

به نام خدا

مواد اپویدی و اختلالات مرتبط با آن

دکتر احد فاضلی

عضو هیئت علمی و استادیار روانپزشکی

دانشگاه علوم پزشکی

آبان ماه ۱۴۰۰



OPIOID DEPENDENCE

See Hand-out listing admission to treatment facilities

WHAT IS AN OPIATE?



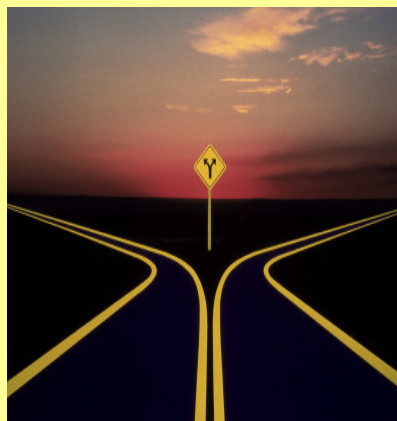


WHAT IS AN OPIATE?

- An Opioid is any substance that has morphine-like effects.
- All are derivatives from opium and the opium poppy (*papaver somniferum*) such as Paregoric® (camphorated opium tincture).
- Examples of semisynthetic opioids are Heroin (Diacetylmorphine), Codeine, Oxycodone, Hydromorphone, Hydrocodone, Fentanyl, and Morphine.
- Examples of synthetic opioids are Dolophine® (D-Methadone), LAAM® (L-^a-Acetylmethadol), Demerol® (Meperidine), Darvon® (Propoxyphene), and Ultram® (Tramadol)

PROPERTIES OF OPIATES

- Cross tolerance (one opiate can be substituted for another in order to avoid or alleviate abstinence syndrome withdrawal).
- Antagonists and partial agonists have stronger affinity for the opioid receptors and can induce withdrawal



PROPERTIES OF OPIATES

■ Examples of partial agonists:

- Talwin® (Pentazocine HCL) oral
- Stadol® (Butorphanol tartrate) injectible and nosedrop
- Nubain® (Nalpbuphine HCl) injectible
- Subuxone® (buprenorphine and naloxone)
Subutex® (buprenorphine) sublingual

Buprenex® (buprenorphine) Initially introduced in 1985 as a low dose (0.3mg) Schedule V narcotic as injectible but evolved into oral forms in 2002



PROPERTIES OF OPIATES

■ Antagonists:

- Narcan® (Naloxone)
- Revia® (oral naltrexone) and Vivitrol® (injectible naltrexone)
- Dolophine® (Methadone) can have antagonistic effects at 80-120mg/day

Both antagonists and partial agonists have the ability to displace opiates from the opiate receptor!



THE OPIOID RECEPTORS

- There are about 2 dozen endogenous opioid receptors and they are broken down into 3 different endogenous systems. Endorphins, Enkephalins, and Dynorphins.
 - Endorphins- Any of a group of peptide hormones that bind to opiate receptors and are found mainly in the **brain**. Endorphins reduce the sensation of pain and affect emotions.
 - Enkephalins- Either of two closely related pentapeptides having opiate qualities and occurring in the **brain, spinal cord, and other parts of the body**.
 - Dynorphins- any of a group of potent opioids found in the **mammalian central nervous system** that have a strong affinity for opiate receptors (particularly kappa receptors)

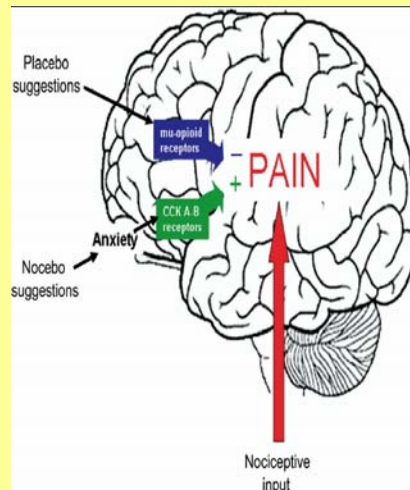
(Merriam-Webster Dictionary, 2013)

THE OPIOID RECEPTORS

- Endorphin Systems:
 - Mu
 - Supraspinal analgesia
 - Respiratory depression
 - Miosis (constricted pupils)
 - Euphoria

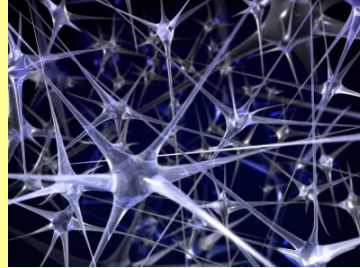
LAB ANIMALS WILL SELF ADMINISTER INDICATING REWARD BENEFIT!

(Miller, Gold, and Smith, 1997)



THE OPIOID RECEPTORS

- Kappa
 - Spinal analgesia
 - Sedation
 - Sleep
 - Miosis
 - Limited respiratory depression



Produces dysphoria and not euphoria.

LAB ANIMALS WILL NOT SELF ADMINISTER!

