OPIOID ADDICTION:
FROM POWDER TO PILL

• The United States is experiencing an epidemic of heroin addiction and a sharp rise in opiate over-dose death. Contrary to addicts being introduced to opiate addiction through street heroin, 75% of new addicts became addicted through prescription opiates. When the OxyContin becomes too expensive ($80/pill), people switch to the cheaper street heroin ($5-10/hit).
OPIOID ADDICTION:  
FROM POWDER TO PILL

• Heroin use more than doubled among young adults ages 18–25 in the past decade.

• More than 9 in 10 people who used heroin also used at least one other drug.

• 45% of people who used heroin were also addicted to prescription opioid painkillers.
CRUDE LATEX
OPIOID ADDICTION: FROM POWDER TO PILL

• OVERVIEW
  • INTRODUCTION
  • OPIOIDS
  • OPIOID RECEPTORS
  • OPIOID ADDICTION
  • TREATMENT OF DEPENDENCE
    • PHARMACOLOGICAL
    • PSYCHOTHERAPEUTIC
INTRODUCTION

• "If we could sniff or swallow something that would, for five or six hours each day, abolish our solitude as individuals, atone us with our fellows in a glowing exaltation of affection and make life in all its aspects seem not only worth living, but divinely beautiful and significant, and if this heavenly, world-transfiguring drug were of such a kind that we could wake up next morning with a clear head and an undamaged constitution-then, it seems to me, all our problems (and not merely the one small problem of discovering a novel pleasure) would be wholly solved and earth would become paradise."

• ALDOUS HUXLEY, 1894 - 1963
VAPOR-OL

VAPOR-OL TREATMENT No. 6
Contains not more than 40 per cent alcohol.
Opium, 3 grains to each fluid ounce.

For Asthma and other Spasmodic Affections.

Price: 50 cents

Prepared expressly for
OPIOIDS

- Morphine
- Codeine
- Thebaine
- Diacetylmorphine (Heroin)
- Hydrocodone (Vicodin)
- Oxycodone (Oxycontin)
- Oxymorphone (Opana)
- Hydromorphone (Dilaudid)

Naturally occurring opioids—also called opiates

Semi-synthetic opioids
OPIOIDS

- Naturally occurring in poppy
  - Morphine
  - Codeine
- Semi-synthetic derived from morphine and codeine
  - Heroin
  - Oxycodone
    - Tylox
    - Percodan
    - OxyContin
OPIOIDS

• Semi-synthetic
  • Oxymorphone
    • Dilaudid
    • Numorphinan
  • Hydrocodone
    • Lortab
    • Vicodin
  • Buprenorphine

• Synthetics
  • Methadone
  • Propoxyphene
  • Lomotil
OPIOIDS

**Partial agonist**
- Buprenorphine
  (e.g. for respiratory depressive effect)

**Pure agonist**
- Hydromorphone
- Fentanyl
- Methadone
- Pethidine
- Oxycodone
- Morphine
- Piritramide
- Buprenorphine
  (e.g. for analgesic effect in man)

**Agonist / Antagonist**
- Nalbuphine
- Pentazocine

**Antagonist**
- Naloxone
- Naltrexone
HEROIN

• Pure heroin is a white powder with a bitter taste that predominantly originates in South America and, to a lesser extent, from Southeast Asia, and dominates U.S. markets east of the Mississippi River. “Black tar” heroin is sticky like roofing tar or hard like coal and is predominantly produced in Mexico and sold in U.S. areas west of the Mississippi River.
July 23, 2014, the U.S. Food and Drug Administration approved Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride extended-release tablets), an extended-release/long-acting (ER/LA) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment. Targiniq ER is the second ER/LA opioid analgesic with FDA-approved labeling describing the product’s abuse-deterrent properties consistent with the FDA’s 2013 draft guidance for industry.
Physical Appearance
New Formulation vs. Original Formulation
40 mg Tablets

New formulation

Original formulation
OXYCONTIN

ORIGINAL FORMULATION

NEW FORMULATION
ACETYL FENTANYL

• Acetyl fentanyl is an opiate analgesic with no recognized medical use. It is five to 15 times stronger than heroin. Users typically use it intravenously as a direct substitute for heroin or pharmaceutical-grade opioids, though many are unaware that what they are consuming is not plain heroin

OPIOIDS

- PHARMACEUTICAL COMPANIES HAVE TRIED TO BREAK THE ADDICTION CYCLE EVER SINCE THERE WERE PHARMACEUTICAL COMPANIES
  - 1898 Bayer Pharmaceutical introduced heroin
  - 1915 Roche introduced Pantopon (made from opium poppy but billed as less addictive than morphine because it contained multiple compounds from the plant)
  - 1930’s desomorphine was the new non-addictive analgesia (see Krokodil)
  - 1996 OxyContin introduced as a less addictive opioid (new version turns into a gel when ground up)
OPIOIDS

• PHARMACEUTICAL COMPANIES HAVE TRIED TO BREAK THE ADDICTION CYCLE EVER SINCE THERE WERE PHARMACEUTICAL COMPANIES

• Drugs in early human trials are based upon the principle that slower entry into the brain reduces addiction risk. New versions of oxycodone and hydrocodone are attached to molecules that prevent them from having any effect unless they first pass through the digestive system.

• A drug called plus-naltrexone acts on immune cells in the brain. When opioid drugs activate LTR4 receptors on immune cells they cause inflammation that exacerbate the pain that pain killers are meant to diminish and also stimulate pleasure-related nerve cells. Blocking LTR4 might reduce overall pain reducing the need for more and more drug and also lowering the “high.”
OPIOIDS

• PHARMACEUTICAL COMPANIES HAVE TRIED TO BREAK THE ADDICTION CYCLE EVER SINCE THERE WERE PHARMACEUTICAL COMPANIES

• UMB 425 is in the animal stage of development and uses compounds that simultaneously activate the pain relief receptor called mu while blocking one that modulates its effects-delta. This prevents delta receptors from adjusting to the high levels of mu activation leading to tolerance.

