Rx drugs now second most common form of drug abuse in the U.S.
- Now responsible for most OD deaths, greater than heroin and cocaine combined
- Violent pharmacy robberies increased 82% between 2006 and 2011
- NSDUH data indicates 70% or Rx drugs were supplied by friends or relatives

Also many horror stories of overzealous restriction of such medications from appropriately medical uses – Pseudo Addictions?

Many states have regulations recognizing pain to be the Fifth Vital Sign of medical treatment and recognize the right of patients to appropriate assessment and management of pain

Some Unethical, Unwise, and Over-Prescribing of Opioids

Many horror stories and tabloid reports especially when a public figure is involved or overdoses (e.g. This dog X-ray used in a sting to get pain meds)

But:
Most diverted opioid and other prescription drugs are obtained from friends or family members

Pseudoaddiction

- Operationally defined as aberrant drug-related behaviors that make patients with chronic pain look like addicts.
- These behaviors stop if opioid doses are increased and pain improves. (Weissman and Haddox, 1989)
- This indicates that the aberrant drug-related behaviors were actually a search for relief
- Little data on the subject – Only a single human report as of 2014, but evidence in rats

Sources of Analgesics for Nonmedical Use as Reported by Users

In a household survey, friends and relatives were a significant source of analgesics for nonmedical use.

July 2013 CDC Report: More Rx med death than car crash death in U.S.

- 1999-2010 Rx Opioid OD death increased 400%, in women, 265% in men. 18 women deaths every day!
- Rx meds (esp. Oxycontin & Vicodin) comprised 34% of suicide deaths in women and 8% in men
- >200,000 women ER visits were due to misuse or abuse of these drugs, ~one every three minutes
- Rx Opioid OD deaths were greater than 4 times as many cocaine and heroin deaths in women
- Dr. Thomas Frieden, CDC Director now estimates 42 women deaths each day from Rx Opioid ODs
Opioid Pain Medications (downers)

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In 2014, Drug ODs kill more than Cars, Guns and Falling

- Falling 28,360 deaths
- Guns 32,351 deaths
- Traffic Accidents 33,692 deaths
- Drug Overdoses 41,340 deaths
  16,917 of which were from opioid pain medications


Increasing Naloxone Availability

OTC at CVS Pharmacies: Arkansas, California, Minnesota, Mississippi, Montana, New Jersey, North Dakota, Pennsylvania, South Carolina, Tennessee, Utah, & Wisconsin

OTC at Walgreens: Alabama, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Texas, Utah, Vermont, Virginia, Washington, Washington DC, & Wisconsin

Naloxone Coprescribing: Prescribing Naloxone OD kit with opioid Prescriptions

Naloxone Standing Orders: State Medical Director providing Order for Health care professional to provide/administer naloxone

John Rogers, Northwestern U.’s Center for Bio-Integrated Electonics develop cutaneous implant that will automatically deliver naloxone when one is overdosing on opioids

The skin implant is loaded with naloxone and injects it when its sensors detect a dangerous drop in blood oxygen levels

Chicago Tribune 12/3/19

Conclusion Part I: The Opiate/Opioid Epidemic is Terrifying but it can “galvanize” Society to develop more effective future Management of Opioid Use Disorder
Video: Use Abuse & Addiction

- Part I: History (15 min)
  - Prevention (19 min)
  - Treatment (14 min)
  - Mental Health & Drugs (16 min)
- Part II: Heredity, Environment & Drugs (14 min)
  - Uppers (13 min)
  - Downers (15 min)
  - Alcohol (17 min)
  - All Arounders (20 min)
  - Other Addictions (20 min)

Chronic Pain – Opiate/Opioid Addiction Co-Morbidity

- Part IIA: Evolving Understanding of Pain and Opiate Addiction Co-Morbidity
- IIB: Opioid Pharmacology
- Part III: Brain’s Addiction Pathway and Developments in Opiate Use Disorder Treatment

Types of Pain (Chronic Pain ≥ 3-6 mo.)

- Nociceptive Pain (sprains, bone fractures, burns, bruises) - special nerve ending which heal with time
- Non-Nociceptive Pain
  - Neuropathic (shingles, Diabetic Neuropathy neuralgia, phantom limb pain, Carpal Tunnel Syndrome /CTS, peripheral neuropathy)-nervous system dysfunction pain
  - Mixed Category (migraine headaches)-complex mixture of nociceptive and neuropathic
  - Central (Fibromyalgia)-caused by dysfunction of nervous system
  - Complex Regional (Type I illness/injury; Type II peripheral nerve damage/injury in both peripheral and central NS
  - Emotional Pain (loss, relationship, humiliation, disappointments, exclusion, fears, psychological trauma)-psychologic trauma
  - Allodynia (Thermal, Mechanical, Movement)-increased chemokines causing sensitization with increased response of pain neuron

Beyond Opiates: Evolving Science of Pain and Addiction a major comorbidity

Pain Relief & Addiction

Chronic and long term use of opiate drugs may lead to dependence

Symptoms of addiction may include, but are not limited to:
- Taking more medicine than you were prescribed or taking it more often
- Feeling your pain worsens when you try to stop taking your medicine
- Feeling you need to take more of your medicine to feel better
- Getting restless, irritable, or overactive when you are not taking your medicine
- Taking more medication than prescribed by the doctor

If you think you may have developed an addiction, talk to your GP immediately or contact a drug treatment service near you.

Percent of male and female patients of various ages with co-morbid bodily pain, psychiatric disorders, alcoholism, and nicotine dependence

Cicero et al., JSA 42(1): 87-94, 2012
Physical Pain Registration in the Anterior Cingulate Cortex (ACC)

Pujol, J et al (2009), PLoS ONE

Neurologic Pain Signature

Wager, Tor (2013), NEJM

Signatures of Various Chronic Syndromes

Wager, Tor (2013), NEJM

fMRI Scans image pain signature, measure intensity and demonstrate when relief occurs

Wager, Tor (2013), NEJM

fMRI Reveal Emotional Pain Signature Pathway

Prefrontal Cortex to Nucleus Accumbens and amygdala

Wager, Tor (2013), NEJM

NIH 2015 Pain White Paper

• Little to No evidence for opioid effectiveness in long-term chronic pain
• Yet, Rx for opioid drugs have more than tripled in past 20 yrs. (219 million Rx in 2011)
• U.S. Rx Drug Abuse Epidemic >16,000 Rx Opioid Deaths in 2012
• U.S. 4.6% of World Population Consumes 80% of World’s Opioid Drugs
• Also, U.S. heroin deaths increased 39% in 2013

CDC 2013 Mortality Data Jan. 2015
Chronic use of opioids for pain management: Expanding Concerns

- **Hyperalgesia** = increasing pain due to PAF activation of chemokines (i.e. cytokines) release with opioid treatment of nociceptive pain that will disappear with healing

- **Neuropathic Pain or Hyperpathia** = increasing pain due to peripheral nerve and spinal dorsal horn sensitization that will persist after the pain stimulus is healed

- **Opiate Hyperalgesia**
  - Analgesic response with tolerance: Pain continues to overcome increased doses of opiates

- **Hyperkatifeia** = hypersensitivity or increased emotional pain/distress with chronic opioid treatment