(Miller, Gold, and Smith, 1997)

THE OPIOID RECEPTORS

- Sigma (part of Lamda subtypes):
 - Dysphoria
 - Delusions
 - Hallucinations
 - Respiratory stimulation
 - Vasomotor stimulation



(Miller, Gold, and Smith, 1997)

THE OPIOID RECEPTORS

- Delta:

Interacts with the mu receptors through endogenous opioids and enkephalins

LAB ANIMALS WILL SELF ADMINISTER INDICATING REWARD BENEFIT!



(Miller, Gold, and Smith, 1997)

OPIOID EQUIVALENTS

Morphine	10mg IM/SC/IV 60mg oral
Heroin	3mg IV
Hydromorphone	1.5mg IM/SC
Codeine	120mg IM/SC 180mg oral
Oxycodone	10-15mg IM 20-30mg oral
Meperidine	75-100mg IM/SC
Methdone	10mg IM/SC/Oral
Fentanyl	125mcg oral
Lomotil®	40-60mg oral
Paregoric®	25ml oral

(Miller, Gold, and Smith, 1997)



OPIOID WITHDRAWAL TIMING

Drug	Onset (hrs)	Peak (hrs)	End (days)
Morphine	14-20	36-48	5-10
Heroin	8-12	48-72	5-10
Methadone	36-72	72-9	14-21
Codeine	24	-----	----
Hydromorphone	4-5	-----	----
Meperidine	4-6	8-12	4-5

(Miller, Gold, and Smith, 1997)

MEDICAL AND EPIDEMIOLOGICAL PROBLEMS ASSOCIATED WITH OPIOID DEPENDENCE

- Spread of infectious diseases such as HIV and Hepatitis
- Spread of sexually transmitted diseases due to poor condom compliance and multiple partners (disinhibited behaviors)
- Phlebitis, abscesses, pulmonary emboli, bacterial endocarditis, and cotton fever with IV drug users
- Respiratory and cardiac arrests
- Increased criminal activity (subsistence theft, robberies, and prostitution) in order to support habit

COTTON FEVER

Cotton fever is characterized by high fever, chills, rigors, myalgia, and elevated WBC count (sepsis-like appearance) with negative blood cultures. The condition results from using cotton to filter the drugs after melting down the substance. Usually self-limiting and lasts less than 48 hours



- Causes of cotton fever:
 - Hypersensitivity to pyrogenic materials found in cotton
 - *Enterobacter agglomerans* (since renamed *Pantoea agglomerans*), a gram-negative bacterium that frequently colonizes cotton and other plants.

(Ramik and Mishriki, 2008)

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- Abstinence
 - Disdain by public for addicts
 - Political fall-out if pursue any other avenue
 - Willful pursuit of misconduct (addiction as a choice)
 - Traynor v. Turnage US Supreme Court decision in April 1988 upheld VA benefits such as the use of expired GI Bill educational benefits cannot be extended beyond the 10-year time limit due to alcoholism because the veteran engaged in "willful misconduct." Original argument by plaintiff was VA view of alcoholism contradicted the rights granted under the Rehabilitation Act of 1973.

(The Supreme Court Center at Justia.com, 1988)



HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- Americans with Disabilities Act
 - “Casual drug use is not a disability under the ADA. Only individuals who are addicted to drugs, have a history of addiction, or who are regarded as being addicted have an impairment under the law. In order for an individual's drug addiction to be considered a disability under the ADA, it would have to pose a substantial limitation on one or more major life activities. In addition, the individual could not currently be using illegal drugs.”



(US Dept. of Justice, 1997)

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- “While a current illegal user of drugs is not protected by the ADA if an employer acts on the basis of such use, a person who currently uses alcohol is not automatically denied protection. An alcoholic is a person with a disability and is protected by the ADA if he or she is qualified to perform the essential functions of the job. An employer may be required to provide an accommodation to an alcoholic. However, an employer can discipline, discharge or deny employment to an alcoholic whose use of alcohol adversely affects job performance or conduct.”

(US Dept. of Justice, 1997)

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- Pure Food and Drug Act of 1906 required distinct labeling for all opiate containing products (**educational effort for the public**).
- Harrison Narcotic Act of 1914 mandating licensing of manufacturers of opiate products and all persons involved in the dispensing of these products (**first effort at monitoring narcotics**).
 - Many providers saw the Harrison Act as the opportunity to legitimately prescribe opioids for maintenance therapy for opiate addicts.



(CSAT, 2005)

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- However, the Department of Treasury interpreted the law as more of a prohibition of such efforts and the interpretation was challenged in a 1918 Supreme Court case.
 - The Supreme Court upheld the Treasury's interpretation and, thus, eliminated opiate replacement therapy legally until the 1960's. Until that time, several cities with large populations of opiate addicts had run successful opiate replacement clinics. The most notable of the treatment programs was in New York City.

(CSAT, 2005)



HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- Governmental efforts in the 1920's sought to criminalize the treatment of addictions but had minimal effect.
- Initial opioid replacement studies were done on prisoners in 1935 with prisoner volunteers at Public Health Hospital in Lexington, KY
 - 90% relapsed after return to NYC
 - showed longer duration and more stable pain coverage with an oral agent but did not appreciate the value in replacement therapy at that time.