OPIOIDS

• RECREATIONAL OPIOID USERS
  • Eight (8) to twenty-three (23) percent become addicted (same with heroin as with all of the pain pills)
  • Less than one (1) percent of people with no prior addiction history become addicted to prescription painkillers
  • Opioids feel alluring, dreamy and blissful to about thirty (30) percent of the people who take them
OPIOIDS

- RECREATIONAL OPIOID USERS
  - Of this thirty (30) percent one-half say “That was so good; I better stay away.” The other half- like “kissing God” as Lenny Bruce described the heroin high.
  - Fifteen (15) percent strongly dislike them
  - The other one-half had a mixed experience where they could “take it or leave it”

http://goo.gl/nkeqSb
OPIOIDS

• ABOUT 50 % OF OPIOID ADDICTS HAVE CO-OCCURRING DISORDERS
  • Anxiety, depression and post-traumatic stress disorder are common
  • The more childhood loss and trauma someone has experienced the higher the risk of addiction.
  • Boys who experienced six or more childhood traumas had a 46 times greater risk of becoming an IV addict (http://goo.gl/6KalC- ACE Study)
• Prescription opioid-based may increase the risk for serious birth defects of the baby's brain, spine, and heart, as well as preterm birth when taken during pregnancy. Use of these medications also can cause babies to suffer withdrawal symptoms when born, a condition known as neonatal abstinence syndrome or NAS.

• Medical consequences of chronic injection use include scarred and/or collapsed veins, bacterial infections of the blood vessels and heart valves, abscesses (boils), and other soft-tissue infections. Many of the additives in street heroin may include substances that do not readily dissolve and result in clogging the blood vessels that lead to the lungs, liver, kidneys, or brain. This can cause infection or even death of small patches of cells in vital organs. Immune reactions to these or other contaminants can cause arthritis or other rheumatologic problems.
OVERDOSE

• Researchers have found that prescription opioids, including methadone, were involved in 67.8 percent of -- or over 135,971 visits to -- emergency department visits in 2010 in the U.S., with the highest proportion of opioid overdoses occurring in the South.

• Every day in the U.S., 114 people die due to drug overdose. It is the leading cause of accidental death for adults in the U.S.
OVERDOSE

- Acute benzodiazepine intoxication was recorded in 22.2 percent of all overdose patients.
- Prescription opioids' involvement in 67.8 percent of all overdoses, the findings showed that heroin played a role in 16.1 percent of all overdoses; unspecified opioids were involved in 13.4 percent; and multiple opioid types were involved in 2.7 percent.

EVZIO FOR OVERDOSE

• In April 2014, the U.S. Food and Drug Administration (FDA) approved a naloxone hand-held auto-injector called Evzio, which rapidly delivers a single dose of naloxone into the muscle or under the skin, buying time until medical assistance can arrive. Since Evzio can be used by family members or caregivers, it greatly expands access to naloxone. NIDA and the FDA are working with drug manufacturers to support the development of nasal spray formulations of this life-saving medication.
OPIOID RECEPTORS

• Mid 1950’s scientists tried mixing radioactive morphine with brain membranes
  • Failed to demonstrate presence of specific opiate receptors
  • Opiate receptors are sparse – 1/1,000,000 of brain’s weight
  • Charged molecules also could engage in non-specific binding at other sites

• 1973 – Pert, Snyder et al, isolated opiate receptors in the brain
  • Used radio-labeled opiate antagonist, naloxone
OPIOID RECEPTORS

• The opioid system controls pain, reward and addictive behaviors. Opioids exert their pharmacological actions through three opioid receptors, mu, delta and kappa whose genes have been cloned (Oprm, Oprd1 and Oprk1, respectively). Opioid receptors in the brain are activated by a family of endogenous peptides like enkephalins, dynorphins and endorphin, which are released by neurons. Opioid receptors can also be activated exogenously by alkaloid opiates, the prototype of which is morphine.
• The finding that morphine's analgesic and addictive properties are abolished in mice lacking the mu-opioid receptor has unambiguously demonstrated that mu-receptors mediate both the therapeutic and the adverse activities of this compound (Matthes 1996). Importantly, a series of studies has shown that the reinforcing properties of alcohol, cannabinoids, and nicotine -- each of which acts at a different receptor -- are also strongly diminished in these mutant mice. The genetic approach therefore highlights mu-receptors as convergent molecular switches, which mediate reinforcement following direct (morphine) or indirect activation (non-opioid drugs of abuse; see Contet 2004).


• Endogenous opioid binding to mu-receptors is furthermore hypothesized to *mediate natural rewards and has been proposed to be the basis of infant attachment behavior* (Moles 2004).

OPIOID RECEPTORS

• Opiate receptors are distributed in distinct patterns in the brain

• Highest densities of opiate receptors are concentrated in areas involved in pain pathways

• Dense in *substantia gelatinosa* of the spinal cord, where sensory nerves make 1st contact

• Also concentrated in the medial area of the thalamus - conveys sensory input associated with deep pain

• Dense clusters in the *periaqueductal* gray zone of the midbrain – integrates pain information

• Dense in the limbic system – a major regulator of emotional behavior – explains euphoria
OPIOID RECEPTORS

The distribution of opiate receptors in the brain of a guinea pig. Red areas = highest density; yellow = moderate density, blue, purple & white = low density.
OPIOID RECEPTORS
REWARD PATHWAY

Ventral Tegmental Area

Nucleus Accumbens

Arcuate Nucleus

Dopamine

Opioid Peptides

Naltrexone
OPIOID RECEPTORS

- Four types of opiate receptors identified: \textit{mu} 1, \textit{mu} 2, \textit{kappa} and \textit{delta} receptors.
- Opioids exert their effects by activating one or more of these receptors.
- The actions of opioids on receptors can vary depending on the location within the body
  - A particular opioid may act as an antagonist at the \textit{kappa} receptors in the brain, but as an agonist at the same type of receptors in the large intestines.
- Tolerance to activation of one receptor type does not necessarily lead to tolerance to the others.
- Sometimes analgesic medication is prescribed to activate only certain receptors
OPIOID RECEPTORS

