



**2018 CALIFORNIA  
BEST PRACTICES  
AND GPRA  
MEASURES  
CONFERENCE**

Addiction, Opioids and Beyond



Chronic Pain

Mental Illness

Substance Dep

Medical Illness

Genetics/Env

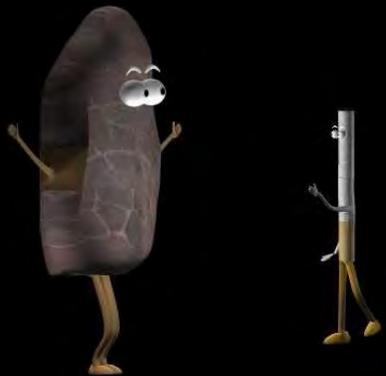
Pathways to Full Recovery



# Objectives

- ▶ Understanding Definitions in Substance Dependency and Addiction.
- ▶ Review of Basic Epidemiology in Opioids
- ▶ Understanding Basic Addiction Physiology and how it relates to Schizophrenia
- ▶ Knowledge the General Overview of SUD Treatment
- ▶ Knowledge of non-pharmacological treatments of SUD.
- ▶ Understanding of Prescription Opioids, Side Effects and Dangers
- ▶ Understanding Prescription Opioids in the setting of Chronic Pain
- ▶ Understand MAT for Opioids (Tip43) with Naltrexone, Methadone and Buprenorphine
- ▶ Naloxone

# WHAT DOES ADDICTION MEAN?



# Opioid and Overdose

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In 2016 11.5 million people 12 years and older misused opioid pain medications

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1.8 million had substance use disorder involving prescription pain medications

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Between 2000 to 2015, more than 500,000 people died from opioid overdoses

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2012 clinicians wrote 259 million prescriptions for opioids

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2.5 million people with Opioid Addiction (JAMA)

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US deaths from drug overdoses hit record high in 2014, propelled by abuse of prescription painkillers and heroin. (CDC)

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Heroin related deaths tripled since 2010.

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Only 2.2% of US Physicians have waiver to prescribe Buprenorphine (JAMA)



Arroyo/AP



## Star's RX For Disaster

**Here's a rundown of what she had in her system when she died:**

- Chloral hydrate (potent sedative)
- Klonopin (anti-seizure, anti-anxiety)
- Valium (anti-anxiety)
- Ativan (anti-anxiety)
- Benadryl (anti-histamine)
- Soma (muscle relaxer)
- Robaxin (muscle relaxer, sedative)
- Topamax (for migraine headaches)
- Ciprofloxacin (antibiotic)
- Atropine (used by medics trying to revive her)
- Tylenol

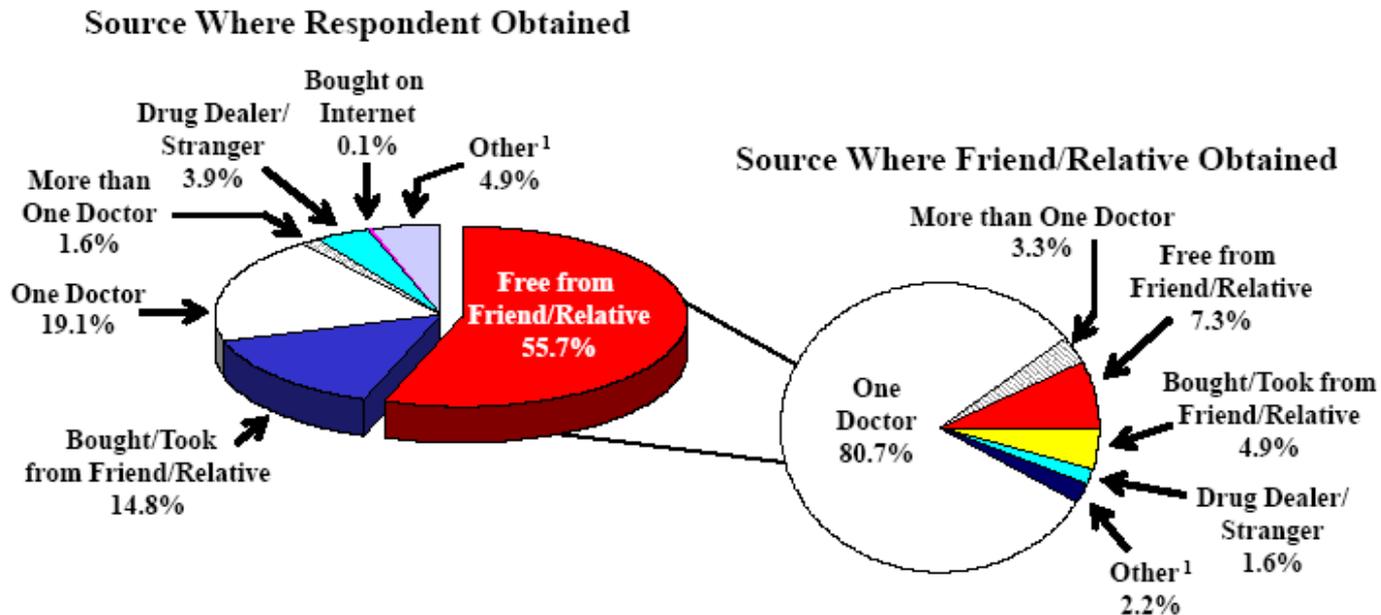
**Here are other drugs she was prescribed or known to use in the days and months before she died:**

- Methadone (potent pain reliever)
- Human Growth Hormone (longevity, anti-aging)
- Vitamin B12 (by injection, longevity)
- Immunoglobulins (longevity)
- Demerol (potent pain relief)
- Dalmane (sleeping aid)
- Nicotine gum

# Where Pain Relievers are Obtained

## Where Pain Relievers Were Obtained

Nonmedical Use among Past Year Users Aged 12 or Older 2006



Source: SAMHSA, OAS, NSDUH data , July 2007

Statistically, nonmedical use of drugs from individuals obtained a majority of their drugs from friends and relatives, however 80% of those “friends and family” obtained from ONE DOCTOR.