- **Allodynia** = development of painful response to normally innocuous stimulus such as light touch on the skin or warm or cool temperature

- **Opioid Addiction** = development of tolerance, tissue dependence, withdrawal and psychological dependence

Beyond Opioids

- **33 min. DVD**
  - Expanding Sciences of Pain and Recovery
  - CNS Productions, Inc. Medford, Oregon
Tools for Assessing Pain should also assess stress

Tools for Assessing Addiction Risk

- Opioid Risk Tool – Clinician Form
  - Family History of Substance Abuse
  - Personal History of Substance Abuse
  - History of preadolescent sexual abuse
  - Psychological disorders
    - (ADHD, ODD, Bipolar, Depression)

- SOAPP 14 Q. - Screener and Opioid Assessment Tool

Treatment Strategies for Prescribing Narcotics to Pain Patients

- Need to monitor carefully for signs of abuse or misuse of medications; dependence and analgesic tolerance often present without behavioral change.
- Narcotic protocol consists of medication contract, consent, psychological evaluation, random urine toxicology.
- Monitoring both urine toxicology and aberrant drug-related behavior (ADRDB) will detect more inappropriate drug-taking than either alone.
- Highest sensitivity (90%) for predicting ADRB: clinical interview combined with Screener and Opioid Assessment for Patients with Pain (SOAPP).

American Chronic Pain Ascn. Tools for management of Chronic Pain

QoL management not elimination of pain is key

Ability Chart – 11 self-evaluation domains on 11 point Likert Scale:

- Pain Level
- Personal Care
- Getting Out of Bed
- Daily Activity
- Climbing Stairs
- Working
- Descending Stairs
- Leisure Activities
- Getting Out of a Chair
- Quality of Life
- Walking

Opioid Misuse Behaviors to Watch for

More Suggestive of Abuse/Addiction

- Selling prescription drugs
- “Renting” Rx to escape med count discrepancy
- Stealing drugs from others
- Repeated dose escalation
- Repeated visits to the E.R.
- Repeated loss of medication or request for early refill

Less Suggestive of Abuse/Addiction

- Openly acquiring pain meds from other doctors
- Drug hoarding during periods of reduced symptoms
- Aggressive complaining about need for more pain meds.
- Reluctance to try alternative treatments

Alternative Medications for Pain

- Nonsteroidal anti-inflammatory drugs (e.g. ibuprofen, Aleve, Clinoril)
- Acetaminophen
- NE RI Antidepressants (e.g. Cymbalta, Effexor)
- Anticonvulsants (e.g. Topamax, Neurontin, Tegretol)
- Steroids (e.g. Prednisone, Decadron, hydrocortisone)
- Muscle relaxants (e.g. Flexeril, Robaxin, Zanaflex, Baclofen, Skelaxin)
- Topical Anesthetic Gels (Pluronic Lecithin Organogel – PLO)
- Cannabidiol (CBD) in marijuana “Charlotte’s Web”
- Low Dose Naltrexone (LDN) (Anti-inflammation. Used in fibromyalgia, MS, complex regional pain and other chronic pain Disorders)
Most Commonly Recommended Alternatives to Opioids for Pain

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Acute Pain</th>
<th>Chronic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC Medication (ASA, NSAID)</td>
<td>90%</td>
<td>76%</td>
</tr>
<tr>
<td>Topical analgesics</td>
<td>68%</td>
<td>61%</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>46%</td>
<td>69%</td>
</tr>
<tr>
<td>Nerve blocks</td>
<td>40%</td>
<td>54%</td>
</tr>
<tr>
<td>Alternative medicine (acupuncture, herbals)</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>32%</td>
<td>45%</td>
</tr>
<tr>
<td>Cognitive-behavioral therapy</td>
<td>33%</td>
<td>52%</td>
</tr>
<tr>
<td>Mindfulness/mind-body interventions</td>
<td>33%</td>
<td>48%</td>
</tr>
<tr>
<td>Device-based treatment (electrical stimulators)</td>
<td>29%</td>
<td>47%</td>
</tr>
<tr>
<td>Other</td>
<td>13%</td>
<td>15%</td>
</tr>
</tbody>
</table>

(Derku, BS [2016])

Kappa Opioid Receptor (KOR) delineated 2018

KOR is activated by dynorphin producing powerful analgesia while suppressing Reward Reinforcement Pathway activity

Tao, C et al. (2018); Bryan L. Roth (2002)

Delta Opioid Receptor

Medication developments targeting this receptor has been shown to effectively relieve allodynia without causing opioid addiction


Or, SR 21502 blocks Opioid D3 receptor and thus block addiction without affecting other dopamine receptors


Low Dose Naltrexone: Non-Opioid Treatment

NFEPP modified fentanyl will only activate mu receptor in low pH environment

Inflamed tissues (pain) are in much lower pH than brain tissues. Thus, NFEPP would only target the pain in tissues outside the brain and not be active in the brain. Adverse CNS opioid effects: Resp. depression (OD), constipation (?), euphoria and addiction would be avoided

Stein, Christoph (2019) Charite-Freie Univ. Berlin Germany

Complementary and Alternative Medical Treatments (CAM)

- Acupuncture, Chi Kung, Ayurveda
- Transcutaneous Elec. Nerve Stimulation (TENS)
- Psychotherapy for Stress or Depression
- Relaxation Tx., Yoga, Reiki, Pilates, Meditation
- Hypnosis, Guided Imagery, Physical Therapy
- Music Therapy, Aromatherapy, Food/Nutrition
- Biofeedback, Hydro-, Oxygen-, Magnet-Therapy
- Chiropractor, Massage, Somatics, Exercise, Pain Revolution – Retrain the Brain
- Puzzles (Sudoku, Crosswords, Etc.)
MEDICAL MARIJUANA

2015: 23 States plus Washington DC have Medical Marijuana Laws

2013 2014

Need to Note Conditions Specified:
- Short-Term use only (< 6 months)
- Documented failure of all other medications
- Only under ongoing medical supervision
- MD routine monitoring for positive outcomes
- MD Review Board to provide guidance for use in specific patients
- Smoking is crude and hazardous delivery system so endorse use of different chemicals

2013 2014

Not a Single Major American Health Association Accepts Smoking Crude Marijuana as Medicine

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Marijuana “Pot”

Marijuana “Pot”

Marijuana “Pot”

Marijuana “Pot”

Three Species, infinite varieties/hybrids/Strains with wide concentrations of some 480 chemicals, 66 are cannabinoids, ~80-100 of which are psychoactive (plus their metabolites >100 identified in human body) cannabinoids; Δ9THC (tetrahydrocannabinol) are considered to be responsible for most effects

• Cannabis sativa
• Cannabis indica
• Cannabis ruderalis

Sensimilla and growth manipulations

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• Cannabis sativa
• Cannabis indica
• Cannabis ruderalis

Sensimilla and growth manipulations
Main Phytocannabinoids
(490 chemicals in pot, ~66 are psychoactive

Three most considered in medical pot:
• THC: Main psychoactive chemical, anti-emetic, appetite stimulant, analgesia
• CBD (cannabidiol): much less psychoactive, anti-seizure, anti-inflammatory, analgesia, sedating, neuroprotective, actually counters many THC effects
• CBN (cannabinol): anti-seizure, anti-inflammatory, phase II sedative effects