- *Mu2* receptors are involved in respiratory depression and intestinal constipation.
- Analgesia involves activation of *Mu1* receptors in the brain and *kappa* receptors in the spinal cord.
- The contribution of *delta* receptors to analgesia is unclear, and may be more closely related to euphoria.
- Activation of *Mu1*, *Mu2*, and *delta* receptors close potassium channels, while *kappa* receptors are linked to calcium channels.
The list of brain receptor targets for opiates reads like a fraternity: Mu Delta Kappa. The mu opioid receptor is the primary target for morphine and endogenous opioids like endorphin, whereas the delta opioid receptor shows the highest affinity for endogenous enkephalins. The kappa opioid receptor is very interesting, but the least understood of the opiate receptor family.
OPIOID RECEPTORS

• The mu opioid receptor received the most attention in alcoholism research. Naltrexone, a drug approved by the U.S. Food and Drug Administration for the treatment of alcoholism, acts by blocking opiate action at brain receptors and is most potent at the mu opioid receptor. In addition, research has suggested that a variant of the gene that codes for the mu opioid receptor (OPRM1) may be associated with the risk for alcoholism and the response to naltrexone treatment.
However, naltrexone also acts at the kappa opioid receptor and it has not been clear whether this effect of naltrexone is relevant to alcoholism treatment. A growing body of research in animals implicates the KOR in alcoholism. Stimulation of the kappa opioid receptor (KOR), which occurs with alcohol intake, is thought to produce unpleasant and aversive effects. This receptor is hypothesized to play a role in alcohol dependence, at least in part, by promoting negative reinforcement processes.
OPIOID RECEPTORS

• In other words, the theory postulates that during development of alcohol dependence, the KOR system becomes overstimulated, producing dysphoria and anhedonia, which then leads to further alcohol seeking and escalation of alcohol intake that serves to self-medicate those negative symptoms.

• They found that the KOR system is dysregulated in the amygdala of alcohol-dependent rats, a vital brain region with many functions, including regulation of emotional behavior and decision-making. Chronic alcohol consumption is known to cause neuroadaptations in the amygdala.
OPIOID RECEPTORS

• Found increased dynorphin A and increased KOR signaling in the amygdala of alcohol-dependent rats. When the rats were in acute alcohol withdrawal, the researchers administered different drugs, each of which target the KOR system in precise ways, directly into the amygdala. Using this site-specific antagonism, they observed that alcohol dependence-related KOR dysregulation directly contributes to the excessive alcohol consumption that occurs during withdrawal.
• Pharmacological compounds that alleviate the negative emotional / mood states that accompany alcohol withdrawal, by attenuating the excessive signaling in the dynorphin / kappa-opioid receptor system, should result in enhanced treatment compliance and facilitate the transition away from alcohol dependence."

DOI: [10.1016/j.biopsych.2013.03.014](http://10.1016/j.biopsych.2013.03.014)
OPIOID ADDICTION

• TWO STAGE MODEL OF ADDICTION

  • **STAGE 1**- OCCASIONAL DRUG USE BECOMES INCREASINGLY CHRONIC AND UNCONTROLLED. THE NEUROBIOLOGICAL SOURCE OF THESE SYMPTOMS IS DRUG-INDUCED DEREGULATION OF THE BRAIN’S REWARD CENTER
    • DOPAMINE
  
  • **STAGE 2**- ADDITIONAL FEATURES INCLUDE WITHDRAWAL SYMPTOMS, PERSISTENT VULNERABILITY TO RELAPSE WITH ALTERATIONS IN DECISION MAKING AND OTHER COGNITIVE PROCESSES
    • DRUG-INDUCED SIGNALS BY NEUROTRANSMITTER GLUTAMATE FROM BRAIN AREAS PRIMARILY ASSOCIATED WITH JUDGMENT (PFC) TO NAc
OPIOID ADDICTION

• Addiction is characterized by a transition from strategic drug-seeking (i.e., where a decision is made to try a drug to generate a desired effect) to habitual drug-seeking (i.e., where the behavior is triggered by the availability of drugs, particularly in contexts associated with drug use). Habitual drug use is less dependent than strategic use on whether the person actually enjoys the effects of the drug or whether there are negative subjective effects or problems associated with taking the substance.
OPIOID ADDICTION

• The transition from strategic to habitual drug-seeking is associated with changes in the brain, where dopamine systems are involved in shifting the representation of drug-taking in the striatum region of the brain from the lower (ventral) part of the striatum, implicated in reward, to the higher (dorsolateral) striatum, implicated in habits.
OPIOID ADDICTION AND THE STRIATUM

• The basal ganglia are nestled inside cortex, surrounding the thalamus. The striatum (part of the basal ganglia circuitry) is composed of the putamen, caudate, and nucleus accumbens. Other important parts of the basal ganglia are the globus pallidus (which has an internal and an external segment, GPi and GPe respectively) and the subthalamic nucleus (STN).
CORTICOSTRIATAL CIRCUITRY
CORTICOSTRIATAL CIRCUITRY

• Impairment could arise from two general pathologies in corticostriatal circuitry: addicts could have pathologically strengthened drug-seeking behaviors, or they could have pathological impairments in the capacity to control drug-seeking behaviors. These two possibilities are not mutually exclusive.

• Corticostriatal circuitry has two subcircuits: the limbic subcircuit, which comprises brain regions such as the prefrontal cortex, the amygdala, the nucleus accumbens (NAc) and the ventral tegmental area (VTA); and the motor subcircuit, which contains the motor cortex, the dorsal striatum and the substantia nigra.
CORTICOSTRIATAL CIRCUITRY
CORTICOSTRIATAL CIRCUITRY

• Corticostriatal projections are responsible not only for generating learnt, well-established behaviors such as in drug taking, but also for changing behaviors in response to a variable environment, and thereby generating new adaptive behaviors.

• Addicts have difficulty modulating drug-seeking behaviors with information that should suppress the behavior.
CORTICOSTRIATAL CIRCUITRY

- The NAc serves as a gateway through which information that has been processed in the limbic subcircuit gains access to the motor subcircuit.