# Addiction Poorly Understood



## Addiction Poorly Understood by Clinicians Experts Say Attitudes, Lack of Knowledge Hinder Treatment

By Ann Vestag

**BAL HARBOUR, Fla.**—A patient with high blood pressure arrives at his usual checkup after another ordinary year. His physician, who has sketchy knowledge about hypertension, notes that the patient has gained 12 lbs and that his blood pressure remains high. She lectures the patient about the importance of willpower in overcoming his life-threatening shortcoming. Without a thought about prescribing one of the several effective antihypertensives, she dismisses the patient, shakes her head, and murmurs to herself about the seemingly hopeless plight of "these hypertensives."

Such a scenario seems absurd—but isn't "drug addiction" in place of "hypertension," and an all-too-common picture emerges, said scientists, clinicians, and other treatment specialists at the College for the Problems of Drug Dependency annual meeting held here in June.

For all the lip service paid to the concept of addiction as a medical disease, the idea has yet to gain traction with a large proportion of physicians. They, like many others in society, often regard abuse of alcohol or drugs as a moral or behavioral problem, said several speakers.

"Addiction is a brain disease," said Charles O'Brien, MD, PhD, a noted addiction specialist, during a keynote address at the meeting. "But when you say that to [an audience], people get very angry. It's something we have to continue selling."

Bob Margolis, PhD, a psychologist who runs an adolescent drug and alcohol treatment program in Atlanta, re-

lated a story indicative of the problem. After delivering a presentation on addiction at a local hospital, several physicians approached him and said, "I wish someone [had] talked about this in medical school."

### COMMON MYTHS

According to *Drug Dependence: A Clinical Approach*, a 1997 report from the Institute of Medicine, just 1% of the typical medical school curriculum is devoted to the subject. Surveys of physicians also consistently show that medical students are screened for alcohol or drug addiction; many believe that medical interventions are inappropriate and ineffective.

Those who do use addiction as a medical problem tend to treat it as an acute, instead of chronic, disorder. And the idea that addiction is simply a consequence of willfulness still permeates the profession. O'Brien, a professor of psychiatry at the University of Pennsylvania School of Medicine, Philadelphia, and colleagues made these points in a review article three years ago (*JAMA*, 2000;284:1686-1695).

"There is such prejudice in the community of doctors, severe prejudice," said National Institute on Drug Abuse Director Nora Volkow, MD, PhD, at an addiction education program for journalists sponsored by Wake Forest University School of Medicine, Winston-Salem, NC, and held concurrently with the College for the Problems of Drug Dependency meeting.

"How do we change this?" she asked. Addiction experts not only have to emphasize that addiction is a disease, but they also have to emphasize that addiction leads to other medical problems—a basically pernicious medicine, Volkow explained. "We can prevent a lot of other problems by addressing addiction, but somehow we have failed to emphasize that," she said.

According to the National Institute on Drug Abuse, some \$133 billion is spent each year treating the short- and long-term medical complications of addiction. Cocaine abusers die from sudden cardiac arrest; heroin and other intravenous drug users contract hepatitis C and human immunodeficiency



Addiction experts say that the widely held view of drug addiction as a moral or behavioral problem rather than a medical disease undermines treatment efforts.

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Reprinted, *JAMA*, September 12, 2003—Vol 290, No. 37 1300

- Regard Addiction as a moral problem
- Fail to adequately screen
- 1% of medical school curriculum
- Believe interventions are ineffective

# Defining the Word "Addiction"

The American Society of Addiction Medicine (ASAM), American Pain Society (APS), and American Academy of Pain Medicine (AAPM) **define addiction as a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations characterized by one or more of the behaviors listed above (ASAM, 2001).**

## ASAM-APS-AAPM BEHAVIORAL CRITERIA:

- Impaired control over use, **compulsive use**
- **Continued use despite harm** due to use
- Preoccupation with use, **craving**

## NEUROBIOLOGICAL:

- An activity which initially stimulates the **"limbic"** system, which results in changes of neurotransmitter levels, which are perceived as euphoria (↑hedonic tone)

## Examples of Specific Drug Seeking Behaviors :

- Frequent loss/theft reported, calls for early renewals, withdrawal noted appointments
- Declining function, intoxication, persistent over sedation
- Nonopioid interventions ignored, recurrent requests for opioid increase/complaints
- Increasing pain in absence of disease progression despite titration

# Drug Seeking Behavior

- Patient has demonstrated a **pattern of overuse or escalation** of use.
- Patient **requests specific drug** and refuses all other suggestions.
- Patient continues **to insist that only the "nonaddictive" drugs do not work (i.e. Allergies)**
- Patient demonstrates **Aggressive behavior** demanding immediate action.
- Patient demonstrates **Evasive/Vague** Medical History.
- **Pitting Physician Against Each Other.** Patient claims or asserts that he/she will go to a more caring or smarter physician.
- **Nonpharmacologic treatment recommendations**, such as Beh Training, Psychotherapy, 12-Step, ever PT are **resisted** by the patient
- Patient has **two if not more physicians** in their attempt to obtain an adequate or increasing supply of controlled prescriptions.
- Patient has demonstrated **"patient-generated" pressure** to prescribe to themselves despite the obvious feelings of physician's hesitancy.
- Patient is demonstrating **Flirting or Complimentary Behavior.**

## ADDICTION DIAGNOSIS: DSM 5 SHOWS SUD CONTINUUM

- Continued use despite adverse consequences, often with physical dependence (tolerance, withdrawal) and craving.
- Main difference between ‘use’ and ‘use disorder’ is loss of control and loss of function in life.
- With DSM 5, the word ‘abuse’ and “dependency” disappears from diagnosis, and addiction is evaluated along a continuum or ‘mild, moderate or severe use disorder.’
- Craving is added as a criterion.
- Legal problems removed as a criterion due to cultural considerations.
- Caveat for prescriptions appropriately prescribed and taken as directed.(ie, differentiates between physical dependence and addiction)
- Caffeine is not on the list

*Criteria from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,. Washington, DC, American Psychiatric Association. p541*

Addiction “ENSLAVED BY”

THE TERM “ADDICTION” IS DERIVED FROM THE LATIN WORD “ADDICERE, MEANING “**BOUND TO**” OR “**ENSLAVED BY**”

ADDICTION is **not Physical Dependency**, some drugs produce PD without Addiction and vice versa.

