Rx Opioid/Heroin Epidemic: Co Morbidity of Pain and Addiction

NAADAC Annual Conference
Washington DC
Oct. 11, 2015: 8:30 – 10 am

Darryl Inaba, PharmD., CATC V, CADC III
I WANT YOU
TO TURN OFF
YOUR CELL PHONE
Part I: Growing Opiate Abuse, Loss of Analgesic Effectiveness in Chronic Pain

Darryl S. Inaba, PharmD., CATC-V, CADC III
Director of Research & Education – CNS
Director Clinical & Behavioral Health Services - ARC
Beyond Opioids
Premiere of New 33min. DVD

Expanding Sciences of Pain and Recovery

CNS Productions, Inc. Medford, Oregon
New Graphic Novella - Beyond Opiates: Evolving Science of Pain and Addiction

companion for DVD Video to promote better Acceptance and understanding of this co morbid condition
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, Conscripted 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
Chicago police officer among dozens arrested in 3 states

Siksik gang ring behind deadly heroin raids

Sleeping pill competition heats up

Prescription reactions sicken 700,000

At least that many

Common drugs

Multiple medications can add to health risks

Professionals warn patients about taking improper combinations

American opium production spikes

Lucrative trade puts more pressure on

Docs say many suffer needlessly from pain

Study: More teens pilfer legal drugs to get their buzz

Overall, fewer teens drank alcohol, the Associated

Don't use!

Deadly abuse of methadone tops other prescription drugs

Only cocaine kills

Study: OTC drugs, prescriptions send more to ER than cocaine

Pharmaceutical abuse rises in 2004, I, million people visited emergency rooms involving the abuse or misuse of drugs: licit drugs such as

Study: USA ranks first worldwide in incidents

- Methadone: GOOD DRUG, BAD DRUG

Soma Addiction Among APAs a Growing Concern

By STEVEN YANAMACHI
Nichi Bei Times
A drug known as "soma" is

Man charged with forging prescriptions instances of drug tampering is a technician at RVMC

Latest trend in drug abuse: Youths risk death for cough-remedy high

Survey: Chronic pain often goes untreated

Survey: More teens using Oxycontin

Pain-pill abuse grows

In a survey by Prevention magazine, 20% of high school seniors report having used pain pills in the last year. The survey also found that 10% of high school seniors report having used pain pills more than once. The survey also found that 10% of high school seniors report having used pain pills more than once.

Mexican drug war death toll tops 2,000

One in five people never come

Stolen, counterfeit drug problems rise

Study: USA ranks first worldwide in incidents

By Julie Appleby
USA TODAY

Counterfeiting, theft and diversion of prescription drugs is a growing problem in the United States. In 2004, the FBI estimated that $1.5 billion worth of prescription drugs were stolen from pharmacies, hospitals and other medical facilities. The organization also estimated that $2 billion worth of counterfeit drugs entered the United States that year.

Survey: Chronic pain often goes untreated

Survey: More teens using Oxycontin

Marijuana, other drug usage declines, but "huffing" of inhalants rebounding

"Huffing," a practice in which people inhale substances such as glue and gas, is a growing problem among young people.

By Donna Leinwand
USA TODAY

Abuse of prescription and over-the-counter drugs is sending more people to emergency rooms than cocaine, according to new

Study: USA ranks first worldwide in incidents

- Pain pills:

Pain pills are the most abused class of prescription drugs, and the use of pain pills has increased over the past decade. According to the Centers for Disease Control and Prevention, the number of emergency room visits related to pain pills more than doubled between 2000 and 2004.

- OxyContin:

OxyContin is the most abused prescription pain pill, and its abuse is a growing concern. The abuse of OxyContin has increased dramatically in recent years, and it is now the most abused pain pill in the United States.

- Other prescription drugs:

Other prescription drugs are also being abused, and the abuse is a growing problem. The abuse of these drugs is increasing, and the problem is becoming more severe.