(Woods, 1994)

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

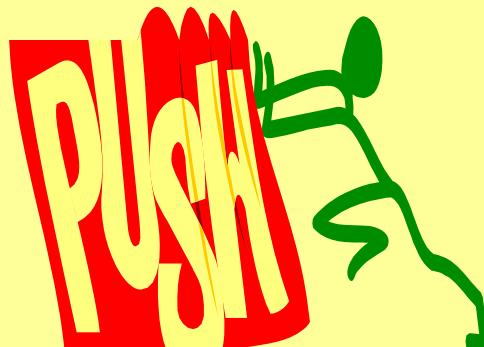
- This effort led to foundational concepts of motivational interviewing and “meeting the addict where they are.”
 - Based upon the Transtheoretical Model of Change developed by Prochaska and DiClemente
 - Asserts that all persons go through certain stages in a definitive order when changing a view or behavior.
 - The goal of motivational interviewing (MI) is to help clients move from one stage to the next when they are reluctant to do so by “breaking down the client’s denial” through an exposure of the discrepancies between what they are and what they want to be.

(Naegle & D'Avanzo, 2001)

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- Motivational Interviewing
 - Roots in Adlerian theory as this philosophy supports that all behaviors in human nature have a purpose and motivations are not only what drives change but is also what maintains current behaviors (Corey, 2005).
 - Attitude of the therapist is one of the most crucial components which will determine the outcome of the MI session (Stuart and Laraia, 2005).
 - avoid argument or confrontations with the patient as this will result in a power struggle
 - roll with the resistance of denial
 - show support for the client by reinforcing strengths and helping them to believe they can achieve this desired goal

WHERE ARE YOU NOW? WHERE DO YOU WANT TO BE?





WHERE ARE YOU NOW? WHERE DO YOU WANT TO BE?

FRAMES

- **Feedback** regarding risk or impairment after assessment of patterns and related problems

Responsibility for change is on the patients shoulders and only they have the right to make that decision

Advice about changing the behavior is given clearly by the therapist but in a non-confrontational presentation

Menus of self-directed change options and alternatives are offered to the patient

Empathetic counseling is the therapist's approach and tone

Self efficacy is strengthened by helping the patient to believe this is an attainable goal

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- **The Controlled Substances Act of 1970** (Public Law [P.L.] 91–513) paved the way for the role of the **DEA in monitoring the distribution of opiates** by physicians, pharmacist, and practitioners. The law provided dispensers of opiate-containing medications must meet certain criteria of knowledge and education regarding the responsible provision of narcotics (CSAT, 2005).
- **The Narcotic Addict Treatment Act of 1974** (P.L. 93–281) amended the Controlled Substances Act of 1970 and, for the first time in federal law, **defined opiate maintenance treatment**. This act affected opiate addiction treatment profoundly by requiring a separate **DEA certificate for providers to prescribe opiates specifically for opiate maintenance therapy** and promoted specific addiction treatment knowledge by requiring all such providers be deemed competent by the DHHS in addiction treatment.



HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- **The Narcotic Addict Treatment Act of 1974** (P.L. 93–281)
 - This coordination of monitoring and accrediting marked the **first governmental joint effort** for the treatment of opioid addiction in the U.S.
 - Also **established** the National Institute on Substance Abuse (**NIDA**) as an entity independent of the National Institutes of Health (NIH)
 - Granted the authority to regulate and treat opioid addiction between the Food and Drug Administration (FDA) and NIDA. **NIDA became responsible for establishing standards of care**, coordinating research efforts, and monitoring public health. The **FDA became responsible for approving drug treatments** based upon safety and efficacy trials (CSAT, 2005).

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- **The Drug Addiction Treatment Act of 2000** (DATA [P.L. 106–310 div. B]), or **DATA of 2000**, amended the Narcotic Addict Treatment Act of 1974 by **relieving providers from the requirement of separate DEA registration certificates for treating opiate** addicts with medication replacement therapy. DATA of 2000 assumes the granting of a DEA certificate notes the competency of the prescribing provider to initiate replacement or maintenance therapy and refer the addict to more specialized counseling or treatment.

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- A 1995 report reviewing the 1972 FDA regulatory practices and a 1997 NIH consensus development report on Effective Treatment of Opiate Addiction paved the way for changes in regulatory practices which would allow greater creativity and individualization of patient treatment plans.
 - The passage of new regulations by the DHHS in 2001 recognized the need for specialized and diverse opportunities for care among opiate addiction treatment providers.
 - Oversight of such treatment facilities was shifted from the FDA to SAMHSA
 - Accreditation processes were changed to one of a peer review instead of compliance. The 42 Code of Federal Regulations, part 8 provides the legislative authority for this practice.
 - The DEA's role remains the same but now has more reliance upon "best practice" guidelines in determining infractions of providers in terms of controlled substance prescription improprieties

(CSAT, 2005).