ADDICTION: The frequent behaviors associated with drug seeking and drug taking become **repetitive and ritualistic**

ADDICTION SHOULD BE VIEWED AT A **CHRONIC DISEASE** WHICH IN TURN SHOULD....

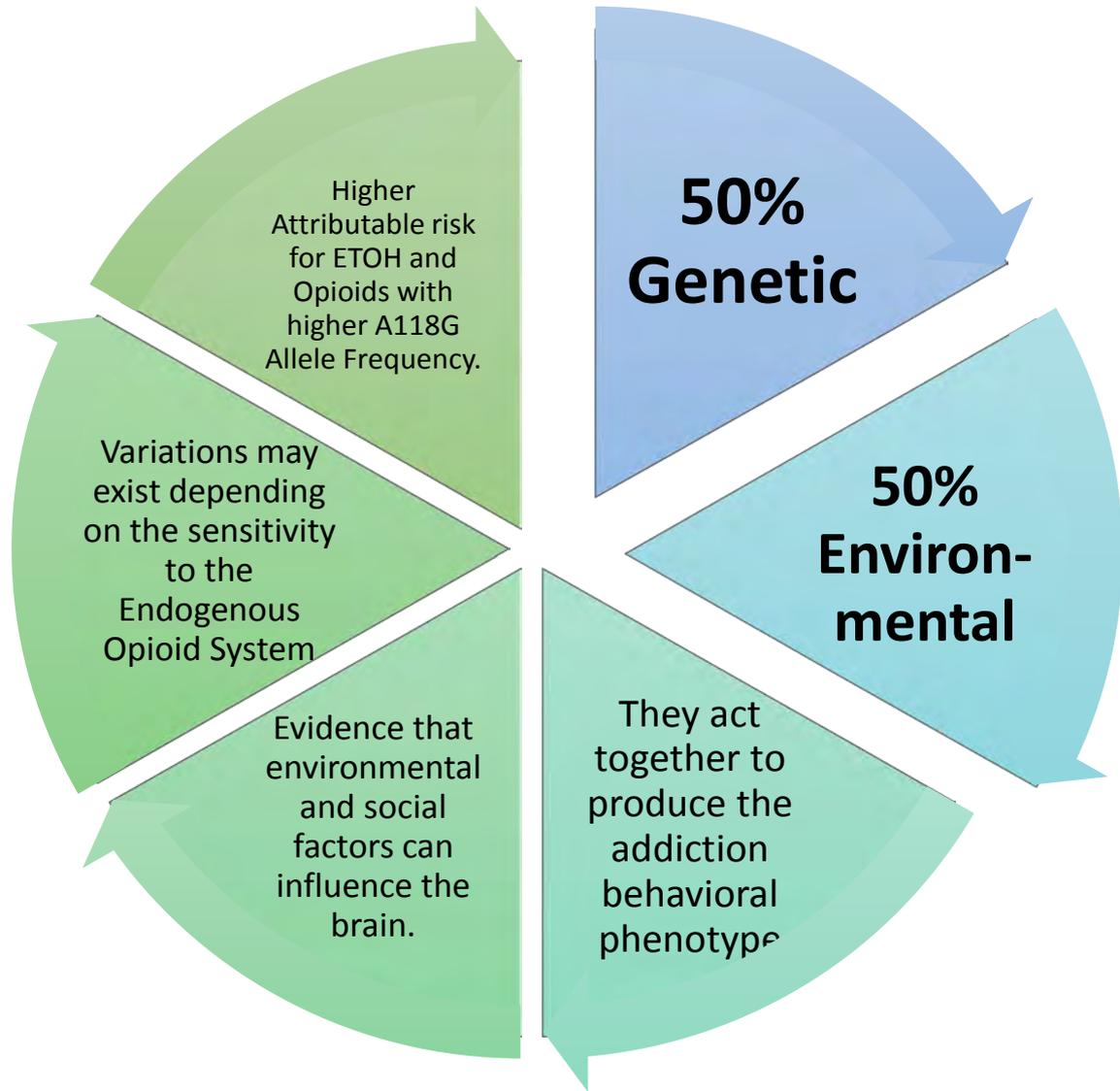
MODIFY THE EXPECTATIONS OF TREATMENT:

1. Relapse should not be interpreted as failure
2. Discontinuation of treatment may result in Relapse
3. Rates of relapse and recovery are similar to chronic medical diseases

4 C's of Addiction:

- **Consequences** (continued use of a behavior despite adverse Consequences)
- **Self-Control** (loss of Self Control over the behavior)
- **Compulsive** (Compulsive engagement in the behavior)
- **Craving** (An urge or Craving before the behavior)

# Contributions of the Disease of Addiction



# Examples of GENES AND their Effects

ADH1B and ALDH2 genes are mutated they increase a patients risk of getting upper GI Cancer.

CYP2A6 is involved in smoking relapse

OPRM1 gene has all of the following

- ❑ Opioid dependence
- ❑ HPA axis response to stress
- ❑ Sensitivity to pain
- ❑ Responsiveness to analgesics

Genetic Alterations of Cytochrome P450 2D6 are **protective against codeine abuse**

Genetic Alterations of Cytochrome P450 2A6 are **protective against nicotine abuse**