- Relapse to compulsive drug seeking arises from an impaired ability of the limbic subcircuit to effectively process and/or use the negative environmental contingencies associated with relapse. The result is that behavior is dominated by the previously learnt, well-established drug-seeking strategies.
OPIOID ADDICTION

• ADDICTION LOOP

  • *First step is liking the drug or at least finding it eases emotional problems*
  • Endorphins and enkephalins relieve stress by making you feel warm, safe, fed and loved
  • If you are a trauma survivor these drugs are especially appealing reinforcing the connection between the drug and life’s fundamental comforts
OPIOID ADDICTION

- ADDICTION LOOP
  
  - Secondly, another feedback loop begins involving the unconscious brain and HOMEOSTASIS

  - When opioid levels get too high the brain kicks out cortisol reducing dopamine levels and causing a feeling or being irritable and discontent

  - The Locus Coeruleus (LC) puts out more norepinephrine to counteract the CNS depression
OPIOID ADDICTION

• ADDICTION LOOP

  • *More drug needed to get the same effect*-TOLERANCE
  • Now one needs the drug just to feel normal
  • Without the drug one is overwhelmed by negative emotions and an acute abstinence syndrome
  • Dopamine replaced by glutamate and drug seeking as the predominant driving force
OPIOID ADDICTION

• Two groups of seven patients in residential treatment for dependence on opioid pain medications. One group had recently gone through medically assisted opioid withdrawal -- within the past one to two weeks. The other group was in extended care, and had been drug-free for two to three months. A group of normal controls were studied for comparison.
OPIOID ADDICTION

- After drug withdrawal, many people with opioid dependence have "persistent changes in the reward and memory circuits" -- they may experience heightened "rewards" or "pleasure" in response to drugs and related stimuli, but greatly reduced responses to naturally pleasurable stimuli (such as good food, or friendship).
OPIOID ADDICTION

- Opiates are potent stimulators of the brain's reward system; over time, the brain adapts to the high level of stimulation provided by opiates, and naturally rewarding stimuli can't measure up. Such dysregulation of the natural reward system may contribute to the high risk of relapse during recovery.
OPIOID ADDICTION

• In brain activity studies, patients with recent drug withdrawal showed heightened responses to drug-related cues, such as pictures of pills. In the extended-care patients, these increased responses to drug cues -- in a region of the brain called the prefrontal cortex, involved in attention and self-control -- were significantly reduced.
OPIOID ADDICTION

• Patients who had recently withdrawn from opiates also had high levels of the stress hormone cortisol. In the patients who had been drug-free for a few months, cortisol levels were somewhat reduced, although not quite as low as in healthy controls. The recently withdrawn group also had pronounced sleep disturbances, while sleep in the extended care group was similar to controls.
OPIOID ADDICTION

• Brain and hormonal responses to drug cues and natural rewards, as well as sleep disturbances -- were correlated with abstinence time. The more days since the patient used drugs, the lower the abnormal responses

Scott C. Bunce, Jonathan D. Harris, Edward O. Bixler, Megan Taylor, Emilie Muelly, Erin Deneke, Kenneth W. Thompson, Roger E. Meyer. Possible Evidence for Re-regulation of HPA Axis and Brain Reward Systems Over Time in Treatment in Prescription Opioid-Dependent Patients. Journal of Addiction Medicine, 2014; 1 DOI: 10.1097/ADM.00000000000000087
# Addiction and Recovery

<table>
<thead>
<tr>
<th>Recovery</th>
<th>Prefrontal Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>MIDBRAIN</td>
</tr>
<tr>
<td></td>
<td>LIMBIC</td>
</tr>
<tr>
<td>Acute Abstinence</td>
<td>BRAIN STEM</td>
</tr>
<tr>
<td></td>
<td>LOCUS COERULEUS</td>
</tr>
</tbody>
</table>
SPECT SCAN-METHADONE BRAIN WITH PRIOR HEROIN

Healthy Brain

7 years Methadone use, some prior Heroin

copyright 2012 Rick Sponsugle, M.D.
TREATMENT OF DEPENDENCE

• PHARMACOTHERAPY
  • Methadone
  • Buprenorphine
  • Naltrexone/naloxone

• PSYCHOLOGICAL/PSYCHOTHERAPY

• EDUCATION

• WELLNESS

• POST-ACUTE WITHDRAWAL (PAW)
OPIOID ABSTINENCE SYNDROME

• Increased anxiety during subjective withdrawal followed by...

• Increased Noradrenergic activity

• Timing influenced by half-life

• Typically begins 10-12 hours after last dose

• Peaks at 2-3 days

• Lasts 7-10 days
OPIOID ABSTINENCE SYNDROME

• Addicts Experience
  • A hyper-aroused state ("fight or flight")
    • Increased (vital signs):
      • Heart rate
      • Blood pressure
      • Restlessness
      • Tremors
      • Hypervigilence
      • Dilated pupils
OPIOID ABSTINENCE SYNDROME

• Addicts experience

• Worst case of flu imaginable
  • Nausea and vomiting
  • Runny nose
  • Cold (cannot get warm), shivering
  • Cramping
  • Tearing
  • Diarrhea
OPIOID ABSTINENCE SYNDROME

OBJECTIVE SIGNS:
1. Pulse 10 bpm or more over baseline or more than 90 if no history of tachycardia and baseline unknown

2. Systolic blood pressure 10 mm Hg or more above baseline or greater than 160/95 in nonhypertensive patients

3. Dilated pupils

4. Gooseflesh, sweating, rhinorrhea, or lacrimation
CLONIDINE AND LOFEXIDINE

• For opiate detoxification, methadone is not always available due to legal limitations and buprenorphine may be undesirable because it is a partial opiate agonist. Clonidine, an $\alpha_2$-agonist, reverses opiate withdrawal by acting on autoreceptors producing presynaptic inhibition of locus coeruleus activity. This effectively reduces the large adrenergic component of opioid withdrawal. Lofexidine is a similarly acting medication but does not produce hypotension.
• In beginning clonidine treatment, the method of Kleber (1985) is worth following: an initial dose of 0.1 mg of clonidine should be given to assess the patient's tolerance of this approach. Hypotension, dizziness, sedation, and dry mouth are common adverse effects.
• If the initial dose is tolerated well by the patient, doses of 0.1–0.2 mg every 8 hours can be given during the early phases of opiate withdrawal, with increases to as high as 0.2–0.4 mg every 8 hours after 2–3 days. Blood pressure should be checked before each dose, and the dose should not be given if blood pressure is less than 85/55. Amelioration of withdrawal symptoms reaches a peak 2 or 3 hours after each dose. Muscle aches, irritability, and insomnia are not well suppressed by clonidine.
SYMPTOMATIC