HISTORICAL EVOLUTION OF OPIOID DEPENDENCE TREATMENT

- In 1963, President Kennedy's Advisory Commission on Narcotics and Drug Abuse recommended research start in earnest to see if opiate replacement therapy would be a viable harm reduction model to treat US opiate addicts and improve overall public health and safety
 - Response to public outrage about addicts' criminal activities and spread of disease
 - First time US seriously considers moving from abstinence to harm reduction policy



(CSAT, 2005).

HARM REDUCTION POLICIES

- Reasons for wanting to shift to harm reduction policies: spread of disease, loss in productivity, deaths, burden of healthcare (Lawrinson et al, 2008).
- Worldwide 10% of new HIV infections are attributed to injection users. In 2003, 420,000 new infections directly attributed to injection users (Lawrinson et al, 2008).

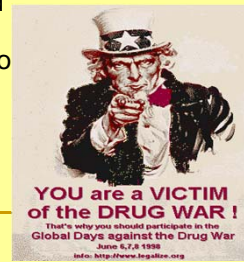


HARM REDUCTION POLICIES

- Is addiction a disability? Treating as a medical problem is “overly narrow.”
- View of addiction as a “rational, reasonable, or at least understandable response to oppressive social conditions; as blunting the desire to achieve goals already foreclosed by poverty or race.” (Wasserman, 2004)
 - Don't focus on the addiction but focus on socio-economic change.
- Two opposing policies: legalize the drugs or adopt harm reduction (view of addiction as an impairment)

HARM REDUCTION POLICIES

- Legalized drugs:
 - Non-addicts take on the burden of supporting ones who have “sustained themselves by enslaving or otherwise exploiting other segments of the population (Wasserman, 2004).”
 - McCoun and Reuter (2002) looked at societies that had legalized drugs and concluded decriminalization of drugs will reduce criminal activity and devastation of the population of poor urban communities but middle class Americans would likely be worse off. In other words, we have chosen to increase the burden on poor addicts and reduce it on middle class.
 - Wealthier addicts are less likely to be caught due to delayed involvement in criminal activities to obtain drugs.
- Alcohol use and heavy taxation
 - Increase in liver disease.
 - Loss of productivity



THE ROLE THE GERMANS IN OPIOID DEPENDENCE TREATMENT



Heroin first isolated in 1898 in Germany during attempt to find a non-addictive replacement for Morphine

- Considered to be non-addictive when first allowed in US but manufacturing outlawed by Congress in 1924 (Rasmussen, 2000)

Methadone developed in WWII by Germans when blockaded from Turkey

- Use studied in 1946 at Public Health Hospital in KY on prisoners.
- First use of Methadone maintenance in 1964.

(Woods, 1994)



AMERICAN PIONEERS

- 1962 Dr. Vincent Dole (**metabolism specialist** at Rockefeller) appointed to look into maintenance program.
 - Read work of Dr. Marie Nyswander (1956) a **psychiatrist** who treated addicts in Public Health Hospital in Lexington, KY and later treated addicted musicians at private clinic in Harlem.
 - Dr. Kreek (**neuroendocrinologist**) joins research with Dr. Nyswander and Dole in 1964.
 - Together they created the first effective harm reduction program with use of Methadone maintenance in 1964.

(Woods, 1994)

IMPORTANT REASONS FOR SHIFT IN THINKING

- Late 1960's, heroin OD leading cause of death in ages 15-35.
- Overcrowded jails and prisons with riots due to drug arrests.
- Original plan was just to keep addicts content without causing medical harm and to provide something safe and effective for long term use that would keep opioid receptors saturated. (Woods, 1994)



A SUCCESSFUL MEDICATION ASSISTED TREATMENT PROGRAM

- **Cultural inclusion** rather than observed outcomes are more predictive of enduring change and increased self-efficacy within a community (Franzblau and Moore,2001).
- The **inclusion of community members** in training and the delivery of services increase the feelings of importance and self-worth (Franzblau and Moore, 2001).
- Crome (2004) notes the importance of a longer duration of retention in a structured treatment program because statistics indicate 66% of **adolescents relapse within the first three months of treatment.**

A SUCCESSFUL MEDICATION ASSISTED TREATMENT PROGRAM

- Advocates for **peer delivered services** report:
 - Such interventions allow for a **clearer identification of patient needs and concerns** that will eventually forge a working relationship with the provider and support recovery (Swarbrick, Hutchison, and Gill, 2008) .
 - Such relationships can **increase** the consistent factor shown across multitudes of studies to be crucial in achieving sobriety-**retention of the patient in treatment** (Jackson, 2002).
- Researchers with extensive experience in the provision of opioid replacement treatment suggest a **structural model** of regulation.
 - General goals are determined by top officials but are written with **sufficient ambiguity to allow some flexibility in interpretation and application** of services at the point they are received (Milstead, 2003).
 - This strategy of administration allows for the mediation of culture within the program (Milstead, 2003).