Note: ~2,000 chemicals produced when pot is combusted

THC & CBD often work in opposition to each others effects

THC - Recreational use interests
Euphoria
Anxiety
Psychosis
Cognitive impairment
Hunger

CBD - Drug Companies Interests
No euphoria
Anxiety
Psychosis
Cognitive impairment
Hunger

CBD medical potentials: reduce atherosclerosis, anti-tumor, Anti-metastasis, Anti-inflammatory, Neuroprotective, Gum protective, Anti-obesity, analgesic, Anti-psychotic, Anti-depressant, Anti-anxiety

Dronabinol (Marinol)
• Dronabinol is 100% THC, the most psychoactive ingredient in cannabis. Natural cannabis is 20% THC or less
• The physiological effect of THC is modulated when the other cannabinoid forms are present. Dronabinol is associated with too many psychoactive effects.
• DEA classifies dronabinol as schedule III
• FDA approved dronabinol for treatment of nausea and vomiting associated with chemotherapy and anorexia associated with weight loss in patients with HIV/AIDS
• Is dronabinol an appropriate substitute for natural cannabis??
• Dronabinol is very expensive
• Sativex is much better but not available in US (50% THC, 50% cannabadiol in a sublingual spray)

But: THC-to-CBD Ratio Continues to Increase

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Medical Synthetic THC
2000’s Synthetic Cannabinoids
• dronabinol (Marinol)
• nabilone (Cesamet)
• THC + CBD (Sativex)
• Cannabinol Extract (Cannador)
• CBD (Epidiolex) FDA approved 6/25/18

FDA-Regulated Cannabinoid-Based Medicines:
Chemicals, Extracts, Botanicals
Sativex™: Oral Spray-THC:CBD = 1

RD Schwartz-Bloom 2011

Sativex Oromucosal Extract

• 1:1 combination from two clonal cannabis cultivars yielding a high THC extract (Tetranabinex®) and a high CBD extract (Nabidiolex®).
• a botanical drug substance (BDS) of defined composition with controlled reproducibility batch to batch.
• THC and CBD comprise some 70% (w/w) of the total BDS, with minor cannabinoids (5 – 6%), terpenoids (6 – 7%, most GRAS), sterols (6%), triglycerides, alkanes, squalene, tocopherol, carotenoids and other minor components (also GRAS).
• each 100 μL pump-action spray provides 2.7mg of THC and 2.5mg of CBD, the minor components, plus ethanol: propylene glycol excipients, and 0.05% peppermint as flavouring.
• Intermediate onset: 15-40 minutes
• Allows dose titration; Reduces first pass metabolism
• MUCH BETTER THAN MARINOL

Courtesy of Dr. Gregory T. Carter 2012

CLINICAL USES OF CANNABIS IN CHRONIC PAIN

• Neuropathic pain; Myofascial pain
• Sleep, mood, and appetite improvement
• Enhances effects of opioids and helps offset opioid side effects
• Helps with muscle spasms
• No constipation or respiratory suppression
• No LD50

Courtesy of Dr. Gregory T. Carter 2012

Cannabinoid Suppression of Neuropathic Pain – Basic Science

• In CCI of infraorbital nerve model, CB1 receptor upregulation was observed in both the ipsilateral and contralateral superficial layer of the trigeminal caudal nucleus (I>C)
• CB2 receptor immunoreactivity is increased in the ipsilateral dorsal horn after L5 spinal nerve transection
• Saphenous partial nerve ligation increased u-opioid, CB1, and CB2 receptor protein levels in ipsilateral/contralateral hind paw skin, DRG, and ipsilateral/contralateral L-cord (1-7 days post-surgery)
• Tibial nerve injury → upregulation of CB1 receptor mRNA in the contralateral thalamus, 1 day post-surgery
• SCI model—mechanical allodynia was reduced with chronic administration of WIN (mixed CB agonist) with no decrease in effectiveness, unlike morphine

Courtesy of Dr. Gregory T. Carter 2012

Arguments for Cannabinoid Pain Management

• Analgesia: different mechanism than opiates, some synergy though.
• Spasticity: likely GABA mediated
• Appetite enhancement: hippocampal?
• Anti-emetic: cerebellar? (2012 C. Hyperemesis Syndrome??)
• Elevated levels of the CB1 receptor are found in areas of the brain that modulate nociceptive processing
• CB1 and CB2 agonists have peripheral analgesic actions
• CBs may also exert anti-inflammatory effects

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Arguments for Cannabinoid Pain Management

Now Medical CBD Liquid for Vaping alleged legal in U.S.

Cannabinoids have suppressed neuropathic nociception in 9 different animal models
- Chronic constriction injury: infraorbital nerve, saphenous nerve
- Partial nerve ligation: sciatic, saphenous nerve
- Spinal nerve ligation: L5
- Spared nerve injury
- Spinal cord injury
- Tibial nerve injury
- Streptozotocin-induced diabetic neuropathy

What is the evidence base?
Medline-Indexed Publications on Cannabis and Cannabinoids: It is estimated that there are now over 15,000 articles on the chemistry and pharmacology of cannabis and cannabinoids and over 2,000 articles on the endocannabinoids in the scientific literature.

23 States and D.C. with Medical Pot Laws & 4 (Co., Wa., Or, Ak) + D.C. permit Recreational Use as of 2015
2012 Meta Analysis of National Surveys: Residents of Med. Pot States have:
- Higher rates of Pot Use
- Higher rates of Pot abuse/dependence
- Much Lower Adolescent Perception of Pot being Harmful and
- Much Higher Adolescent Average Pot Use As compare to States with no Med. Pot Laws

In the past 15 years
- There have been 33 completed and published American controlled clinical trials with cannabis
- Compared with placebos or standard drugs, including sometimes dronabinol
- Assessed appetite stimulation, pain in HIV neuropathy and other types of chronic and neuropathic pain, spasticity in multiple sclerosis, weight loss in wasting syndromes, intraocular pressure in glaucoma, dyspnea in asthma, and emesis due to cancer chemotherapy

End Part II A lot of information compressed in a very short time!
Still confused on how to treat pain effectively without creating more pain or addiction? Current advances being made in the understanding of both conditions to better address this conundrum in the near future.
Part IIB: Opioid Pharmacology

Darryl S. Inaba, PharmD, CATC-V, CADC III
Director Clinical & Behavioral Health Services - ARC
Director of Research & Education - CNS

The Pharmacology (effects)

Smoking/Inhalation = 5-8 seconds for Drug to reach the brain
Marijuana Use by Scythians

Inhaling - 7 to 10 seconds

Injecting
- Intravenous (IV) 15-30 seconds
- Intramuscular (IM) 3-5 minutes
- Subcutaneous 3-5 minutes

Adult 6 - 8 quarts of blood
12 year old 3 - 4 quarts of blood
Drugs that affect brain activity are Psychoactive

WHAT ARE PSYCHOACTIVE DRUGS

- Psychoactive Drugs: Drugs that alter the state of the brain (Kellar & Hale, 2012)
- There are four types of psychoactive drugs (Kellar & Hale, 2012)
  - Stimulants
  - Depressants
  - Hallucinogens
  - Narcotics