- PRN meds for the first days.
  - Bentyl 10mgs. for abdominal cramps.
    - 30mgs. po q 4-6hours.
  - Imodium 2mgs. for diarrhea.
    - 1-2 caps after 1st observed stool.
    - Not to exceed 60 mgs. Per day.
  - Robaxin 750mgs. for muscle spasm or pain.
    - 1-2 q 6-8 hours.
- Phenobarbital
METHADONE

• Methadose, Dolophine
• The drug is currently a Schedule II and is available in oral solutions, tablets, and injectable forms. And although there is no one manufacturer responsible for producing methadone, the active ingredient is always the same: methadone hydrochloride
METHADONE

- Methadone is a synthetic, narcotic analgesic (pain reliever). Often used by and associated with the treatment of heroin addicts it is also used for other medical purposes such as pain relief. The drug shares many of the same effects and characteristics of morphine and acts in similar ways to it and other narcotic medications. Methadone has a gradual and mild onset of action reducing the intense euphoric effects experienced by insufflation and injection.
METHADONE

• Whereas the law of 1974 limited methadone to those who had been addicted for a year, the SAMSHA (2012, Tip 43) guidelines allow for those who are not physically dependent on opiates to receive methadone. While initially the goal was to wean patients off, SAMSHA (2012) advises directors of clinics when a patient requests a dosage reduction that they should “educate” the patients on the importance of staying on their Medication Assisted Treatment.
METHADONE

- There is no duration limit on MAT. Moreover, there is no longer a limit on dosage. Given that stress is a reliable precipitant to relapse in drug abusers, SAMSHA discusses increasing dosage during stressful times (see page 77, in SAMSHA’s Tip 43, Medication-Assisted Treatment).
METHADONE
METHADONE-DETOXIFICATION

• Methadone, a long-acting opiate, is used to treat withdrawal because of its superior pharmacokinetics (a long half-life). A short-acting drug like morphine would have to be given every few hours to block withdrawal, whereas methadone accomplishes this when given only twice a day. The initial methadone dose should be 10 mg orally, in liquid or crushed tablet form, so as to blind the patient to that dosage and subsequent dosages during detoxification.
METHADONE-DETOXIFICATION

• The patient should be evaluated every 4 hours, and an additional 10 mg of methadone should be administered if at least two of the four criteria of objective abstinence are met. Unless the patient is being withdrawn from high-dose methadone maintenance therapy, no more than 40 mg of methadone should be required in the first 24 hours.
• The total dose of methadone given in the first 24 hours should be considered the stabilization dose. This dose is then given the next day in two divided doses (e.g., 15 mg at 8:00 A.M. and 8:00 P.M.) in crushed or liquid form. It should be consumed under the direct observation of a staff member to avoid illicit diversion.
METHADONE-DETOXIFICATION

• The stabilization dose should then be reduced by 5 mg/day until the patient is completely withdrawn from the drug. A patient who is physically dependent on sedative drugs and opiates should continue taking the stabilization methadone dose without tapering until he or she is completely withdrawn from the sedative drug.
The Adventures of Methadone Man and Buprenorphine Babe
BUPRENORPHINE

• Subutex-Buprenorphine. sublingual (SL)
  • 2mg and 8mg tablets
• Suboxone-Buprenorphine/Naloxone SL tablets and film
• Zubsolv sublingual
• Bunavail buccal
• Partial agonist
  • Increasing dose does not increase effect like a full agonist
    • “Ceiling Effect”
THE SCIENCE OF RECOVERY: DOPAMINE (DA) TONE

• **EQUIVALENTS:**
  - Zubsolv 5.7/1.4 mg buccal equals Suboxone 8/2 mg SL
  - Bunavail 2.1/0.3 mg buccal equals Suboxone 4/1 mg SL
  - Bunavail 4.2/0.7 mg equals Suboxone 8/2 mg SL
  - Bunavail 6.3/1 mg buccal equals Suboxone 12/3 mg SL
PURE AGONISTS

Complete opioid agonists (e.g., heroin) fit the receptors almost perfectly and strongly stimulate them.
PARTIAL AGONIST

Partial opioid agonist (Buprenorphine) has a strong affinity for the receptors, but fits only partially. This prevents withdrawal symptoms and reduces or blocks the effects of other opioids. Buprenorphine
SUBOXONE SL TABLETS

SUBoxone
(buprenorphine HCl/naloxone HCl dihydrate)
SUBOXONE FILM
BUPRENORPHINE-AFFINITY AND DISSOLUTION

• Very high affinity for mu opioid receptor (pleasure and pain relief)

• Kappa-receptor antagonist
  • Kappa-receptor plays role in opposing the rewarding effect of drugs of abuse
    • Blocking this dysphoric effect elevates mood
    • Blocking may play role in analgesic effects

• Mu receptor will choose buprenorphine over other opioids

• Buprenorphine will displace other opioids
BUPRENORPHINE-AFFINITY AND DISSOLUTION

• Slow dissolution from mu receptor
  • Half-life on receptor is 34-36 hrs
  • Heroin on and off receptor in millisecond
  • At Buprenorphine dose of 16mg almost no binding to other opioids

• Street use
  • Used on street for “bridging” and often combined with benzodiazepines
  • “Bupe” combined with promethazine (phenothiazine with antihistaminic effect-Phenergan), hydroxyzine (antihistamine and CNS depressant-Atarax and Vistaril), and benzodiazepines are “new heroin substitute”
BUPRENORPHINE/NALOXONE

• Buprenorphine equally effective as 60 mg of Methadone per day
• If patient needs 80-100 or more mgs of Methadone to be comfortable, Buprenorphine probably will not work
• With client dependent on short-acting opioids
  • Instruct client to abstain for 12-24 hours
  • Need to be in mild withdrawal before first dose
BUPRENORPHINE

• Buprenorphine also may be an excellent agent to facilitate detoxification from illicit opioids and abused prescription opioids. Although it has a relatively short plasma half-life (about 4 to 6 hours), buprenorphine has a long duration of action resulting from its high affinity for and correspondingly slow dissociation from the mu receptor
Another feature of buprenorphine is that it can be used on a daily or less-than-daily basis. The interdosing interval is extended by doubling or tripling the daily dose to permit alternate-day or thrice weekly dosing which is possible because, although larger doses do not increase buprenorphine’s agonist activity, they do lengthen its duration of action.
NALTREXONE/NALOXONE