METHADONE

- Dole, Nyswander, and Kreek suggested the use of Methadone as a replacement opiate medication because
 - long-acting, provided pain and craving relief without producing euphoria or cognitive and motor deficits, could be administered once daily, and decreased the risk of death in overdose due to the absence of tolerance properties (Woods, 1994).
- LAAM had the same desirable properties of Methadone but, whereas Methadone provided effects for about 24 hours, LAAM could provide opiate receptor coverage for 48-72 hours.
 - LAAM has been limited in its availability since 2001 due to research findings of increased risk for heart problems and the cessation of production of the medication by Roxane Pharmaceuticals in 2004 (CSAT, 2005).

METHADONE

- A successful methadone maintenance program
 - Relieves cravings (usual dose >60mg/day)
 - Has a high enough dose to protect against overdose from any other opiate and block euphoric effects of other opiates (usually at doses of 80-120mg/day)
 - Pt can function without impairment
 - Corrective not curative (stabilizes endocrine and neurobiological processes)
 - Allows pt time to develop coping skills and change opioid receptor(Woods, 1994)



METHADONE

- Pharmacology of Methadone:
 - Absorbs into the liver and releases over time. Steady states are obtained for 24-36 hours. Peak at 2-6 hours after ingestion. Tegretol, Rifampin, Barbs, and alcohol can decrease levels of Methadone.
 - Neurobiological properties of why effective became evident in 1970's when Dr. Kreek discovered almost immediately after ingestion of dose of Methadone, 99% of the drug binds in tissue in equilibrium with the blood
 - The tissue is constantly releasing into the blood to keep levels constant and thus decrease cravings and pain and allow pt to not be preoccupied with obtaining next dose. (Absorption is reversible). Stability of receptor occupation allows for the pt to function normally.

METHADONE

- Best retention rates on Methadone doses >60mg/day (avg 60-80mg of d-methadone).
 - Laws initially limited dose to 50mg/day despite research.
 - Want Methadone blood levels at 150-600ng/ml.
 - Gradual dose increase over 4-6 weeks.
 - Absorption is reversible and stability of receptor occupation allows for the pt to function normally.
- (Woods, 1994)



METHADONE

- Benefits of Methadone as opioid replacement was discovered accidentally when large doses of Methadone had to be given to opiate addicts who had been tried on other opiates and experienced tolerance and withdrawal.
- Found out Methadone in high doses begins to occupy other receptors and gives long-acting release.
- In opiate naïve pts, Methadone is short acting in a single dose.
- Originally used a racemic blend of D and L isomer methadone and realized the L isomer was what was causing the withdrawal. D isomer methadone used for maintenance.
- Withdrawal from Methadone can resemble a catatonic severe depression.

(Woods, 1994)

OPIOID DEPENDENCE TREATMENT IN PREGNANCY

- Methadone and Suboxone are both class C pregnancy categories but methadone is preferred medication for use.
- Prefer no medical withdrawal of pregnant women before 14 weeks and after 32 weeks.
 - No use of Talwin, Nubain, or Stadol in pregnant women due to withdrawal of infant.
 - Never give Naltrexone or Naloxone unless life-threatening OD because can cause spontaneous abortion.
- Maintenance treatment preferred to start in first trimester.
- Dose usually needs to be increased in 3rd trimester due to greater plasma volume and renal blood flow. Will usually need to raise and split dosing.

(Woods, 1994)



OPIOID DEPENDENCE TREATMENT IN PREGNANCY

- Higher birthweights due to less stress on fetus related to recurrent withdrawal states on short-acting heroin.
- Can safely breastfeed because only small amounts cross.
- Paregoric (preferred) and phenobarb are used to withdraw the infant.
 - Dose of methadone used in mom is irrelevant of dose given to infant.
 - Withdrawal in infant will most likely begin within 72 hours of birth but can be minutes to 2 weeks after birth.

(Woods, 1994)

GENERAL RULES OF OUTPATIENT TREATMENT PROGRAMS (OTP'S)

- May 2001, MMT programs shifted from FDA to SAMHSA Centers for Substance Abuse Treatment.
- May 22, 2003 Buprenorphine comes to public and changes from schedule V to schedule III.
- DATA waived physicians outside of a registered OTP have a limit on pts they can treat. Certified Opioid Treatment Centers (OTP's) do not.
- OTP's originally restricted regarding take home doses of Suboxone but DATA waived physicians were not restricted. This rule was challenged based upon principle of Methadone being a schedule II medication and Suboxone being a schedule III medication. As of Jan 7 2013, OTP's could give take home Suboxone.