AKA: Uppers, Downers, All Arounders (Psychedelics)
or even Up Town, Downtown, Out of Town

Brain is the most vital organ in the body and thus the most protected

Bone/Skull

Hair

Skin

All surround the Brain to protect it

Every thought, feeling, awareness and action is brain initiated

Thus, any psychoactive drug gets to and impacts all body organs not just the brain
**Somatic = voluntary**

**Autonomic = involuntary**

**Sympathetic = Immediate**

**Parasympathetic = Not Urgent (SSLUDD)**

---

**Neurotransmitters**

- Acetylcholine
- Substance P
- Norepinephrine
- Anandamide
- Epinephrine
- Glycine
- Dopamine
- Histamine
- Endorphin
- Nitric oxide
- Enképhalin
- Glutamic acid
- Serotonin (5HT)
- Cortisone
- GABA
- Aspartic Acid
- Oxytocin

---

**Endogenous Opioid Peptides**

- Endorphins: α-, β-, γ-, or Σ-Endorphin,
- Enképhalins: Leu-, Met-
- Dynorphins
- Adrenorphin, amidorphin
- Opiorphin
- et al.

---

**The Nervous System**

- Central
- Peripheral

**The Synapse**

- Neurotransmitters
- Neuron terminal
- Neuropeptide
- Neurotransmitter transporter
- Sodium ion
- Chlorine ion
- Potassium ion
- Neuropeptide
5 Opioid Receptors

- **Delta** = analgesia, dependence, mood – 2 subtypes
- **Kappa** = analgesia, dependence, miosis, ADH inhibition – 3 subtypes
- **Mu** = euphoria, analgesia, dependence, miosis, respiratory depression, decreased GI motility – 3 subs
- **Nociceptin** = anxiety, depression, appetite
- **Sigma?** = antitussive, hallucinations, psychedelic (Beta, Epsilon, Zeta Receptors?)

Methamphetamine
**Opioid Addiction Adaptations:**
- Tolerance – 10 fold in just 10 days & unlimited for most opioids
- Tissue & Cross Dependence – Animal studies show 25% decrease in VTA cells
- Withdrawal Syndrome – Can be evoked with naloxone in just 3 days with 4-6 mg. morphine every 6-8 hours, 3-4 wks for Abstinence to evoke
- Psychological Dependence – Neuroses, Reinforcement, Allostasis, & PAWS?

**Pharmacological Overview of Chemical Dependency**
- Tolerance – various types (Dispositional, Behavioral, Pharmacodynamic, Reverse, Inverse, Acute, Cross, Select)
- Tissue Dependence – Cross Dependence
- Withdrawal Phenomena: Purposive, Non-Purposive, Protracted, PAWS
- Psychological Dependence
  - Drug Automatism
  - Positive / Negative Drug Reinforcement
  - Social Reinforcement

**Opioid Withdrawal Symptoms**
- Bone, joint, & muscular pain
- Anxiety, insomnia
- Sweating, runny nose, chills
- Stomach cramps, vomiting
- Diarrhea, anorexia
- High blood pressure
- Excessive yawning, teary eyes

**Part II: Opioid Use Disorder and Recovery**

**Kinds of Tolerance**
- Dispositional
- Pharmacodynamic
- Behavioral
- Reverse sensitization
- Acute (tachyphylaxis)
- Inverse (kindling)
- Cross-tolerance
- Select
Rebound hyperactivity of locus coeruleus, interpeduncular and PAWS – PTSD emotional memory spines. Perhaps also due to selective tolerance activation of excitatory receptors from low levels of drug.

Theories of Addiction
- **Addictive Disease Model**
  Genetic irregularities
- **Behavioral/Environmental Model**
  Environment is important
- **Academic Model**
  Body adapts to drugs (tolerance, tissue dependence, withdrawal, dependence)
- **Diathesis-Stress Theory**
  Heredity, environment, drugs, or behavioral addiction

Substance-Related Disorders
- **Substance-Use Disorders**
  Substance abuse
  Substance dependence
- **Substance-Induced Disorders**
  Substance intoxication
  Substance withdrawal
  Substance-induced mental disorders

Kinds of Withdrawal
- **Nonpurposive**
  (Objective, physical signs)
- **Purposive**
  (Addict exaggerates symptoms)
- **Protracted**
  (Stimuli trigger withdrawal symptoms)
- **Post-Acute Withdrawal Symptoms (PAWS)**
  (Post-cessation of symptoms for months)

[Rebound hyperactivity of locus coeruleus, interpeduncular and PAWS – PTSD emotional memory spines. Perhaps also due to select tolerance activation of excitatory receptors from low levels of drug]
Opioid-Related Disorders DSM-5

- Opioid Use Disorder
- Opioid Intoxication
- Opioid Withdrawal
- Other Opioid-Induced Disorders
  - (e.g. Opioid-Induced Depressive, Anxiety, Sleep-Wake, Sexual, Constipation Disorders)
- Unspecified Opioid-Related Disorders

DSM-5 Opioid Use Disorder Diagnostic Criteria

1. Larger amounts or Longer time than Intended
2. Unsuccessful efforts to Control Use
3. Excess time to get, use and recover from use
4. Craving to use
5. Failure to fulfill work, school or home duties
6. Continued use despite social and interpersonal problems
7. Decreased social, work or recreational activities
8. Continued use in physically hazardous situation
9. Continued use despite physical or mental problems
10. Tolerance: Increased amounts or diminished effects
11. Withdrawal: Characteristic symptoms or Op. taken to avoid symptoms
   2 or more of the above within a 12-month period

Specify: Early Remission, Sustained Remission or on Maintenance Therapy (agonist, partial agonist or antagonist) and if client is in a controlled environment where opioid access is restricted

Levels of Use
- Abstention
- Experimental
- Social / Recreational
- Habitual
- Abuse
- Addiction

Substance Dependence (Addiction)
- Practices the addiction most of the time
- Continues use despite adverse consequences
- Denies there is a problem
- Strong tendency to relapse after withdrawal
- Has lost control
- Has altered brain chemistry

Why Can’t Addicts Just Quit?

Because Addiction Changes Brain Circuits

Non-Addicted Brain
- Control
- Drive
- Memory
- Sleep

Addicted Brain
- Control
- Drive
- Memory
- Sleep

NIDA
Addiction Pathway
Brain Circuits & Processes

- **Reward/Reinforcement (Go)**
  [I prefer Survival/Reinforcement]
  Hyperactivity then Hypoactivity
- **Control (Stop)**
  Impaired, dysfunctional or disconnection of Go and Stop

Bill Cohen: “Overactive go, Damaged Stop & Lack of Communication between them”

Neurons in Earth’s Fossil Record: Spinal Cord to Diencephalon to Mammalian-Meso Cortex to Neo Cortex

Earth 4.5 Billion Years, Life from 4 Billion Years

VTA Dopamine Cells of Opiate Addict vs. Non Addict Rat

Location of the nucleus accumbens in human CNS

Addiction Pathway
Reward/Reinforcement Pathway
Survival Reinforcement Pathway

Blum K. et al. (2014)

**Dopamine**
**Opiate Peptides**
**Glutamate**

VTA Dopamine Neurons:
Control
Morphine-treated
Medial Prefrontal Cortex: Value
Lateral Prefrontal Cortex: Consequence

Control Circuitry = Stop Switch

- Orbital Prefrontal Cortex – Especially left ventral medial OFC
- Fasciculus Retroflexus (anterior)
- Lateral Habenula (posterior and mesocortex terminal)

Age of first use correlation to future addiction
Brain Imaging: Impact of Addiction Pathology

Brain on Cocaine
1-2 Min, 3-4, 5-6, 6-7, 7-8, 8-9, 9-10, 10-20, 20-30 Minutes after shooting or smoking

Brain on Marijuana
Normal Brain, Marijuana Abuse

SPECT Scans Show Impact of Opiate Addiction on the Brain
Normal Brain, Methamphetamine Abuse, Normal Healthy Brain Activity, Heroin Addict’s Brain Activity (~7yrs.)