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% of Teens Who Have Used a Substance Not Prescribed to Them

- Alcohol  77%
- Nicotine  53%
- Marijuana  37%
- Inhalants’  19%
- Vicodin  18%
- OxyContin  10%
- Ritalin or Adderall  10%
- Cough Med. (DXM)  10%

(PATS, 2004; University of Michigan, 2005)
% of Teens Who Have Used a Substance Not Prescribed to Them

- Cocaine or crack 9%
- Ecstasy (MDMA) 9%
- Methamphetamine 8%
- LSD 6%
- Ketamine 5%
- Heroin 4%

(PATS, 2004; University of Michigan, 2005)
Increase in New Starts of Prescription Opioid Abuse Among Teenagers

Also 24% of teens reported abuse of Rx Drug in 2012. This was an Increase of 33% since 2008. PATS 2013

542%—Incidence of new starts of prescription opioid abuse among teenagers
150%—Prescriptions written for controlled substances
14%—US population

1992  2003

700  600  500  400  300  200  100  0

Percent Increase

Courtesy of Dr. John Hart Portland, Oregon

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

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

Marijuana/Hashish 36.4%
Synthetic Marijuana 11.3%
Adderall 7.6%
Vicodin 7.5%
Cough Medicine 5.6%
Tranquilizers 5.3%
Hallucinogens 4.8%
Sedatives* 4.5%
Salvia 4.4%
OxyContin 4.3%
MDMA (Ecstasy) 3.8%
Inhalants 2.9%
Cocaine (any form) 2.7%
Ritalin 2.6%

SOURCE: University of Michigan, 2012 Monitoring the Future Study
Prevalence: Illicit Use of Rx Pain Relievers Is Greater Than Cocaine and Hallucinogens Combined

Number of Estimated Illicit Drug Users (Millions)

- Alcohol (Heavy Use): 16.0
- Marijuana: 14.6
- Cocaine: 2.4
- Hallucinogens: 4.7
- Rx Pain Relievers: 1.8
- Rx Tranquilizers: 1.1
- Rx Stimulants: 0.27
- Rx Sedatives: 0.0

N=67,500 people surveyed


Courtesy of Dr. John Hart
Portland, Oregon
Incidence: New Illicit Use of Rx Pain Relievers Has Surpassed New Illicit Use of Marijuana

*526,000 new nonmedical users of OxyContin®.


Courtesy of Dr. John Hart
Portland, Oregon
Drug-Related Emergency Department (ED) Visits Involving Nonmedical Use of Opioid Analgesics

- Of all ED visits due to nonmedical use of prescription or OTC pharmaceuticals in 2004, 1 out of 4 were due to opioid analgesics
- Of these, oxycodone and hydrocodone accounted for about 60%

In a household survey, friends and relatives were a significant source of analgesics for nonmedical use.
OD deaths in Oregon by Drug Type

Drug poisoning mortality: rate and frequency by year and select drug type, Oregon, 1999-2008

Oregon Public Health Division- Injury Prevention Program

- Number of cocaine deaths
- Number of heroin deaths
- Number of prescription opioid deaths
- Rate of drug poisoning

*2008 mortality data are preliminary; drug death categories are not necessarily mutually exclusive- deaths may involve multiple drugs. Includes unintentional and undetermined drug poisonings. Data source: Oregon Center for Health Statistics mortality data file.
Oregon Rx Opioid Deaths Age Distribution

Age distribution of prescription opioid deaths, Oregon, 1999-2009

Oregon Public Health Division - Injury Prevention Program
Analysis of all Jackson County Medical Examiner cases 2006
(approximately 280 suspicious deaths)

- 46 people died in Jackson County as a result of overdosing on prescription pain killers.
- 56% of those 46 individuals had prescriptions from their doctors for the opioid listed as the cause of death.
- 66% of those that died had more than one drug of abuse present (opioid or benzodiazepin)
Jackson County Rx OD deaths

Number of deaths caused by prescription drug overdose annually

2002 2003 2004 2005 2006 2007 2008 2009

12 14 24 28 46 35 33 19

Jackson County Rx OD Deaths
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.
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
The Substances
Opiates/Opioids

Directly from the opium poppy
opium, morphine, codeine
Also “Phyto-opioids”?

Semisynthetic
heroin, hydrocodone, Oxycontin

Synthetic
fentanyl, methadone, Darvon,
buprenorphine, demerol

Opioid Antagonists
naloxone (Narcan),
naltrexone (Revia)

Endorphins, Enkephalins, Dynorphins
Heroin: making a big comeback in 2010 on!

Batches of Heroin can be as different as night and day.