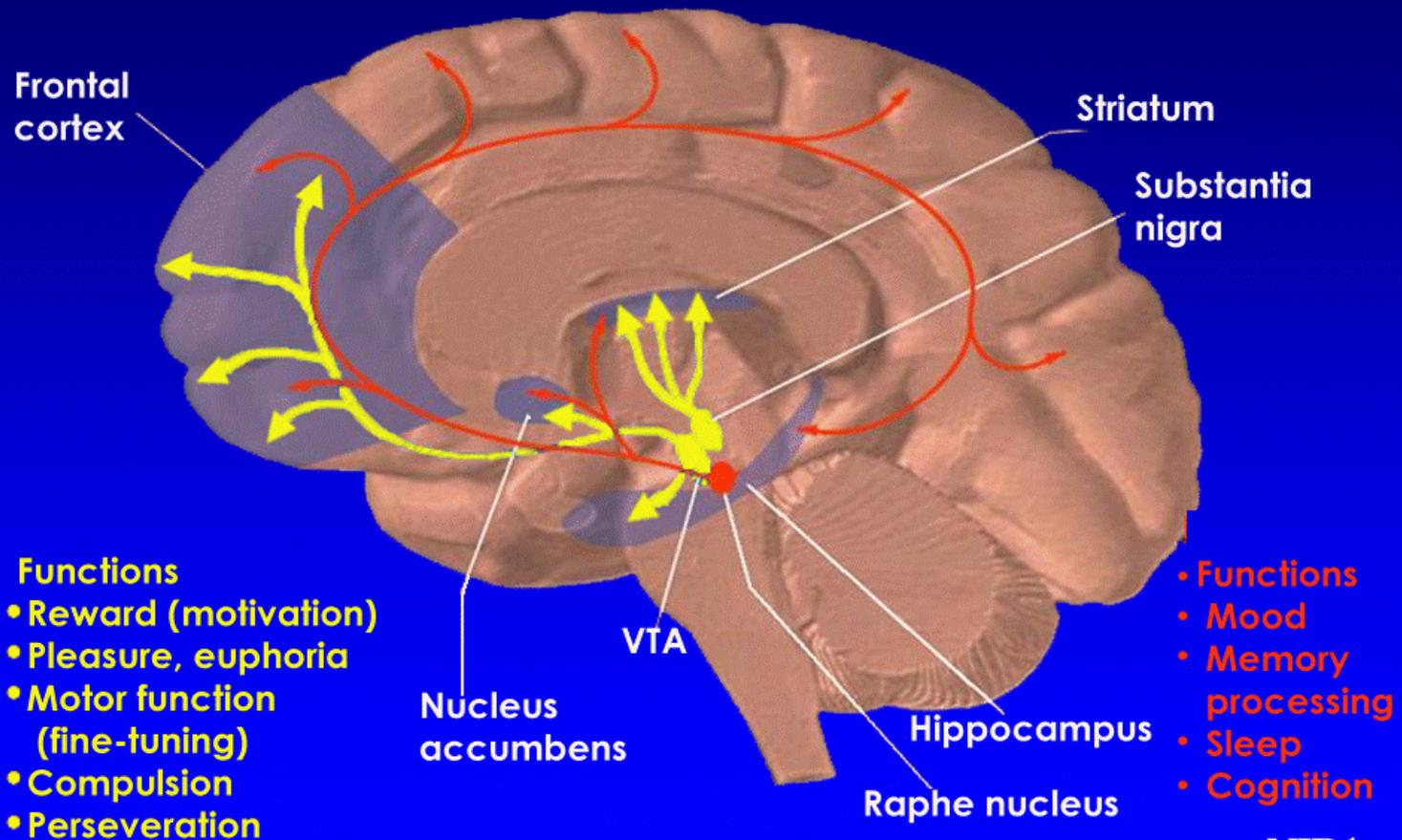
Genetic Alterations of D2-Receptor that are linked to higher vulnerability to drug addiction in general.

# ADDICTION PHYSIOLOGY

# Dopamine and Serotonin Pathways

## Dopamine Pathways

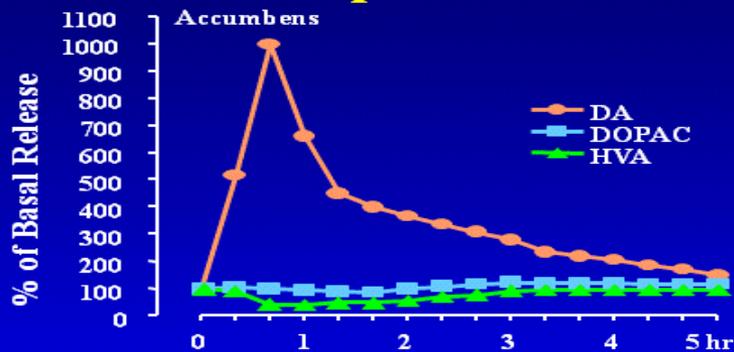
## Serotonin Pathways



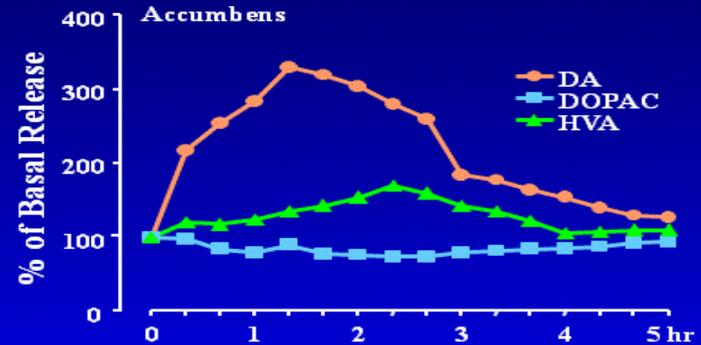
# Dopamine Levels with Drugs of Dependency