- Naltrexone (Revia, Vivitrol, Depade)
  - Pure antagonist
  - Poor compliance
    - Less than 10% for street addicts
  - Better compliance
    - Healthcare professionals
    - Parole/Probation
  - Suspension with q30d administration increases compliance and reliability of drug
NALTREXONE/NALOXONE

• A special formulation of Naltrexone, which is designed to release slowly over a 6-12 week period. It is placed under the patient's skin and so it is effective and does not allow the patient to forget or skip their medicine. We highly recommend it because it is so effective. There are some potential side effects with the Naltrexone Implant including infection, irritation or inflammation and sometimes even some skin breakdown over the implant site.
VIVITROL is given as an intramuscular (IM) gluteal injection every 4 weeks or once a month
- VIVITROL should not be given subcutaneously or in the adipose layer
- VIVITROL must not be administered intravenously
- VIVITROL should be administered by a healthcare professional, into alternating buttocks each month
- VIVITROL should be injected into the upper outer quadrant of the buttock, deep into the muscle—not the adipose.
Opioid binding to the μ-opioid receptor
VIVITROL
VIVITROL
VIVITROL microspheres

Microsphere

Naltrexone

Microsphere

Naltrexone
EMERGENCY PAIN MANAGEMENT

VIVITROL antagonizes the effects of opioid-containing medications. Patients receiving VIVITROL may not benefit from opioid-containing medications.

- Patients should be advised to carry a patient alert card that informs medical personnel they are taking VIVITROL.
- A suggested plan for pain management is:
  - Regional analgesia
  - Use of non-opioid analgesics
- In an emergency situation requiring opioid analgesia, the amount of opioid required may be greater than usual and the resulting respiratory depression may be deeper and more prolonged.
  - Such patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure.
  - The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.
  - A rapidly acting opioid analgesic that minimizes the duration of respiratory depression is preferred.
  - Patients should be closely monitored by trained personnel in a setting equipped for cardiopulmonary resuscitation.
PHARMACOLOGICAL

• Those who received counseling plus methadone maintenance in prison with continued treatment in the community upon release were significantly less likely to be opioid- or cocaine-positive according to urine drug testing than those who received counseling only with passive referral or those who received counseling in prison with transfer to methadone upon release.

A study of Vivitrol among people addicted to heroin in Russia found a median 90% rate of opioid-free urines in the group receiving the medication versus 35% among controls; a 50% reduction in opioid craving versus no change for placebo; and a 75% longer retention in treatment for Vivitrol patients versus the control group.
PHARMACOLOGICAL

• Methadone may prove to be an effective treatment for cocaine as well as opioid abuse, if the results of a recent study with rats, funded by NIDA and the Canadian Institutes of Health Research, can be replicated and applied to people

• Methadone might have unexploited potential as a medication to treat cocaine abuse in patients both with and without histories of opioid abuse
PHARMACOLOGICAL

• The animals' cocaine seeking dropped in response to methadone given in doses that produce blood levels equivalent to those therapeutically effective for opioid addiction. Methadone at more than twice that dose abolished cocaine seeking.
PHARMACOLOGICAL

![Graph showing the effect of methadone dose on time associated with cocaine (20 mg/kg) and not associated with cocaine.](graph.png)
The team first tested whether methadone would suppress the normal tendency of rats to seek cocaine once they have been repeatedly exposed to the stimulant. To prepare their animals for the test, the researchers put some on methadone (20 or 55 mg/kg/day) via implanted mini-pumps and gave others saline by the same route.
During these regimens, for 2 weeks, the researchers trained the animals to associate one designated chamber with cocaine injections and another with saline injections. Daily for 3 days, they injected each animal once with cocaine (1, 5, or 20 mg/kg) and once with saline. Immediately after each cocaine injection, they placed the animal in the first chamber; after each saline injection, they placed it in the second chamber.
PHARMACOLOGICAL

- On the day of the test, the researchers placed each rat between the two chambers without giving it any cocaine or saline, and monitored where it went. Among the animals given the highest dose of cocaine, those that received no methadone showed a strong preference for the cocaine-associated chamber; those that received the lower methadone dose showed less preference; and those maintained on the higher methadone dose, no preference at all, indicating a total loss of motivation to seek cocaine (see graph).
In the second experiment, they first trained rats to press a lever for cocaine, then implanted mini-pumps: Eight animals received 30 mg/kg/day of methadone, while another six received only saline. The rats were allowed to self-administer cocaine, but the system was programmed to require progressively more presses before it would release each successive infusion.
The eight methadone-treated animals gave up pressing the cocaine lever after six presses, on average, whereas the rats that did not receive methadone continued to press it more than 30 times to receive a single dose (see graph).
PHARMACOLOGICAL

![Graph showing responses over continuous availability and increasing-effort tests for inactive infusion and 30 mg/kg/day methadone.]
PHARMACOLOGICAL

• In the experiments, rats exposed to three injections of 5 or 20 mg/kg doses of cocaine were found to have more mu-opioid receptor messenger RNA (mRNA)—an indicator of receptor production rates—than animals exposed to three injected doses of the drug at 1 mg/kg. These elevations were less pronounced, however, in rats that were being maintained on 20 mg/day of methadone at the time of the cocaine exposures. Moreover, rats exposed to cocaine while being maintained on 55 mg/kg/day of methadone had mu-opioid mRNA levels that were indistinguishable from those of rats that received no cocaine.
PHARMACOLOGICAL

• From these results, the researchers hypothesize that methadone probably blocks cocaine seeking by inhibiting cocaine-induced enhancement of mu opioid receptor production.

• People who are dependent on both heroin and cocaine respond well to methadone because methadone reduces the number of mu-opioid receptors in the reward system of their brains or whether they respond because cocaine depletes endorphins and methadone brings the endorphins back.
• When rats were required to respond with more and more lever presses to receive cocaine, the six animals infused with an inactive substance dramatically increased their average number of responses, while the eight animals infused with methadone kept their responses at the same level as their earlier responses to continuously available cocaine.
PHARMACOLOGICAL

• In the absence of methadone, each rat in a group of eight spent, on average, more time in a compartment that it associated with cocaine than in one not associated with the drug. When implanted mini-pumps delivered high-dose methadone to the rats, there was no significant difference between the times spent in the two compartments.