Texas “Cheese Heroin” = Black Tar Mixed with Tylenol PM

Black Tar heroin
“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 than mixed with grapefruit extract.
Illicit “Designer” fentanyl
Sold as: “China White”, Oxycontin or added to heroin to \( \uparrow \) potency

- Fentanyl = up to 100 x stronger than morphine, heroin is twice as strong as morphine
- Various Illicit “designer” isomers: \( \alpha \)-methylfentanyl (AMF) & \( \beta \)-methylfentanyl
  3-methylfentanyl
  acetylfentanyl
  sufentanyl
  \( \alpha \)-methylthiofentanyl & 3-methylthiofentanyl
- Sufentanyl is 5 to 10 x stronger than fentanyl and thiofentanyls are even much stronger
Also Concern over Kratom: “Legal Phyto-Vicodin?”

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, mitraphylline, & 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
Continued Rise in Prescription Opioid Abuse
OxyContin 80mg
New Oxycontin® Formulation to Mitigate Abuse April 2010

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

Or, 3. Heroin

Oxycodone

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

2014 Zohydro gets FDA approval: 50 mg of hydrocodone with no acetoaminophen as 63% of US liver deaths due to acetoaminophen toxicity.
Buprenorphine (Suboxone)
Buprenorphine IV Abuse

Also Suboxone Film and Zubssolv
Methadone (Dolophine, Methadose)
Leading Cause of Rx OD Deaths 2010-2011
Methadone (Dolphine)
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
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
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
Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)
Abusing Prescription Drugs

Prescription drug abuse is the nation’s fastest growing drug problem. Drug overdoses are the leading cause of accidental death in 16 states and D.C.

Painkillers dominate

Prescription opioid painkillers, such as OxyContin, caused the largest share of accidental overdose drug deaths in 2007.

- Total deaths: 37,658
- 42% Opioid painkillers
- 58% All other drugs

Comparing killers

Deaths from prescription opioid painkillers were almost twice as high as those from cocaine; in thousands:

- Opioid painkillers: 11,499
- Cocaine: 5,943
- Heroin: 2,137

Drug overdose deaths

Per 100,000 population, 2007

- Less than 9.0
- 9.0-10.9
- 11.0-13.9
- 14.0 or more

Highest W.Va. 21.1

© 2011 MCT
Source: U.S. Centers for Disease Control and Prevention, NCHS, NCHS

State: Graphic: Judy Tedio
Amount of prescription painkillers sold by state per 10,000 people (2010)
Drug overdose death rates by state per 100,000 people (2008)
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 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
• Oct. 2012 ONDCP stated U.S. now in an epidemic of Rx. Opioid abuse and OD deaths
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
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.
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 Haddock, 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.
Types of Pain (Chronic Pain = lasts 3-6 months or longer)

- **Nociceptive Pain** (sprains, bone fractures, burns, bruises)-special nerve ending which heal with time
- **Neuropathic Pain** (shingles, Diabetic Neuropathy neuralgia, phantom limb pain, Carpal Tunnel Syndrome /CTS, peripheral neuropathy)-nervous system dysfunction pain
- **Mixed Category Pain** (migraine headaches)-complex mixture of nociceptive and neuropathic
- **Central Pain**-caused by dysfunction of nervous system such as Fibromyalgia
- **Emotional Pain** (loss, relationship, humiliation, disappointments, exclusion, fears, psychological trauma)
Percent of male and female patients of various ages with co-morbid bodily pain, psychiatric disorders, alcoholism, and nicotine dependence

(A) Bodily Pain

(B) Psychiatric Disorder

(C) Alcohol Dependence

(D) Nicotine Dependence

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

Pujol, J et al (2009), PLoS ONE
Brain Morphological Signatures for Chronic Pain

Marwan N. Baliki¹, Thomas J. Schnitzer², William R. Bauer³, A. Vania Apkarian¹,⁴,⁵*

¹ Department of Physiology, Northwestern University, Chicago, Illinois, United States of America, ² Department of Physical Medicine and Rehabilitation, Northwestern University, Chicago, Illinois, United States of America, ³ Department of Neuroscience, University of Toledo, Toledo, Ohio, United States of America, ⁴ Department of Anesthesia, Feinberg School of Medicine, Chicago, Illinois, United States of America, ⁵ Department of Surgery, Feinberg School of Medicine, Chicago, Illinois, United States of America

2011

Chronic Back Pain
Complex Regional Pain Syndrome
Osteoarthritis
fMRI Reveal Emotional Pain Signature Pathway

Prefrontal Cortex to Nucleus Accumbens and amygdala

Wager, Tor (2013), NEJM
Neurologic Pain Signature

Wager, Tor (2013), NEJM
fMRI Scans image pain signature, measure intensity and demonstrate when relief occurs

Wager, Tor (2013), NEJM
• 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 Rxs 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
With chronic injuries, most people will usually get used to it and won't let it bother them. As long as the injury or nerve damage does not progress, the pain will become more tolerable. Being completely pain free is usually not possible.