(SAMHSA, 2007)



GENERAL RULES OF OUTPATIENT TREATMENT PROGRAMS (OTP'S)

- Admission criteria;
 - Age 18 and over with at least one year history of opioid dependence
 - Programs will accept under the age of 18 if failed 2 short-term detox efforts in a 12-month period and guardian must sign for admission
 - One year of addiction requirement can be waived for pregnant women, previously treated pts (within 2 years), and people released from prison with relapse within 6 months.
- All OTP's must provide:
 - Medical services and pts receive a PE
 - Educational, counseling and vocational services. (SAMHSA, 2007)

GENERAL RULES OF OUTPATIENT TREATMENT PROGRAMS (OTP'S)

- Initial dose of Methadone cannot exceed 30mg unless clearly documented that withdrawal not abated in 3 hour observation period.
 - Methadone 60mg usually chosen as stable dose for 3-5 days before increasing.
 - Best retention rates on Methadone doses >60mg/day (avg 60-80mg of d-methadone).
 - Want Methadone blood levels at 150-600ng/ml. Gradual dose increase over 4-6 weeks.
- (Woods, 1994)



GENERAL RULES OF OUTPATIENT TREATMENT PROGRAMS (OTP'S)

- Take homes doses of Methadone can be dispensed to pts:
 - Stable in treatment for 9 months, can get 6 day supply of Methadone to take home.
 - After one year, max of 2 weeks take home.
 - After 2 years max of one month take home.
- To wean off of Methadone:
 - Reduce Methadone by 2.5-10mg per week.

[\(SAMHSA, 2007\)](#)

DSM-IV Criteria for Opioid Abuse

- A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one or more of the following criteria occurring within a 12 month period:
 - Recurrent substance use resulting in failure to fulfill major role obligations at work, school or home
 - Recurrent substance use in situations which is physically hazardous
 - Recurrent substance related legal problems
 - Continued substance use despite having persistent or recent social or interpersonal problems caused or exacerbated by the effects



DSM-IV Criteria for Opioid Dependence

- 3 or more of the following occurring at any time in a 12 month period:
 - Tolerance as defined by a need for marked increase amounts of the substance to achieve intoxication or the desired affect or marked diminished affect with continued use of the same amount of the substance
 - Withdrawal as manifested by either withdrawal symptoms or substance is taken to relieve or avoid withdrawal symptoms
 - The substance is often taken in larger amounts over a longer period of time than intended
 - There is a persistent desire or unsuccessful attempts to cut down or control substance use
 - A great deal of time is spent in activities necessary to obtain the substance used or recover from its effects
 - Important social, occupational or recreational activities are given up or reduced because of substance used
 - Substance is continued to be used despite knowledge of having persistent or recurrent physical or psychological problems that have likely been caused by or exacerbated by the substance

PROBLEMS WITH DSM-IV

- Physical Dependence does not = drug dependence
- Abuse may not precede or progress to dependence
- Does not use the word addiction
- DSM-V will do away with abuse and dependence



The 3 C's OF ADDICTION

- Craving/Compulsion to take a substance
- Continued Use of substance
- Loss of control/ Cannot limit amount of substance used due to emergence of a negative emotional state when substance is not used

ASAM DEFINITION

- Inability to ABSTAIN
- Loss of BEHAVIORAL control
- CRAVING
- DECREASED recognition of significant problems
- Dysfunctional EMOTIONAL response

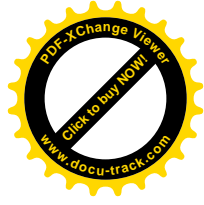
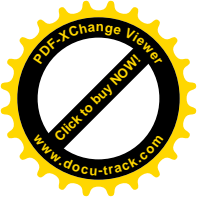


Opioid Pharmacology

- Types of Opioid Receptors
 - Mu
 - Kappa
 - Delta
- Addictive effect of opioids occur through activation of mu receptors
- Role of kappa and delta receptors in addictive process not well defined

Mu Receptor Activation

- | | |
|-----------------|-----------------|
| • Morphine | • Heroin |
| • Methadone | • LAAM |
| • Hydromorphone | • Buprenorphine |
| • Codeine | • Oxycodone |
| • Fentanyl | • Hydrocodone |



Mu Receptor – Full Agonist Binding

- Activates the mu receptor
- Highly reinforcing
- Most abused opiate type
- Includes heroin, oxycodone, methadone and others

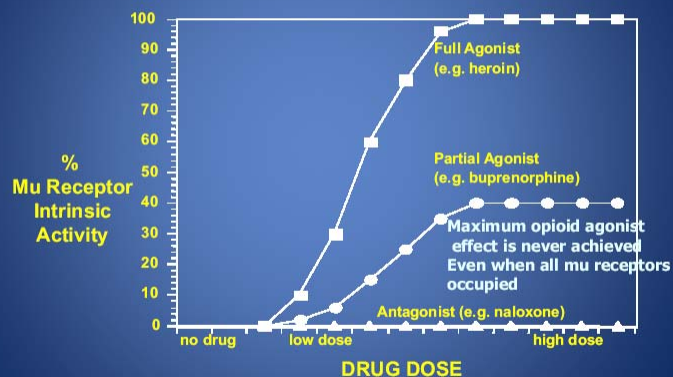
Mu Receptor – Partial Agonist

- Activates the receptor at lower levels
- Relatively less reinforcing
- Less abused opiate type
- Includes buprenorphine

Mu Receptor - Antagonist

- Occupies without activating
- Is not reinforcing
- Blocks abused agonist opiate types
- Includes Naltrexone and Naloxone