CLONIDINE AND STRESS-INDUCED RELAPSE

• Acute stress is a cause of relapse
• Animal studies suggest alpha-2 adrenoceptor agonists (ex.-clonidine) specifically reduce stress-induced relapse compared to relapse induced by other factors (i.e. “cues”)
• Opioid patients who had demonstrated a successful response to buprenorphine (5-6 weeks of abstinence) were randomly assigned to two groups
CLONIDINE AND STRESS-INDUCED RELAPSE

• Patients were continued on buprenorphine for 14 weeks. One half of the patients were also place on clonidine while the other half were not.

• Patient drug use was monitored and daily reports (4 times per day at random) of patients mood and craving were electronically monitored in real time.
CLONIDINE AND STRESS-INDUCED RELAPSE

• Clonidine reduced the temporal association between stress and relapse.

First consideration:

*Is the patient a candidate for rehabilitation or do they need habilitation?*
PSYCHOLOGICAL

If Habilitation
Emphasis is on:

*Neuroplastic development of the prefrontal cortex*

*Staff as healthy family*

*Discharge planning*
PSYCHOLOGICAL

Second consideration:

Is there presence or absence of a recovery-oriented environment and/or support system?
PSYCHOLOGICAL

• Managing feelings
  • *Psychoeducation* - “The opioid experience”
  • *Emotional management strategies such as cognitive-behavioral options*
  • *Varieties of Contemplative Experiences*

• Wellness
• Spiritual
• Self-help
<table>
<thead>
<tr>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABNORMALLY NORMAL</td>
</tr>
<tr>
<td>SUBJECTIVE W/DRAWAL</td>
</tr>
<tr>
<td>ACUTE ABSTINENCE SYN.</td>
</tr>
</tbody>
</table>
THE OPIOID EXPERIENCE

- Parasympathetic Nervous System
- Dissociation mediated by endorphins/enkephalins
- In the Abnormally Normal stage of the experience the addict is functional and experiences little or no negative emotions
- During Subjective Withdrawal the negative emotions come back
- In early recovery when flooded with emotions the addict may leave AMA
VARIETIES OF CONTEMPLATIVE EXPERIENCE

• FOCUSED ATTENTION:
  • Typically concentrates on the in-and-out cycle of breathing

• MINDFULNESS:
  • Also called open-monitoring meditation, mindfulness entails observing sights, sounds and other sensations, including internal body sensations and thoughts, without being carried away by them.

• LOVING KINDNESS AND COMPASSION
  • Cultivation of a feeling of benevolence directed toward others
FOCUSED ATTENTION

• FOUR PHASES OF A COGNITIVE CYCLE:
  • An episode of mind wandering
  • A moment of becoming aware of the distraction
  • A phase of reorienting attention
  • Resumption of focused attention
• Each of the four phases involve different brain networks
**Focused Attention**
This practice typically directs the meditator to concentrate on the in-and-out cycle of breathing. Even for the expert, the mind wanders, and the object of focus must be restored. A brain-scanning study at Emory University has pinpointed distinct brain areas that become involved as attention shifts.

**Mindfulness**
Also called open-monitoring meditation, mindfulness entails observing sights, sounds and other sensations, including internal bodily sensations and thoughts, without being carried away by them. Expert meditators have diminished activity in anxiety-related areas, such as the insular cortex and the amygdala.

**Compassion and Loving Kindness**
In this practice, the meditator cultivates a feeling of benevolence directed toward other people, whether friend or enemy. Brain regions that flare up when putting oneself in the place of another—the temporoparietal junction, for instance—show an increase in activity.

1. **Mind Wandering**
Imaging of a meditator in the scanner illuminates the posterior cingulate cortex, the precuneus and other areas that are part of the default-mode network, which stays active when thoughts begin to stray.

2. **Distraction Awareness**
The salience network, which includes the anterior insula and the anterior cingulate cortex, underlies the meditator's awareness of the distraction. Once cognizant that the mind has roved, the volunteer pushes a button to let researchers know what happened.

3. **Reorientation of Awareness**
Two brain areas—the dorsolateral prefrontal cortex and the inferior parietal lobe—are among those that help to disengage attention from a distraction to refocus on the rhythm of the inhalations and exhalations.

4. **Sustaining Focus**
The dorsolateral prefrontal cortex stays active when the meditator directs attention on the breath for long periods.
FOUR PHASES OF A COGNITIVE CYCLE:

• *An episode of mind wandering*
  
  • Increased activity in the default-mode network (DMN) which includes areas of the medial prefrontal cortex, the posterior cingulate cortex, the precuneus, the inferior parietal lobe and the lateral temporal cortex. The DMN plays a role in updating and building internal models of the world

• *A moment of becoming aware of the distraction*
  
  • The salience network involving the anterior insula and the anterior cingulate cortex. This network regulates subjectively perceived feelings which might lead to being distracted from a task. Has a role in detecting novel events and in switching activity among neurons
FOUR PHASES OF A COGNITIVE CYCLE:

• A phase of reorienting attention
  • Engages the dorsolateral prefrontal cortex (DLPC) and the lateral inferior parietal lobe that “takes back” one’s attention by detaching it from any distracting stimulus

• Resumption of focused attention
  • The DLPC continues to maintain a high level of activity as the attention is focused on the breath
MINDFULNESS

• *Attentional blink* reflects the limits of the brain's ability to process two stimuli presented to the observer at close intervals
• Mindfulness training reduces the propensity to “get stuck” on the first stimuli
• P3b brain waves used to assess how attention is allocated
• In pure awareness the mind is calm and relaxed not focused on anything in particular yet vividly clear, free from excitation or dullness
• Activity is diminished in anxiety-related regions such as the insular cortex and the amygdala
COMPASSION AND LOVING KINDNESS