If opioids are used only for a few days and/or in limited amounts, the pain can usually be kept tolerable and tolerance to the drug will not advance. The body will have time to heal itself to a certain extent.

If a person starts to take an opioid too often, tolerance develops and it will take larger and larger amounts to keep the pain at the lower level.

In contrast to the development of tolerance through using more and more opioids over a period of time, with hyperalgesia, the increased sensitivity of the nerve cells makes the person hurt more and more in spite of the increases use of opioids. The increased sensitivity can get to the point where the slightest pain is magnified to the point of being unbearable.
Opiate Hyperalgesia

Analgesic response with tolerance:
Pain continues to overcome increased doses of opiates

Courtesy of Andrew Mendenhall M.D.
Chronic use of opioids for pain management: Expanding Concerns

- 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 – “Addiction Pain Syndrome”

Drs. Steve Grinstead & Terry Gorski
Thalamic sensitization transforms localized pain into widespread allodynia
Tools for Assessing Pain should also assess stress.

**LEGO PAIN ASSESSMENT TOOL**

- **0**: No Pain
  - Alert, Soothing
  - No issues
  - Can be ignored

- **1**: Mild Pain
  - Face slightly raised
  - Single eye
  - Interferes with tasks

- **2**: Moderate Pain
  - Indoor rest
  - Groans
  - Interferes with concentration

- **3**: Serious Pain
  - Patented
  - Sneeze
  - Interferes with sleep

- **4**: Severe Pain
  - Tense
  - Fathers
  - Unbearable

- **5**: Worst Pain Possible
  - Agonizing screams
  - Fear
  - Death imminent

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Low Stress  |  Mild Stress  |  Stressed Out
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
- Getting Out of Bed
- Climbing Stairs
- Descending Stairs
- Getting Out of a Chair
- Walking
- Personal Care
- Daily Activity
- Working
- Leisure Activities
- Quality of Life

ACPA Rocklin, CA 800-533-3321
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
    - (ADD, OCD, 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\(^1\)

- Narcotic protocol consists of medication contract, consent, psychological evaluation, random urine toxicology\(^2\)

- Monitoring both urine toxicology and aberrant drug-related behavior (ADRB) will detect more inappropriate drug-taking than either alone\(^3\)

- Highest sensitivity (0.90) for predicting ADRB: clinical interview combined with Screener and Opioid Assessment for Patients with Pain (SOAPP)\(^4\)

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Opioid Misuse
Behaviors to Watch for

More Suggestive of Abuse/Addiction
- Selling Prescription drugs
- 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”
Delta Opioid Receptor

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

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
- Puzzles (Sudoku, Crosswords, Etc.)

Pohl, Mel (2011), *A Day Without Pain*
MEDICAL MARIJUANA
2015: 23 States plus Washington DC have Medical Marijuana Laws

Washington/Colorado Nov. 2012 then Oregon/Alaska + Wash. DC Nov. 2014 Legalize Non-Medical Use of Marijuana
Not a Single Major American Health Association Accepts Smoking Crude Marijuana as Medicine

National Cancer Institute
American Cancer Society
National Eye Institute
National Glaucoma Society
American Academy of Ophthalmology
National Multiple Sclerosis Society
American Medical Association
Institute of Medicine Medical Marijuana (chemicals) Endorsement 1982

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

- Alzheimers, ALS, cachexia/wasting syndrome, Cancer, Crohns Disease, epilepsy & seizures, glaucoma, HCV, HIV, MS & muscle spasticity, severe & chronic pain, nausea, PTSD
- Insufficient evidence to support medical marijuana for most of these conditions
- Moderate support for effective use in cachexia/wasting and some support of use in pain but need dosing and side effect profile
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; $\Delta_9$THC (tetrahydrocannabinol) are considered to be responsible for most effects

- 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, -spasmodic, -emetic, -inflammatory, analgesia, sedating, neuroprotective, actually counters many THC effects
- CBN (cannabinol): anti-seizure, -inflammatory, phase II sedative effects