Comparison of Activity Levels



© McCance-Katz, E. 2012

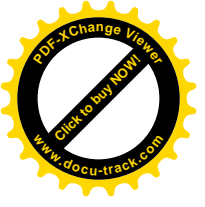


Pharmacology of Opiates

- First pass after oral ingestion varies: morphine only 15% available but methadone 80-90% available
- Metabolized by liver either by glucuronidation or P450 CYP 2D6, 2B6, 3A4
- Duration of analgesia 3-5 hours (constipation or respiratory depression may last longer in drugs such as methadone)
- Excreted in urine and bile
- Impaired hepatic and renal function, increased bioavailability and metabolites

Opioid Tolerance

- Need more drug for same effect
- Less effect with same amount of drug
- Occurs for euphoria, sedation, respiratory depression, vomiting, and analgesia
- Tolerance DOES NOT occur for constipation, miosis, sweating



Opioid Overdose

- Usual cause of death is respiratory depression
- Symptoms include pinpoint pupils, hypotension, coma and noncardiogenic pulmonary edema
- High dose meperidine or propoxyphene can cause seizures
- Treatment is naloxone i.n.

Opioid Withdrawal

- Dysphoric mood
- Nausea or vomiting
- Muscle aches/cramps
- Lacrimation
- Rhinorrhea
- Insomnia
- Hypertension
- Pupillary dilation
- Sweating
- Gooseflesh
- Diarrhea
- Yawning
- Tachycardia

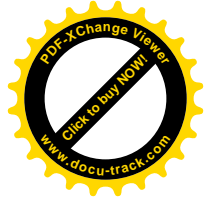
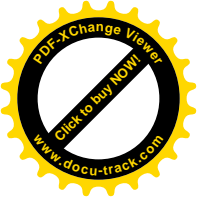


Opiate Withdrawal

- The timeframe for withdrawal is dependent on half life of opiate used
- For short acting opioids including heroin, hydrocodone, and oxycodone, withdrawal usually begins 6-12 hours after the last dose and peaks at 36-72 hours and lasts about 5 days
- For longer acting opiates such as methadone, and morphine withdrawal usually occurs between 36-72 hours after the last dose and peaks within 4-5 days and typically lasts 7-10 days

Pharmacological Treatment of Opioid Withdrawal

- OPIOID DETOXIFICATION
 - methadone
 - buprenorphine
- NON OPIOID DETOXIFICATION
 - clonidine

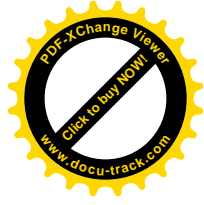
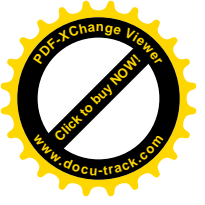


Non Opioid Detoxification

- Clonidine: Alpha-2 adrenergic agonists suppresses noradrenergic activity from the locus cereuleus
 - Helps autonomic symptoms
 - Causes sedation, dry mouth, hypotension
 - Is not approved by the FDA
 - Does not treat craving

OPIOID Detoxification

- Methadone (long term)
 - Federally regulated
 - Need to have a specific license
 - Once day dosing
 - Start low, go slow
 - Look for signs of withdrawal prior to the first dose
 - The first dose is <30 mg



OPIOID Detoxification

• Methadone (long term)

- Dose increases should only occur every 5-7 days
- Increase dosing by 5-10 mg
- If intoxication occurs at first dose, reduce next day dose by 5-10 mg After first dose you have to watch in the clinic for 2 hours

OPIOID Detoxification

• Buprenorphine (short or long term)

- Typically have less withdrawal
- Have to wait for objective signs of withdrawal
- All opioid receptors occupied at 16 mg **NO NEED FOR HIGHER DOSES**
- Various schedules for tapering typically can be accomplished in 5 days



OPIOID Detoxification

- Buprenorphine (short or long term)
 - None to minimal withdrawal symptoms
 - Comfort meds can be used for mild withdrawal symptoms (Robaxin, imodium, Zofran, Seroquel)

Efficacy of Detoxification

- Studies report 80% relapse within the first 12 months
- No difference in 7 vs. 28 days with morphine taper (Ling 2009)
- Looks like the same is true for buprenorphine



Pharmacology Treatment for Opioid Dependence

- Opioid Agonist (Methadone)
- Opioid Partial Agonist (Buprenorphine)
- Opioid Antagonist (Naltrexone)

Opioid Agonist Treatment

- Definition – Use of long acting medication in the same class as the abused drug
- > 18 years of age
- Greater than 1 year of opioid dependence
- Medical compromise
- Infectious disease
- Pregnant women

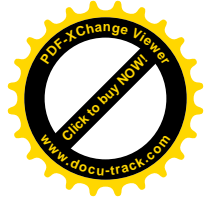
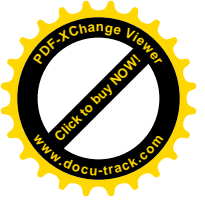


Opioid Agonist Treatment

- Document dependence by history
- Signs of dependence (withdrawal symptoms, urine toxicology, Naloxone challenge)
- Can help prevent relapse
- Improves functioning including social, familial and work
- Decreases medical consequences