Courtesy of Nora Volkow, Ph.D.
Courtesy of Daniel Amen, M.D.
Dopamine Depletion in Addiction = Endogenous Craving and Anhedonia

Addiction & Relapse Related Brain Circuits & Processes
- Reward/Reinforcement (Go)
  [I prefer Survival/Reinforcement]
- Control (Stop)
- Stay Stopped (Slip Decisions)
- Emotional Memory (Cravings)
- Stress Hormone Cycle (Hypersensitivity)

Addiction = Hijacking of brain’s Survival Instincts
Relapse = Conspiracy of that brain to get back to use ASAP

Part III: Brain’s Addiction Pathway and Developments in Opiate Use Disorder Treatment
Part III: Opioid Use Disorder and Recovery

Addiction Pathway and Related Brain Circuitries

- Reward/Reinforcement (Go)
- Control (Stop)
- Stay Stopped (Slip)

Relapse Related Brain Circuits and Processes

- Stay Stopped (Slip Decisions)
- Emotional Memory (Cravings)
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Addiction Pathway Brain Circuits & Processes

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Bill Cohen: Overactive go, Damaged Stop & Lack of Communication between them

VTA Dopamine Cells of Opiate Addict vs. Non Addict Rat
The last area of the brain to develop is the Prefrontal Cortex (PFC), which includes the Medial PFC and Lateral PFCs. The Medial PFC involves value-related functions, while the Lateral PFCs involve costs or consequences. The Control Circuitry, or Stop Switch, is crucial for reasoning, impulse control, temporal processing, planning, and judgment. It includes the Orbital Prefrontal Cortex (especially left ventral medial OFC), Fasciculus Retroflexus (anterior), and Lateral Habenula (posterior and mesocortex terminal). This area's age of first use correlation to future addiction is significant.

Diffusion Tensor Imaging (DTI) and SPECT scans show the impact of opiate addiction on the brain. Normal healthy brain activity in the Prefrontal Cortex, Nucleus Accumbens, Arcuate Nucleus, Ventral Tegmental Area, and Brain Reward Pathways is contrasted with the activity in a heroin addict's brain at approximately 7 years old. The age of first use correlates with future addiction risk.

Brain Reward Pathways include the Nucleus Accumbens, Arcuate Nucleus, and Ventral Tegmental Area, with neurotransmitters such as dopamine, glutamate, and opioid peptides. These pathways play a critical role in reward processing and addiction.
Limbic Area
- Role: Drive Generation (SURVIVAL)
- Intervention: Pharmacotherapy

Prefrontal Cortex
- Role: Executive Function
- Intervention: Counseling

Relapse Related Brain Circuits and Processes
- Stay Stopped (Slip Decisions)
- Emotional Memory (Cravings)
- Stress Hormone Cycle (Hypersensitivity)

Relapse Processes I:
Slip/Stay Stopped Brain Anomalies

Relapse Processes II:
Memories Formation & Role In Drug Cravings
Neuro-development of Memories

Dendritic spines, bumps or protrusions

Dendritic Memory Spines
• Amygdala process emotional memories, hippocampus all other memories
• Also known as Bumps, Spikes – I like the term memory protrusions = less triggering
• 4 to 6 sensory inputs of the same stimulus per hour results in development of a semi-permanent memory protrusion
• The more often a memory protrusion is activated the larger it grows and the more permanent it becomes

Hypersensitivity of Stress Hormone Cycle in Addiction

1. Stress activates hypothalamus release of corticotropin releasing factor (CRF)
2. CRF activates pituitary release of adrenocorticotropic hormone (ACTH)
3. ACTH activates kidney adrenal glands to release cortisol

“Addiction is a stress-induced defect in midbrain’s ability to perceive pleasure”

Dr. Kevin McCauley

• CRF & ACTH are neurotransmitters as well as hormones they modulate novelty-seeking and dopamine activity in the brain
• Severe stress increase risk-taking behaviors in all and suppress dopamine’s ability to perceive reward, survival reinforcement, “pleasure?” resulting in anhedonia since
• CRF & ACTH as neurotransmitters produce the unpleasant emotional reactions associated with stress
• Cortisol usually turns off these secretions to terminate a stress reaction but extreme stress overrules cortisol
Addictive drugs first release of dopamine in the midbrain fools it as being a coping mechanism for the relief of stress

- Opiates & endorphins shown to also inhibit CRF & ACTH as cortisol would naturally do
- But, withdrawal from opiates cause increase release of CRF, ACTH and creates hypersensitivity to stress that overrule cortisol's regulation of cycle = craving
- Cocaine directly releases the CRF and ACTH mistaken as part of or covered by the rush, stimulant withdrawal also activates the stress mechanism = craving
- Research: metyrapone validation (shuts off cortisol production increasing CRF & ACTH) and CP-154,526 treatment (blocks CRF and thus suppresses ACTH release)

Heilig and Koob 2007, Lowery et al. 2008

Addiction is a battle between the old primal brain and the new brain

Etiology (Causes) of Opiate/Opioid Addiction

Diathesis-Stress Model of Addiction & Related Disorders

- HEREDITY – Type I
- ENVIRONMENTAL – Type II
- Stress (esp. Trauma) & Poor Nutrition
- PSYCHOACTIVE DRUG TOXICITY – Type III

Note: each phenotype has to have elements of the others to be activated
**Type I: Heredity**


Most Project 40 - 60% Contribution to Addiction

---

**DRD$_2$A$_1$ is found in**

- 20% of non-addicted people
- 30% of social drinkers
- 70% of severe alcoholics

DRD$_2$A$_1$ is also found in:

- 45% of compulsive overeaters
- 48% of smokers
- 52% of cocaine addicts
- 51% of pathological gamblers
- 76% of pathological gamblers with drug problems
- 33% of US population have a DRD$_2$A$_1$ gene

---

**Dr. Kenneth Blum UT Austin now focusing on 9 Genes & 18 Alleles**

- MAOA
- 5HTTLP
- SLC6A3 & SLC6A4
- DRD4
- DRD2
- COMT
- GABRG2, GABRA2 & GABRA6

These determine his Genetic Addiction Risk Score (GARS)

---

- CREB
- CHRM$_4$
- GABRA$_3$
- Leu-Pro allele
- NQD$_2$
- ADH$_4$
- KMALDH$_1$
- COMTmet158met
- DRD$_2$A$_1$, Allele
- Tipsy Gene: CYP2E1
- AUTS$_2$
- GABRG$_2$
- TAS$^2$R16
- SNCA
- OPRK$_1$
- PDYN
- CYP$_1$D$_2$
- CHRNA$_9$
- DeltaFosB
- Novelty Gene: DRD$_4$
- Finnish Rage/Alcohol Gene: HTR2B

Epstein DRD4 Novelty Seeking Gene for Opioid Deprn. 89 genes associated & > 900 suspected

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**Genetic Propensity is not Inevitability**

Brain of Psychopath can be overcome by Early Nurturing - Love

Compared to a control brain (top), neuroscientist James Fallon’s brain (bottom) shows significantly decreased activity in areas of the frontal & temporal lobe linked to empathy and morality—anatomical patterns that have been linked with psychopathic behavior.