## *Effects of Drugs on Dopamine Release*

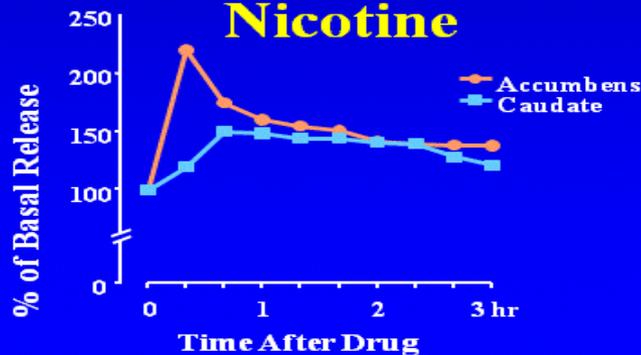
### Amphetamine



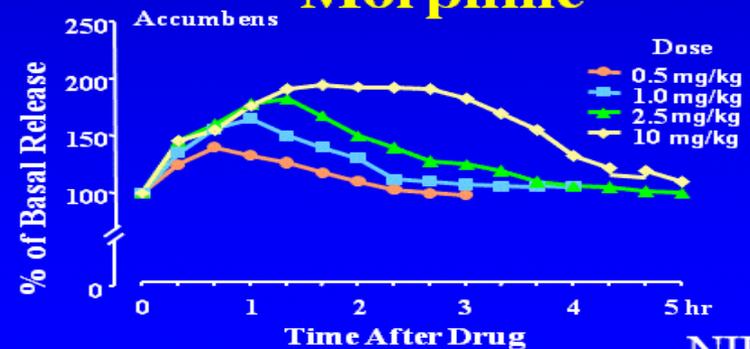
### Cocaine



### Nicotine



### Morphine



# General Concepts

The VTA-NAc pathway is perhaps the most important area of the brain for acute rewarding effects of all drugs of abuse. **The VTA-NAc pathway is also involved in “natural addictions”** such as pathological overeating, pathological gambling and sexual addictions, although the pathway for natural reward systems is not as well understood.

Natural Addictions and Negative Emotional Symptoms: THE " HIJACKED" BRAIN HYPOTHESIS: Addictive drugs act on the same brain-reward substrates and mechanisms as do natural biologically essential rewards (e.g. food, sex), in fact addictive drugs derive much of their addictive power by activating these brain-reward substrates and mechanisms more powerfully than natural rewards.

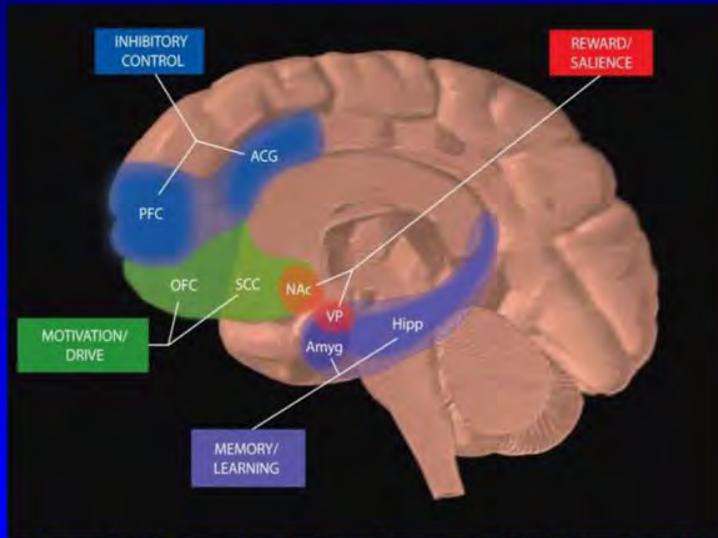
Chronic exposure to any drugs of abuse **impairs the dopamine system**, baseline levels of dopamine function are reduced, and normal rewarding stimuli may be less effective. IT IS THESE CHANGES THAT MAY CONTRIBUTE TO THE NEGATIVE EMOTIONAL SYMPTOMS that occurs in drug exposure. Prolonged drug exposure leads to reduction in the reinforcing effects of natural rewards, reduce motivation and promoting depression.

All drugs of abuse converge on a common circuitry in the brains limbic system, the mesolimbic dopamine pathway which include VTA and the NAc. Chronic exposure to several drugs of abuse can create changes in the **frontal cortical regions** and their glutamatergic outputs, which are implicated **in impulsivity and compulsivity** that characterizes a state of addiction.

Additionally, other drugs activate the brains endogenous opioid and cannabinoid systems within the VTA-NAc.

# Limbic and Frontal Areas

## *Circuits Involved In Drug Abuse and Addiction*



All of these brain regions must be considered in developing strategies to effectively treat addiction

NIDA

## Limbic System

- Several additional brain areas also interact with VTA and NAc are also important, which includes the Amygdala, Hippocampus, Hypothalamus and several areas of the frontal cortex, these structures are associated with the Limbic System and are essential not only **for learning and memory but also for the emotional context** and the affective response to learned associations. This leads to **EMOTIONAL MEMORIES**.

## Hypofrontality

- Chronic exposure can also result in “hypofrontality”, reduced baseline activity of several regions of frontal cortex. These areas control executive function, including working memory, attention and behavioral inhibition and are important in **controlling response** to environmental stimuli, in part via glutamatergic projections from these regions to the NAc and VTA.
- MORE ABOUT THE FRONT LOBE →

# Saliience

**SALIENCE: Increased dopamine from sensory stimuli (sights, sounds, etc.) that are associated with the drug or drug taking elicit the desire for the drug.**

**This explains why a person is at greater risk of relapse when exposed to an environment where he or she has previously taken the drug.**

**In fact, data suggests that drug cues can stimulate drug cravings even before there is conscious awareness.**

**Specifically, drug users show increase in brain activity in the limbic areas and the PFC following presentation of drug-associated cues (such as pictures of drugs or paraphernalia) when compared to nondrug users, and even DECREASED responsiveness when presented with nondrug reinforcers (e.g. provocative pictures).**