Opioid Agonist Treatment

- Should never be used without psychosocial treatments
- Protected by Title 42 Part 2 Code of Federal Regulations (42 CFR Part 2)
- Good medical record keeping
- Monitor with urine toxicology
- Have a treatment contract
- Withdrawal from buprenorphine is not a medical emergency



Opioid Agonist Treatment

- Methadone
 - Schedule II
 - Highly regulated
 - Can only be used in narcotic treatment programs
 - Approved for pregnancy

Methadone

- Target Dose: 60-100 mg
- Prior to starting Methadone obtain EKG to document pre-existing prolonged QT intervals
- Repeat EKG at 30 days
- QTc greater than 500 msec, then reduce dose
- Risk of prolonged QTc greater with dosages above 100 mg per day
- Be aware of accumulations the first 5-10 days
- Do not make rapid dose changes
- METHADONE 40 MG WILL BLOCK WITHDRAWAL IN EVERYONE; WILL NOT ADDRESS CRAVINGS; NO NEED TO RAPIDLY INCREASE THE DOSE



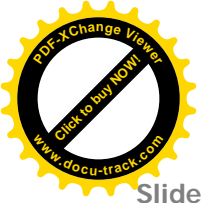
Methadone Side Effects

- Minimal sedation once tolerance achieved
- Increased appetite and weight gain
- Decreased libido
- Decreased gonadal hormone levels
- Constipation
- Benefits include:
 - Lifestyle stabilization
 - Improved health
 - Decrease in criminal behavior
 - Employment
 - Decrease in IV drug use

31

Opioid Agonist Treatment

- Buprenorphine
 - Schedule III
 - Can be prescribed in physician offices
 - Safer in overdose
 - Partial mu agonist
 - Maximal effect is less than that of full agonist such as methadone or heroin
 - Higher doses can be given without adverse side effect of respiratory depression compared to full mu agonist



Slide 82

C1

Cherye, 3/10/2013



Buprenorphine Pharmacology

- High affinity for mu receptor
- Due to high affinity for mu receptor withdrawal can be precipitated; Displaces morphine, heroin, methadone and other full agonists from the receptor
- Dissociates slowly from the mu receptor therefore it is difficult for opiate agonist to displace buprenorphine and activate the receptor; however, this also means it is difficult for opiate antagonists such as Naltrexone to displace the buprenorphine and precipitate withdrawal

Buprenorphine Pharmacology

- It does have abuse potential; however, relatively low when compared to full mu agonist opioids
- Acute parenteral doses produce typical mu agonist opioid effects (papillary constriction and mild euphoria)
- Similar effects seen with sublingual dosing
- Onset of effects slower with sublingual dosing than with parenteral dosing suggesting lower abuse potential



Buprenorphine Pharmacology

- Metabolized by cytochrome P450 3A4
- Beware of other medications that use the same pathway(Nifedipine, Erythromycin, HIV inhibitors, Rifampin, BCP's, anticonvulsants(Tegretol, Pb, dilantin),antidepressants(Paxil, Serzone, TCA's)
- Metabolites do not cross the blood brain barrier
- First pass affect counts for low bioavailability
- Detected in blood, urine and hair
- Primarily excreted in the feces

Buprenorphine Pharmacology

- Average dose is 8-10 mg daily.
- Max dose 16 mg due to “ceiling” effect
- Dosing can be less than once a day such as 3 times per week
- Administered sublingually due to poor oral bioavailability
- Avoid giving first dose when patient has recently used opioids
- Ideally time period of 12-24 hours when no opiates have been used should occur before receiving the first dose of buprenorphine



Buprenorphine Preparations

- Subutex- buprenorphine
- Suboxone-buprenorphine/naloxone in 4:1 ratio(tablet or film)
- Naloxone is to decrease diversion to IV abuse
- If injected will precipitate withdrawal in opioid dependent person
- Naloxone only effective if given parenterally
- 2013-subutex and suboxone tablet not available

Buprenorphine Side Effects

- May cause elevated liver function tests
- Respiratory depression
- Overdose
- Teratogenesis
- Precipitated withdrawal
- Cognitive psychomotor effects
- Sweating
- Constipation



Respiratory Depression

- Unlike full mu agonists buprenorphine overdose does not appear to produce lethality through respiratory depression
- Buprenorphine has been shown to have a ceiling effect
- Higher doses do not produce additional mu agonist effects
- Risk of death associated with abuse of benzodiazepines.

Opioid Antagonist

- Naltrexone
 - Blocks agonist effects
 - Prevents impulsive use of drugs
 - Oral Naltrexone 50 mg a day, 100 mg every 2 days, 150 mg every 3rd day
 - Potential side effects include hepatotoxicity
 - Monitor liver function studies every 3-6 months
 - Biggest issue is lack of compliance
 - Injectable Naltrexone is Vivitrol – 380 mg per month; decreased hepatotoxicity; improves adherence
 - Some benefit for patients with other comorbid substance disorders (alcohol)