Note: ~2,000 chemicals produced when pot is combusted
**THC & CBD often work in opposition to each others effects**

<table>
<thead>
<tr>
<th>THC - Recreational use interests</th>
<th>CBD - Drug Companies Interests</th>
</tr>
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<tbody>
<tr>
<td>Euphoria</td>
<td>No euphoria</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Anti-anxiety</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Anti-psychotic</td>
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<tr>
<td>Cognitive impairment</td>
<td>No cognitive impairment</td>
</tr>
<tr>
<td>Hunger</td>
<td></td>
</tr>
</tbody>
</table>

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

RD Schwartz-Bloom 2011
But: THC-to-CBD Ratio Continues to Increase

JR Burgdorf et al. 2011
Medical Synthetic THC
2000’s Synthetic Cannabinoids

- dronabinol (Marinol)
- nabilone (Cesamet)
- THC + CBD (Sativex)
- Cannabinol Extract (Cannador)
- CBD (Epidiolex) in IND-Phase III trials
FDA-Regulated Cannabinoid-Based Medicines: Chemicals, Extracts, Botanicals

Dronabinol (Marinol™) 1985
Nabilone (Cesamet™) 1985
Cannabis Sativa Extract (Sativex™) 2006
Cannabis Sativa L. Cigarettes 1976

- Approximately 460 chemical constituents, >100 phytocannabinoids
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)

**Courtesy of Dr. Gregory T. Carter 2012**
Sativex™: Oral Spray-THC:CBD = 1
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
Now Medical CBD Liquid for Vaping alleged legal in U.S.
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 ipsalateral 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 ipsalateral/contralateral hind paw skin, DRG, and ipsalateral/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
- **Analgesic effects not blocked by opioid antagonists**

Courtesy of Dr. Gregory T. Carter 2012
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.

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

Courtesy of Dr. Gregory T. Carter 2012
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

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

Conclusion: 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.
Any Questions?
Thank You!
Questions?

PowerPoint available at www.Cnsproductions.com

Darryl Inaba, PharmD., CATC V & William Cohen CADCI
Break Time?
Part II: Opiate Addiction and Recovery

Healthy Brain

Opiate Dependence, 7 years
The Pharmacology (effects)
Endogenous Opioid Peptides

- Endorphins: Α-, β-, Γ-, or Σ-Endorphin
- Enkephalins: Leu-, Met-
- Dynorphins
- Adrenorphin, amidorphin
- Opiorphin
- et al.
The Synapse

1. Incoming electrical signal
2. Neurotransmitters
3. Vesicles
4. Synaptic gap
5. Reuptake port
6. Chlorine ion
7. Sodium ion
8. Transmitted signal
9. Ion gate
10. Autoreceptor

- Sodium ion
- Chlorine ion
- Potassium ion
- Neurotransmitter
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?]
Effects: Opiates/Opioids

- Pain suppression
- Pinpoint pupils
- Lowered heart rate, blood pressure, respiration
- Constipation
- Cough suppression
- Lax muscle tone
- Dryness of mouth
- Euphoria
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. mophine every 6-8 hours, 3-4 wks for Abstinence to evoke

• Psychological Dependence – Neuroses, Reinforcement, Allostasis, & PAWS?
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
Addiction Pathway and Related Brain Circuitries

- Reward/Reinforcement (Go)
- Control (Stop)
- Stay Stopped (Slip)
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
Relapse Related Brain Circuits and Processes

- Stay Stopped (Slip Decisions)
- Emotional Memory (Cravings)
- Stress Hormone Cycle (Hypersensitivity)
reward/reinforcement pathway

Prefrontal Cortex
Nucleus Accumbens
Lateral Hypothalamus
Amygdala
VTA
VTA Dopamine Cells of Opiate Addict vs. Non Addict Rat
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
Diffusion Tensor Imaging (DTI)
SPECT Scans Show Impact of Opiate Addiction on the Brain

Normal Healthy Brain Activity

Heroin Addict’s Brain Activity (~7yrs.)
Brain Reward Pathways

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

Chemical pathways:
- Dopamine
- Glutamate
- Opioid Peptides

Courtesy of Dr. John Hart, Portland, Oregon
Acute Reinforcing Effects

Courtesy of Dr. John Hart

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

Courtesy of Paulus, M.P.; Tapert, S.F.; and Schuckit, M.A. NIDA, Archives of General Psychiatry, 62(7), 2005
RELAPSERS, NONRELAPSERS MAKE DECISIONS DIFFERENTLY

During a decisionmaking exercise, nonrelapsers activated five brain regions that relapsers did not.