# Pre-Frontal Decision Processing

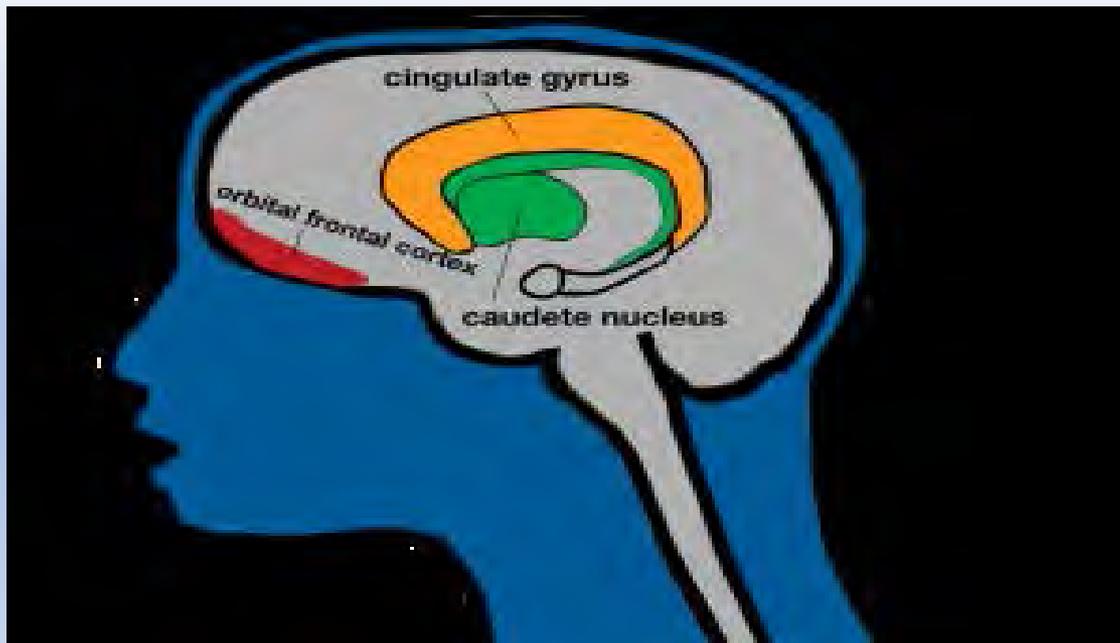
1. The orbital frontal cortex detects a problem. The problem can be anything that is out of the ordinary. You have germs on your hands
2. The orbital frontal cortex sends a message to the cingulate gyrus. The cingulate gyrus is the panic center. It triggers physical reactions in the body to perform actions to alleviate the anxiety caused by the “problem”, i.e., washing to eliminate germs
3. Once the person corrects the problem (e.g., by washing hands), the caudate nucleus is activated and moves the brain to a different thought. At this point, the orbital frontal cortex (1) and the cingulate gyrus (2) return to their normal state and the problem detection is inactivated since it’s no longer a concern.

**Orbio-Frontal Cortex:** Involved in the Compulsive Behavior

**Cingulate Gyrus: Regulates Inhibition:** (Medial Prefrontal Cortex—neurobiological substrate for “executive function” that is compromised in drug dependence and plays a key role in facilitating relapse. Contains major glutamatergic projection to nucleus accumbens and amygdala)

In fact, lesions that occur in the Pre-Frontal Cortex of the brain one can see changes in eating, sub use and sexual behaviors

*“Decisions surrounding drug seeking and drug taking seem to be driven more by emotion and instinct rather than by logic.”*



# ADDICTION CYCLES

ADDICTION IS CHARACTERIZED BY A CYCLE THAT IS COMPRISED OF THREE PHASES:

## PHASE 1: BINGE/INTOXICATION STAGE:

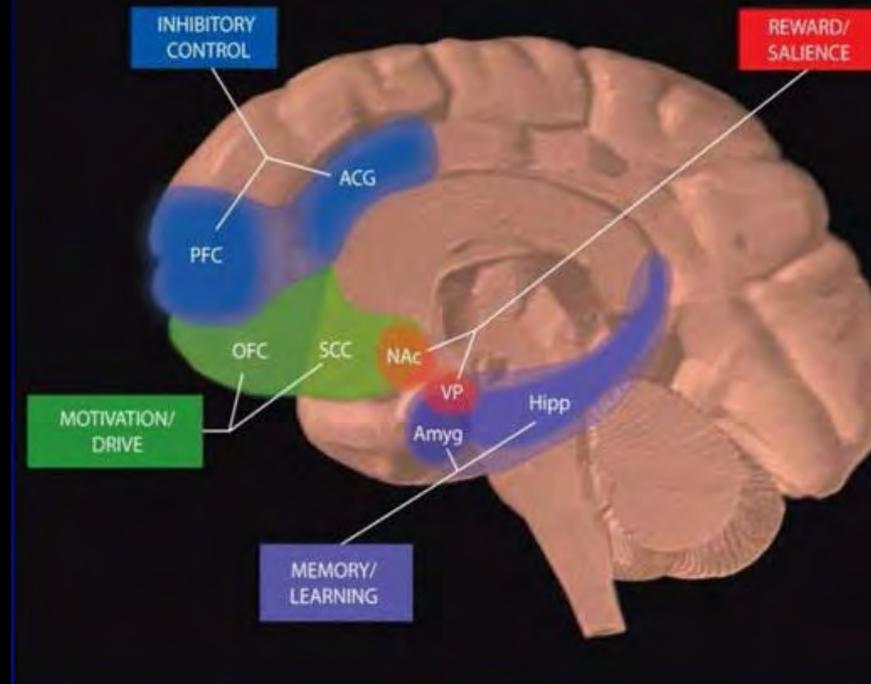
VTA AND VS (INCLUDES NA):  
Euphoria is associated with Dop Elevation in this Brain Region

## PHASE 2:

**WITHDRAWAL/NEG:**  
AFFECT: AMYGDALA IS HEAVILY INVOLVED

## PHASE 3: PREOCCUPATION/ANTICIPATION (or Craving):

NUMBER OF BRAIN REGIONS INCLUDING THE PRE-FRONTAL CORTEX AND HIPPOCAMPUS



# Actions of Drugs of Abuse on VTA-NAc

**Stimulants** directly increase dopaminergic transmissions in the Nac. In fact Cocaine and Amphetamine exert analogous actions on serotonergic and noradrenergic systems, which may also contribute to the reinforcing effects of these drugs.