Image via James Fallon
Type II: 
Environment 
Stress & Nutrition

Epigenetic changes result from environmental influences

Environment
• Early Childhood Trauma (physical, sexual, emotional abuse, tragic event, grief, anything that is traumatic to an individual)
• Stress including Mental Health Disorders
• Nutritional Deprivation and Imbalances

All recently associated with epigenetic changes resulting in different expression of dominant & recessive traits or turning on or off of genes

Major Traumatic Event: Impact on the Brain
• 50% of U.S. population experiences at least one major traumatic event in their life, 75% of behavioral health workers and 90% of behavioral health patients
• Trauma changes structure and chemistry of the brain making one more susceptible to addictions and mental health disorders
• Increased vulnerability partly due to Epigenetic Expressions that result from trauma (stress), toxins, diet and even behaviors

Epigenetic Expression

Methylation, Acetylation, Phosphorylation of genetic peptide and 5hmC tags result in altered expression of genes

Identical Twin Mice with Divergent Epigenetic Expression
Even Identical Twin with Epigenetic Expression of Different Races

Psychoactive Drugs Affect Perception, Mood, and States of Consciousness by mimicking or Disrupting the Natural Chemistry of the Brain

Expanded Definition = Any Behaviors (e.g. Gambling) that Alter Moods and Affect the Brain’s Addiction Circuitries and Pathways

Chang and Eng Bunker Conjoined Identical Twins born 1811

Neuron Homeostasis: Brain in Dynamic Equilibrium

Type III: Toxicology Neurochemical & Neurofunctional Allostasis

Electron Microscopy of Neurons, Dendrites and Axons

Professor Terry Wiseth, Northland College
Drugs Mimic, Disrupt, or Block Neurotransmitters

SOME EXAMPLES -

UPPERS: Catecholamines (Norepinephrine, Epinephrine, Dopamine) + Serotonin and Acetylcholine

DOWNERS: Endorphin, Enkephalin, GABA, Serotonin

PSYCHEDELICS: Serotonin, Acetylcholine, Alpha Psychosin, Norepinephrine, Dopamine, Anandamide & endocannabinoids

Neuronal Allostasis

All addictive drugs and behaviors force brain cells to adapt and adjust to what it views as an imbalance of its own neurotransmitters thus resulting in an allostasis that requires continued drug use or addictive behaviors to maintain its functioning even though it is an imbalanced abnormal functioning.
Diathesis-Stress Model of Substance-Related & Addictive Disorders is actually:

*Heredity, Environment, Psychoactive Drugs*

Copyright 2009, CNS Productions, Inc.

Levels of Use
- Abstention
- Experimental
- Social / Recreational
- Habitual
- Abuse
- Addiction

DBA/2j = Genetic alcohol/Drug avoiding mice

C57bl/6j = Genetic alcohol/drug loving mice

Hereditary hater of alcohol
Hereditary lover of alcohol
Alcoholic mouse

Level of susceptibility: Low Moderate High

Levels of use
- Addiction
- Abuse
- Habituation
- Social/recreational use
- Experimentation
- Abstinence

Susceptibility

TREATMENT

RECOVERY JUST AHEAD
Part III: Developments in Addiction Treatment

Screening, Assessment, Intervention And Treatment Resources

Research-Validated SUD Diagnosis and Assessment Tools

- Addiction Severity Index (ASI)
- Michigan Alcoholism Screening Test (MAST) B-MAST, MAST/AD, M-SAPS, SMAST-G
- DSM-IV-Tr, DSM-5, SCID-1
- CAGE-AID, SASSI-3 & -A2, CRAFFT
- 4P-Plus, TICS, PADDI
- TWEAK, DAST
- ASAM PPC-2R (Six Dimensions)
- ASSIST & NM ASSIST

Thus, Both the Unconscious & Conscious Brain Require Treatment

TREATMENT CONTINUUM

- Detoxification
- Initial Abstinence
- Long-term Abstinence
- Recovery
- ASAM 4 Levels of Treatment: 4, 3.7, 3.4, 3.2, 2.5, 2, 1, 0.5, et al.
Clinical Interventions: Evidenced-Based & >100 yrs of Practiced-Based Interventions

- National Registry of Evidence-Based Program and Practices: SAMHSA & State
- Cognitive Behavioral Therapies: Motivational Interview/Enhancement, DBT
- Levels of Change
- Individual and/or Group Counseling (process, therapy, education, topical, open)
- Manual Driven Curricula (e.g. Matrix)
- Self-Help Groups (12-Steps, et. al.)

Sumer: earliest known civilization 5,500-4,000 BC, Firsts: written language, brew beer and opium use

Manco Capac ~1200 AD
Founder of Inca Empire

In Other Words: Drink Responsibly!

Attempts to Deal with addiction has a long history in humanity

And our Temperance Movement → “failed” Prohibition of 1919

Carrie A. Nation
Women’s Christian Temperance Union arrested 33 times between 1900 - 1910
Treatments Targeted for SubCortical (unconscious) Processes of Addiction

- i.e. ~400 vaccines, genetic therapy, pharmacogenomics, and ~more medication treatments in developments than any other medical condition

Realized Benefits:
- Decreased Overdose Drug Deaths
- Decreased Disease and Violent Crimes
- Increased Addiction Treatment Positive Outcomes

Detox: Development of Withdrawal Management Assessment Tools

- CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol-Revised
- COWS, Clinical Opiate Withdrawal Scale
- ACSA, Amphetamine Cessation Symptom Assessment Scale
- BWAS, Benzodiazepine Withdrawal Assessment Scale
- WAT-1, Withdrawal Assessment Tool
- MSSA, Modified Selective Severity Assessment Detoxification Scoring

Initial Abstinence: Pharmacological Cue Extinction via naltrexone and acamprosate

Opioid Use Disorder Treatment Gap

- Only 31% of U.S. illicit drug abusers receive any treatment for addiction
- Of those who received treatment only 20% were treated by addiction focused facility
- Of the 20%; 31% of OUD patients & 37% of heroin use disorders received MAT (but too short & low dose)
- OUD without MAT: 80% relapse; With MAT 50% relapse