• Cultivation of attitudes of compassion for others
• Involves becoming aware of another’s needs and experiencing a sincere, compassionate desire to help
• An unselfish desire akin to unconditional love
• Generally accompanied by repetition of a phrase such as “may all beings find happiness and be free from suffering.”
• Causes increase in several brain areas while listening to distressed voices—the secondary somatosensory and insular cortices which are involved in empathy (share feelings but do not get overwhelmed by them)
COMPASSION AND LOVING KINDNESS

• Greater activity in temporoparietal junction, the medial prefrontal cortex and the superior temporal sulcus areas activated when we put ourselves into another's position

• A critical factor is not just the development of empathy (resonating deeply with the negative feelings of another) which could lead to “burn out” but compassion and unconditional love which lead to increases in the orbitofrontal cortex, ventral striatum and anterior cingulate cortex which are involved with positive emotions and maternal love
PSYCHOTHERAPY

• *Cognitive-behavioral approaches*
  • Foundation Program
  • Safety Plans
  • Change Patterns
  • People, Places and Things experiential exercises

• *Contingency Management*
FOUNDATION PROGRAM

• In an inpatient setting the patient schedule serves this purpose
• On an outpatient basis or upon discharge from inpatient a recovery plan or contract is appropriate
• Remember that most addicts have little or no recent experience living a drug free lifestyle
## FOUNDATION PROGRAM

<table>
<thead>
<tr>
<th>TASK</th>
<th>MON</th>
<th>TU</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NUT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SAFETY PLAN

MY PERSONAL SAFETY PLAN

• Remember that craving go away
• I can write in my journal
• I can call my sponsor (299-289-5555)
• I can call my lover (299-426-1776)
• I can read from my favorite recovery book
• I can read affirmations
SAFETY PLAN

• TH: "On the back of the index card, come up with a saying or a prayer that gives you strength."

• CT: "I have always liked ‘Lord help me to be the best possible person I can be today’."
# PEOPLE, PLACES AND THINGS WORKSHEET

<table>
<thead>
<tr>
<th></th>
<th>CAN CHANGE</th>
<th>CANNOT CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEOPLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLACES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THINGS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PSYCHOTHERAPY

• Approaches such as contingency management (CM) and cognitive-behavioral therapy have been shown to effectively treat heroin addiction, especially when applied in concert with medications. Contingency management uses a voucher-based system in which patients earn “points” based on negative drug tests, which they can exchange for items that encourage healthy living. Cognitive-behavioral therapy is designed to help modify the patient’s expectations and behaviors related to drug use and to increase skills in coping with various life stressors.
Research has demonstrated the effectiveness of treatment approaches using contingency management (CM) principles, which involve giving patients tangible rewards to reinforce positive behaviors such as abstinence. Studies conducted in both methadone programs and psychosocial counseling treatment programs demonstrate that incentive-based interventions are highly effective in increasing treatment retention and promoting abstinence from drugs.
TREATMENT-CM

• To Reduce Unwanted Behavior
  • Present something undesirable (additional chores)
    • “Positive Punishment”
  • Keep something desirable (restrict access to video games)
    • “Negative Punishment”

• To Increase Desired Behavior
  • Provide something desirable (borrow the car)
    • “Positive Reinforcement”
  • Remove or reduce aversive conditions
    • “Negative Reinforcement”
CRAVING MANAGEMENT

• Situational triggers
  • Environment (People, Places And Things)
• Emotional triggers
  • Internal (Hungry, Angry, Lonely, Tired, Reward and Bored)
• Acute Abstinence Syndrome
• Stress
CHANGING PATTERNS

31 yo Nicki-a recovering heroin addict- just got her first paycheck. She cashed her check and cruised thru the neighborhood where she used to score dope. Rock music blared from her speakers. Soon she was thinking, "I worked hard all week. I deserve a little fun."
EDUCATION

• Cognitive deficits in chronic drug abuse
  • Withdrawal produces cognitive symptoms
    • Cocaine-deficits in cognitive flexibility
    • Amphetamine-deficits in attention and impulse control
  • Opioids-deficits in cognitive flexibility
  • Ethanol-deficits in working memory and attention
  • Cannabis-deficits in cognitive flexibility and attention
  • Nicotine-deficits in working memory and declarative learning
EDUCATION

• Utilize short and simple didactic or film clips to teach basic recovery points
• Use a feedback mechanism to determine comprehension
  • I think ..............
  • I feel ..............
  • I learned ..........
  • My future behavior will change ........
POST-ACUTE WITHDRAWAL (PAW)

• STRESS SENSITIVE
• NEUROLOGICAL SYNDROME
• STARTS AFTER THE ACUTE ABSTINENCE SYNDROME
  • Some people have shown persistent acute withdrawal signs for many months
• MOOD SWINGS AND SLEEP PROBLEMS CAN LAST 6 MONTHS TO A YEAR
POST-ACUTE WITHDRAWAL (PAW)

• **SYMPTOM SEVERITY BASED ON LEVEL OF NEUROLOGICAL DYSFUNCTION AND DEGREE OF PSYCHOSOCIAL STRESS**
  
  • *Sleep disturbances and mood swings very common*
  
  • Restlessness and Irritability
  
  • Euphoric Content Dreams
  
  • Anxiety
  
  • Distractibility
  
  • Intense Craving
POST-ACUTE WITHDRAWAL (PAW)

- **MUST RULE OUT ANY CO-OCCURRING DISORDER**
  - POSTTRAUMATIC STRESS DISORDER
  - OTHER ANXIETY DISORDERS
  - ATTENTION-DEFICIT/HYPERACTIVITY DISORDER
  - CLOSED HEAD INJURY
  - PERSONALITY DISORDERS
    - EXAMPLE-BORDERLINE PERSONALITY DISORDER
  - SLEEP DISORDERS
  - PAIN DISORDERS
POST-ACUTE WITHDRAWAL (PAW)

• **NEUROPSYCHOLOGICAL REHABILITATION**
  • EDUCATION
    • MANAGEMENT OF CRAVING AND PAW
  • LIFESTYLE ASSESSMENT
    • NUTRITIONAL
    • SLEEP/WAKE
• BEHAVIORAL MANAGEMENT
  • FOUNDATION PROGRAM
  • SAFETY PLAN
• PHARMACOLOGICAL (SYMPTOM BASED)