**Opiates** inhibit GABAergic interneuron in the VTA, which disinhibits VTA dopamine neurons.

**Opiates** also directly act on Opioid receptors on NAc neurons

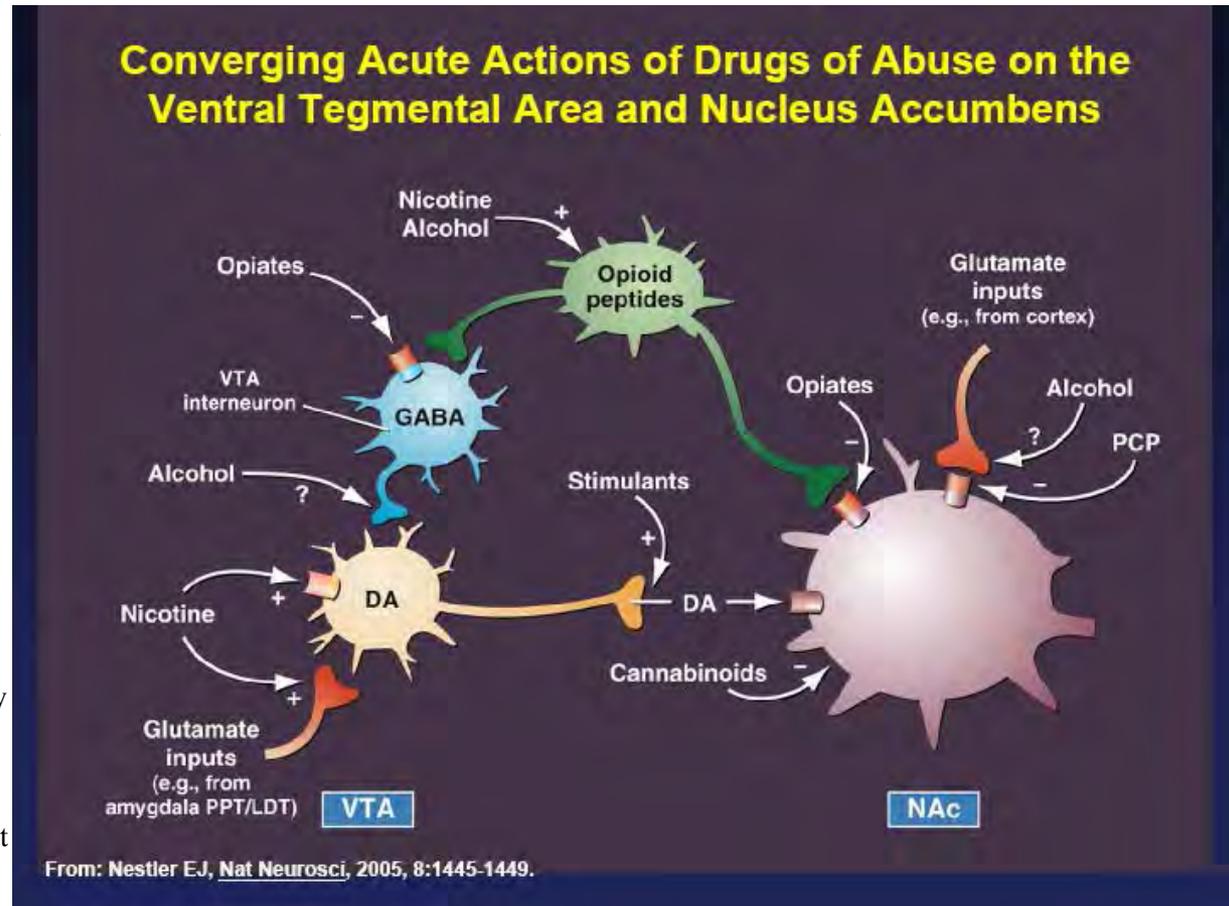
**Nicotine** seems to activate VTA dopamine neurons directly via nicotinic cholinergic receptors and indirectly via stimulation of its receptors of glutamatergic nerve terminals that innervate the dopamine cells

**ETOH** by promoting GABA receptor function, may inhibit GABAergic terminals in the VTA and hence disinhibit VTA dopamine neurons

**ETOH** may also inhibit glutamatergic terminals that innervate NAc terminals

There is some evidence that **Nicotine and ETOH** may activate endogenous opioid pathways

*Nature Neuroscience, Volume 8, Number 11, Nov 2005 by Eric Nestler*



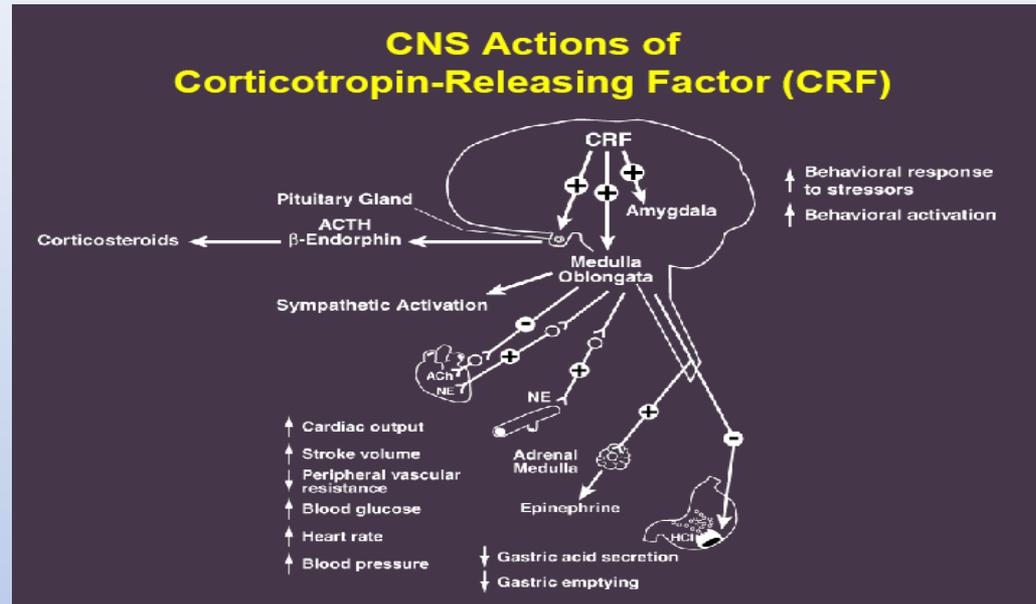
# Positive and Negative Reinforcement

## **Positive and Negative Reinforcement —Definitions—**

**Positive Reinforcement** — the process by which presentation of a stimulus (drug) increases the probability of a response (includes non dependent drug taking paradigms).

**Negative Reinforcement** — the process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (includes dependence-induced drug taking)

# Activation of CRF-Stress Mediated



**CRF is involved in the stress-induced reinstatement of drug taking and vulnerability to relapse and in the responses to acute drug withdrawal.**

Abrupt withdrawal from virtually any drug of abuse leads to activation of CRF-containing neurons in the amygdala.