Stern, JB. (2018), Adv. in Ad & Rec. 6(2): 22-25

Maintenance pharmacotherapy, replacement therapies, chemically assisted detoxification or recovery; agonist mediated “anti-priming” treatments, pharmacologic restoration of neurohomeostasis, addiction vaccines, pharmacogenomics and genetic treatment “resetting” the addicted brain. Such terms would have been incomprehensible or even oxymoronic in the recovery field just a few short years. Now, increased understanding, Addiction Equity Act of 2008 and Affordable Health Care Act are rapidly increasing the “medicalization” of addiction treatment.
Meds for Opioid Treatment

- buprenorphine (Suboxone®)
- naltrexone (Revia®, Trexan®, & Vivitrol®)
- methadone
- levo-alpha-acetyl-methadol (LAAM)
- Lofexidine (Lucemyra®) approved 5/16/18
- Off-Label: clonidine
- Off-Label: Rapid Opioid Detoxification (naloxone or naltrexone with midazolam, lorazepam, clonidine, anesthetics, et al.)
- Illicit in U.S.: Ibogaine

Buprenorphine (Suboxone) Ceiling Effect

Suboxone more Rxed than methadone

Jackson County Rx OD deaths

Buprenorphine Dosage Forms
Opioid Antagonists: Naloxone, Naltrexone, Nalmefene, et al.

Morphine

Note similar structure to Morphine
Can cause false positive opioid UDT

Pharmacogenomics: Those with OPRM1 G along with DAT1 10/10 or COMT val/val genes and those with OPRM1 A along with DAT 9-repeat or COMT met respond better to Naltrexone

Anton RF, et al. (2020) Alc. Cl, & Exp. Research

VIVITROL and Brain Reward Pathways

Vivitrol® is Naltrexone In 30 day injection form

Lofexidine and Clonidine mitigate opiate/alcohol withdrawal

Medical Devices Treatment of Addiction

The NSS-2 BRIDGE is a percutaneous nerve field stimulator (PNFS) device system, that can be used as an aid to reduce the symptoms of opioid withdrawal, through application to branches of Cranial Nerves V, VII, IX, and X, as well as branches of the occipital nerves identified by transillumination

FDA Approved 11/15/17
Repetitive Transcranial Magnetic Stimulation - rTMS

Bellamoli, E et al. (2014) Beh. Neurology

Transcranial Magnetic EEG/EKG Guided Resonance Therapy (TMeR)

Magnetic e-Resonance Therapy (MeRT)

MeRT (deep signal) across multiple bands, personalized to an individual's intrinsic profile, and guided by q-EEG to specifically targeted areas (brain navigation)

Addiction Treatment Evolution: Physical to Behavioral (Spiritual) to now Physiologic Health Interventions

Deep Brain Stimulation for Opioid Use Disorder Nov. 2019

University of West Virginia

Deep Brain Stimulation and Optogenetics

Deep Brain Implants for Methamphetamine & Opioid Use Disorder

Part IV:

Preventing Recrudescence (relapse), Promoting Long-Term Sobriety
Challenges to Maintenance of Continued Abstinence

- Cognitive Impairment (30-80%)
- Endogenous Craving (Allostasis)
- Environmental Triggers or Cues
- Post Acute Withdrawal Symptoms (PAWS)
- Unaddressed Physical and/or Mental Health Treatment Needs

1. Cognitive Impairment During Addictive Behavior and in Early Recovery

COGNITIVE IMPAIRMENT
11.3% of Limbic system of which 7.8% of Hippocampus plus 24% of dopamine transporters
- Attention, memory, understanding problems
- Word meaning, problem solving, Strop paradigm
- Inflexibility, abstract thinking, judgment
- Temporal processing: planning, processing goals, delayed discounting

2. Endogenous or Intrapersonal Addiction Cravings via Neural-Physiological Allostasis
ENDOGENOUS CRAVING

Analogous to diabetes, hypothyroidism, et. al., an allostatic develops with continued use of an addictive substance. When abstinence is initiated, the brain craves the substance in an effort to maintain its imbalanced state through a variety of mechanisms: amygdala via emotional memories, attachment and bonding via the cingulate gyrus facilitated by delta fosB transcriptase and hypo-functioning of PFC.

Any Negative Mood State can initiate a Craving Reaction

- HALT – Hungry, Angry, Lonely, Tired
- RIID – Restless, Irritable, Isolated, Discontent
- BAAD – Bored, Anxious, Angry, Depressed

Dopamine Depletion in Addiction = Endogenous Craving and Anhedonia

3. Environmental or Interpersonal Triggers and Cues via Dendritic Emotional Memory “Spines, Bumps, or Protrusions”
Environmental Triggers and Cues

- Any Sensory Input to addiction memories: visual, odor, auditory, physical withdrawal, etc.
- Thoughts of using or of withdrawal
- Intrapersonal factors: any negative mood states
- Interpersonal factors: relationship problems, social/vocational pressures, no support system, negative life events, untreated dual diagnoses
- Other causes: dishonesty, exhaustion, cocky, complacent, self-pity, overconfidence, impatience

Craving can be caused by the sight, smell, and taste of:

* a using partner
* a using place
* a dealer
* cash
* the drug itself
Gender Variance in Craving and Relapse?

Women: brain areas associated with craving are more activated by stress on MRI scans. Intrapersonal, Endogenous triggers

Men: drug cues/triggers activate craving areas of the brain more = Environmental, Interpersonal triggers

But: David Sacks’ most common causes of relapse in women: Romantic relationships too soon and Unrecognized love, relationship or sex disorders

Potenza, Marc et al. (2012) Am. J. of Psychiatry

Potenza, Marc et al. (2012) Am. J. of Psychiatry

Meso-Limbic Reward-Reinforcement Circuitry of the MFB

- Phase I – Environmental Cue triggers the Ventral Tegmental Area to release dopamine; anticipation of use
- Phase II – Cues or actual use of addictive drug choice activates dopamine “go” switches of lateral hypothalamus and Nucleus Accumbens: “On a mission!”
- Phase III – Control circuitry of the prefrontal cortex is disrupted by excess dopamine

MEMORIES

Both Endogenous & Environmental Triggers activate memory pathways where neurons search for the most convenient way it resolved the issues or needs in the past: USE DRUGS!