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Percent difference in activity during decisionmaking relative to activity during simple response.
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 relieve 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
Also Neural Crux of Relapse with Stress March 2013

VTA’s (ventral tegmental area): GBA-releasing neurons, dopamine-releasing neurons and Kappa opioid receptors interaction in stress. Drugs and natural satiations 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.

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

Old Brain = Survival (5X faster and more powerful) than Neocortex = Control, Planning and Decision Making.
Brain Imaging: Impact of Addiction Pathology
Normal Brain  Methamphetamine Abuse

Courtesy of Daniel Amen, M.D.
Chronic Alcohol Abuse

Heroin Abuse
Normal Brain

Marijuana Abuse

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

Dopamine D2 Receptors Are Lower in Addiction

Cocaine

Meth

Alcohol

Heroin

Control

Addicted
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
- CREB
- CHRM$_2$
- GABRA$_2$
- Leu-Pro allele
- NQD$_2$
- ADH$_4$
- KMALDH$_1$
- COMTmet158met
- DRD$_2$A$_1$ Allele
- Tipsy Gene: CYP2E1
- AUTS$_2$

- GABRG$_3$
- TAS$^2$R16
- SNCA
- OPRK$_1$
- PDYN
- CYP$_2$D$_6$
- CHRNA$_4$
- DeltaFosB
- Novelty Gene: DRD$_4$
- Finnish Rage/Alcohol Gene: HTR2B

Epstein DRD4 Novelty Seeking Gene for Opioid Depn.

89 genes associated & > 900 suspected
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)
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
Epigenetic Expression

Epigenetic mechanisms are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Health endpoints
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

Histones are proteins around which DNA can wind for compaction and gene regulation.

Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
Identical Twin Mice with Divergent Epigenetic Expression
Even Identical Twin with Epigenetic Expression of Different Races
Type III:

Toxicology Neurochemical & Neurofunctional Allostasis
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
Neuron Homeostasis: Brain in Dynamic Equilibrium
Electron Microscopy of Neurons, Dendrites and Axons

Professor Terry Wiseth, Northland College
Synapse @ 50,000x Electron Microscopy

Credit: Thomas Deerinck, NCMIR/Photo Researchers, Inc.

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
Neurotransmitters

- Acetylcholine
- Substance “P”
- Norepinephrine
- Anandamide
- Epinephrine
- Glycine
- Dopamine
- Histamine
- Endorphin
- Nitric oxide
- Enkephalin
- Glutamic acid
- Serotonin (5HT)
- Cortisone
- GABA
- Aspartic Acid
- Oxytocin
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.
SPECT Scan: Opioid Allostasis

Healthy Brain

7 years Methadone use, some prior Heroin
Diathesis-Stress Model of Addiction & Related Disorders is actually:

Heredity, Environment, Psychoactive Drugs

Copyright 2009, CNS Productions, Inc.
DBA/2j = Genetic alcohol/Drug avoiding mice

C57bl/6j = Genetic alcohol/drug loving mice
Hereditary hater of alcohol DBA/2J
Hereditary lover of alcohol C57bL/6J
Alcoholic mouse

+ 🍷 = 🐭

+💥+ 🍷 = 🐭

−🧀+ 🍷 = 🐭

+ 🍷 = 🐭
Levels of Use

- Abstention
- Experimental
- Social / Recreational
- Habitual
- Abuse
TREATMENT
TREATMENT CONTINUUM

- DETOXIFICATION
- INITIAL ABSTINENCE
- LONG-TERM ABSTINENCE
- RECOVERY
Medications for Opioid Treatment

Remember, Mesocortex/Limbic intervention is pharmaceutical, Neocortex/Frontal Cortex is counseling and education

- buprenorphine (Suboxone®)
- naltrexone (Revia®, Trexan®)
- methadone
- levo-alpha-acetyl-methadol (LAAM)
- Non FDA Approved: clonididine, Rapid Op. Detox, ibogaine, amino acids, DXM
Meds for Opioid Treatment

- buprenorphine (Suboxone®)
- naltrexone (Revia®, Trexan®, & Vivitrol®)
- methadone
- levo-alpha-acetyl-methadol (LAAM)
- Off-Label: clonidine, lofexidine
- Off-Label: Rapid Opioid Detoxification (naloxone or naltrexone with midazolam, lorazepam, clonididine, anesthetics, et al.)
- Illicit in U.S.: Ibogaine
Buprenorphine (Suboxone) Ceiling Effect
Jackson County Rx OD deaths

Number of deaths caused by prescription drug overdose annually

- Year: 2002
  - Number of deaths: 12
  - Description: Jackson County Rx OD Deaths

- Year: 2003
  - Number of deaths: 14

- Year: 2004
  - Number of deaths: 24

- Year: 2005
  - Number of deaths: 28

- Year: 2006
  - Number of deaths: 46

- Year: 2007
  - Number of deaths: 35

- Year: 2008
  - Number of deaths: 33

- Year: 2009
  - Number of deaths: 19
Figure 1. Impact of buprenorphine in France. (See also [69].)
Suboxone more Rxed than methadone
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
Chronic Alcohol Abuse  Herion Abuse

Courtesy of Daniel Amen, M.D.
RELAPSERS, NONRELAPSERS MAKE DECISIONS DIFFERENTLY

During a decisionmaking exercise, nonrelapsers activated five brain regions that relapsers did not.

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Percent difference in activity during decisionmaking relative to activity during simple response.
2. Endogenous or Intrapersonal Addiction Cravings via Neural-Physiological Allostasis
Analogous to diabetes, hypothyroidism, et al., an *allostasis* 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.
Dopamine Depletion in Addiction = Endogenous Craving and Anhedonia

Courtesy of Paulus, M.P.; Tapert, S.F.; and Schuckit, M.A. NIDA, Archives of General Psychiatry, 62(7), 2005
During a decision-making exercise, nonrelapsers activated five brain regions that relapsers did not.
Any Negative Mood State can initiate a Craving Reaction

- **HALT** – Hungry, Angry, Lonely, Tired
- **RIID** – Restless, Irritable, Isolated, Discontent
- **BAAD** – Bored, Anxious, Angry, Depressed
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 fMRI 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
Sacks, David (2012), Psych Central
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!
Amygdala not lit up

Nature Video

Amygdala activated

Cocaine Video

Courtesy of Anna Rose Childress, Ph.D.
Memories

Formation & Role In Drug Cravings
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
Brain of newly abstinent meth abuser
Craving and Relapse

Cue-Induced Brain Activity

- Brain regions activated while viewing alcohol-related cues

Courtesy of Dr. John Hart, Portland, Oregon

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

Dopamine

Glutamate

Opioid Peptides

Courtesy of Dr. John Hart, Portland, Oregon
Acute Reinforcing Effects

Limbic Area
- Role: Drive Generation (SURVIVAL)
- Intervention: Pharmacotherapy

Prefrontal Cortex
- Role: Executive Function
- Intervention: Counseling

Courtesy of Dr. John Hart
Pharmacological Cue Extinction via naltrexone and acamprosate
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)
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
VTA’s (ventral tegmental area): GABA-releasing neurons, dopamine-releasing neurons and Kappa opioid receptors interaction in stress. Drugs and natural satiations 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.

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.

Regier et al., 1990; Merikangas, Stevens, & Fenton, 1996

- Recovery difficult if MH disorders are not addressed
• 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
<table>
<thead>
<tr>
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<tr>
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</tbody>
</table>
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

One does not cure addiction, you treat it and manage it like any other chronic persistent medical disorder.
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

Belenko, et al. 2005
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

Normal Control  METH Abuser (1 month detox)  METH Abuser (24 months detox)


Dopamine Transporter Binding (DAT) Recovery in Meth Addiction

DAT Recovery with prolonged abstinence from methamphetamine

Volkow et al. J. of Neuroscience 2001
7 years Methadone use

Deborah - Methadone 100 mg/day
Xanax 20 mg/day FOR 20 YEARS

ONLY SIX WEEKS FOLLOWING DETOX
Dr. Ken Blum’s patented: Synapta GenX, KB220Z

Neuronutrient complex “normalization” of caudate, accumbens and putamen regions of heroin addicts demonstrated by fMRI Scan
Conclusions

Questions?
• 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!*"
Thank You!
Questions?

PowerPoint available at www.Cnsproductions.com

Darryl Inaba, PharmD., CATC V & William Cohen, CADCI

Eighth Edition
Have A Great Evening!