New NIH Details on Addiction Craving Pathway

- Hippocampal memory process activates
- Lateral Septum via glutamate and this in turn activates
- Ventral Tegmental Area via gamma-aminobutyric acid (GABA) that then activates
- Nucleus Accumbens Septi (“go switch”) via dopamine

Potenza, Marc et al. (2012) Am. J. of Psychiatry
**Craving and Relapse**

*Cue-Induced Brain Activity*

Brain regions activated while viewing alcohol-related cues. Courtesy of Dr. John Hart, Portland, Oregon

- **Cingulate**
- **Nucleus Accumbens**
- **Ventral Tegmental Area (VTA)**


**Physiology of Craving**

- Increased heart and pulse rate
- Specific electrical changes in skin activity and spindle effects on EEG
- Increased peristalsis activity of gut
- Pupil dilatation and cortisone stress reaction
- Two degree or more core temperature drop
- Extinction: Nonuse weakens triggers

**Key:** Never Initiate any action to use ~ 95% of Slips = Relapse

**Stop Signal Test (SST) Research**

- London, Edythe, Director Center for Addictive and Biobehavioral Sciences, UCLA

**Relapse Prevention “tool kit”**
Other Effective Relapse Prevention Tools

- Emotional Freedom Techniques (EMDR, Brain Spotting, Tapping, Elastic Snapping)
- Yoga Breaths, Somatics, Figure 8 Pacing
- Mindfulness meditation & other grounding interventions, acupuncture, Laughter Yoga
- Consequence Reminders (family photo, car keys, consequence cards)
- Paradoxical Interventions (emptied Librium capsules, empty Copenhagen can, turn shirt inside out, wash off and reapply makeup, et al.)
**Brain Reward Pathways**

- Prefrontal Cortex
- Nucleus Accumbens
- Arcuate Nucleus
- Ventral Tegmental Area

**Clinical Interventions**

- National Registry of Evidence-Based Program and Practices: SAMHSA & State
- Cognitive Behavioral Therapies: Motivational Interview/Enhancement, DBT
- Levels of Change
- Individual and/or Group Counseling (process, therapy, education, topical, open)
- Manual Driven Curricula (e.g. Matrix)

**Acute Reinforcing Effects**

- Prefrontal Cortex: Role: Executive Function / Intervention: Counseling
- Nucleus Accumbens: Role: Drive Generation (SURVIVAL) / Intervention: Pharmacotherapy

**Hypersensitivity of Stress Hormone Cycle in Addiction**

1. Stress activates hypothalamus release of corticotropin releasing factor (CRF)
2. CRF activates pituitary release of adrenocorticotropic hormone (ACTH)
3. ACTH activates kidney adrenal glands to release cortisol

**Pharmacological Cue Extinction via naltrexone and acamprosate**

**Also Neural Crux of Relapse with Stress March 2013**

VTA’s (ventral tegmental area): GABA-releasing neurons, dopamine-releasing neurons and Kappa opioid receptors interaction in stress. Drugs and natural satiatiations release dopamine in the VTA. GABA applies a brake to this via strengthening synapses (known as long-term potentiation or LTP) but stress interrupts this process leading to unabated dopamine reinforcement. Nor-BNI blocks Kappa receptors in the VTA and prevents stressed out rats from relapsing to cocaine use. Graziane, Poller, Bland, Pierce, Kauer (2013), J. Neuron
4. Post Acute Withdrawal Syndrome (PAWS) & Protracted Withdrawal Syndrome: Role in Evoking Slips and Relapses

Post Acute Withdrawal Syndrome (PAWS) – episodic or recurrent
- Sleep Disturbances – insomnia, nightmares
- Memory Problems – Short-term, learning
- Thought Problems – concentration, rigidity, repetitive thoughts/behaviors, abstract thinking & problem solving difficulties
- Anxiety, irritability, hypersensitivity to stress
- Inappropriate emotional reactions, mood swings
- Physical and coordination difficulties, fatigue
- Syndrome persists for 3-6 months, sleep problems maybe longer – can be up to 2 years

PAWS Cause is Unknown
Projected Etiology
- Slow reversing tolerance and tissue dependence
- Returning neurotransmitter allostasis back to homeostasis
- Developed hyperexcitability of neuronal pathways


PAWS Treatment
- Clinical: CBT “grounding exercises”
- acamprosate for alcohol PAWS
- carbamazepine (Tegretol)
- Trazodone
- naltrexone

5. Mental Health and/or other Medical Conditions Must be Stabilized and Medically Managed During Recovery

May be Pre-Existing or Addiction-Induced?

Co-Occurring Disorder, Dual Diagnosis, MICA
- Prevalence depends on population studied
- 44% alcohol abusers and 64.4% other substance abusers met diagnoses for at least one major psychiatric disorder.
- 29% - 34% of those in mental health treatment met diagnostic criteria for an addiction and related disorder.
- Recovery difficult if MH disorders are not addressed

Ref: Regier et al., 1990; Merikangas, Stevens, & Fenton, 1996
Need for “Rule-Out” careful diagnosis: Substance Induced vs. Pre-Existing
Best Outcomes when both disorders treated at the same time in one treatment system
Same neurochemical imbalances involved with both disorders
Major MH disorders: Thought, Affective, Mood, Anxiety, and Personality

Dr. Kenneth Minkoff
Four Quadrant Treatment Model

Quadrant 4
More Severe Mental Disorder
More Severe Substance Use Disorder

Quadrant 3
Less Severe Mental Disorder
More Severe Substance Use Disorder

Quadrant 1
Less Severe Mental Disorder
Less Severe Substance Use Disorder

Quadrant 2
More Severe Mental Disorder
Less Severe Substance Use Disorder

Recovery
- Continued Abstinence
- Discovery of Natural Highs
- Recovery of neurotransmitters and of natural brain functions
- Positive lifestyles and quality of life enhancements
- Remember: Not an Event but a Process

Addiction Recovery
- Continued Abstinence
- Discovery of Natural Highs
- Recovery of neurotransmitters and of natural brain functions
- Positive lifestyles and quality of life enhancements
- Remember: Not an Event but a Process

Treatment Works!
- 3 to 5 Yrs. Continued sobriety = 50% (1yr 80%)
- Decrease Crime = 75%
- $7-$12 Savings for every $1 Spent
- Positive results from 6-8 mo. Treatment
- Coerced treatment better than voluntary
- Decreased Psychiatric (40%), Family/Social (50-60%), Medical (15-20%), Employment Problems (15-20%)
- Culturally consistent better than generic treatments

RECOVERY
The Resilient Brain
8-10 Months Rigorous Uninterrupted Treatment for Reasonable Outcomes
Implies time needed for brain to become functional
Takes up to 2 years for greater functioning to return
4. ADDICTION CAN BE TREATED

Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence

Dopamine Transporter Binding (DAT) Recovery in Meth Addiction

Alcohol Brain Resiliency

Intoxication  Sober: 30 days

Healthy Brain  Opiate Dependence, 7 years

7 years Methadone use  Xanax 20 mg/day FOR 20 YEARS

ONLY SIX WEEKS FOLLOWING DETOX


Source: Volkow, N. et al., Journal of Neuroscience 21, 9414-9418, 2001
Dr. Ken Blum's patented:
Synapta GenX, KB220Z

Neuronutrient complex "normalization" of caudate, accumbens and putamen regions of heroin addicts demonstrated by MRI Scan

Video Presentation (31 minutes)
CNS Productions, Inc.

Neurochemistry of
Relapse & Recovery

Questions/Comments?

Conclusions

◆ Addiction treatment results in miraculous outcomes for those who commit to and maintain continuous recovery efforts.
◆ Developments in treatments of addiction continues to improve outcomes that improve lives and health for all.

Questions/Comments?

• Good News!
  Recovery Works and the brain is resilient!
• Not so Good News
  It takes time, several months to years to just become functional, and a bit more to enjoy life again
• Memory Protrusions
  Shrink with Disuse and new alternate pathways become established but addicted neurons are permanent and Recovery is a Life-Long Process!

Wonderful to work with all of you over these past two very intense days

May you continue to find rainbows in all your endeavors and again, thank you for all that you do!
Thank you all for attending
The 2020 IAAP Virtual Conference