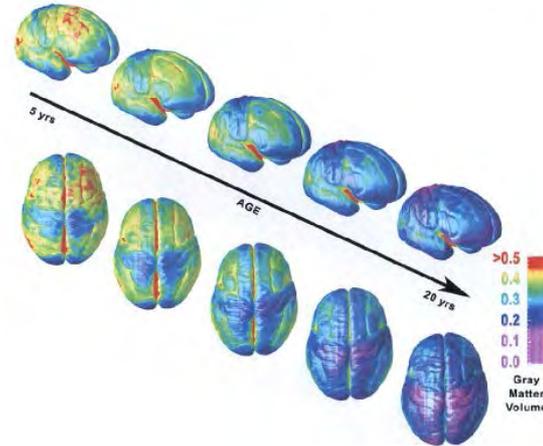
Activation of these neurons during drug withdrawal contributes to the negative emotional symptoms and many somatic symptoms that occur upon drug withdrawal, and may contribute to drug craving and relapse.

The role of stress is mediated in part by CRF and related peptides

- CRF controls the pituitary-adrenal axis
- CRF serves as a neuropeptide co-transmitters in neurons in the central effects of stress
- CRF is well know to be involved in the regulation of energy balance and food intake

# Adolescent Brain & Drug Use

Maturation Occurs from Back to Front of the Brain – Jay Giedd, NIMH



**Adolescents have delayed maturation of the prefrontal cortex, a brain region that is involved with judgment and inhibitory control. (Nature Neuroscience, Volume 8, Number 5, May 2005) Adolescence is the critical period for the onset of substance use and its consequences:**

1. Teen brain is more prone to risk taking, including substance use
2. Teen brain is more vulnerable to damage from substances, including addiction
3. Prefrontal cortex is one of the last regions to develop with maturation ending around 25-30 y/o
4. This process promotes increase impulsivity in younger adults and adolescents, this combined with enhanced impulsivity from Marijuana could possible promote drug experimentation.
5. Drug Exposure during Adolescence might result in different neuroadaptations from those that occurring during adulthood. Therefore those who start using psychoactive drugs in adolescence could be at a higher risk of addiction than those who start using drugs later in life. In fact the earlier the first use of ETOH the higher the associated risk ETOH Abuse/Dep/MVA's, violence and Earlier Smoking, and as expected overall Drug Abuse/Dep.

## **In Fact Statistically:**

1. Nearly greater than 40% of Adults who use ETOH, used before the age of 14 y/o
2. Nearly 90% of adults with current Substance Use Disorders, started using before the age of 18 and ½ before the age of 15.
3. 9 out of 10 People Who Are Addicted\* Begin to Smoke, Drink and/or Use Other Drugs Before Age 18

# Psychiatric Illness & Addiction

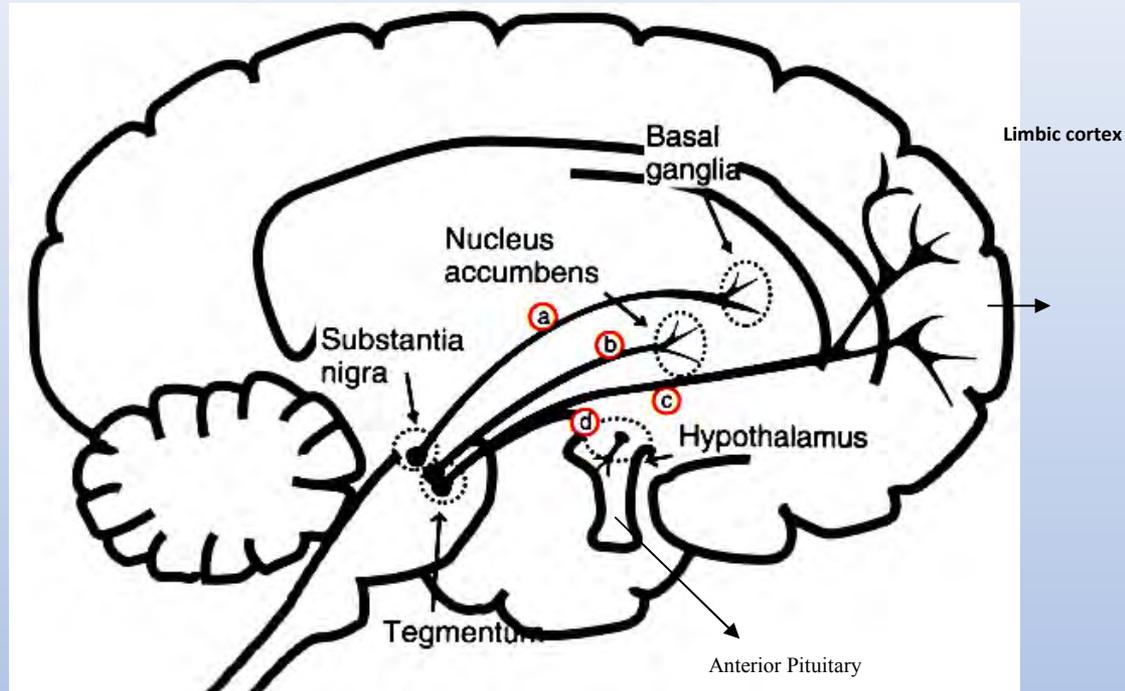
Many clients have undiagnosed mental illness which influence SD.

## *Substance induced Psychiatric Disorders need to be considered.*

- For example, stimulant dependency can cause psychosis and might present like schizophrenia.
- Conclusion: Consider waiting 30-60 days before diagnosing a Client with a Psychiatric Disorder, because it may be caused by the drug of abuse.
- **Psychiatric Co-morbidities need to be treated (MUST), for example Depression, okay to treat at the same time if felt necessary.**
- ALWAYS REFER WHEN NEEDED

Psychiatric assessment is crucial in treatment of client with Substance Use Disorders

# Additional Dopamine Pathways



**a = nigrostriatal pathway**

**b = mesolimbic pathway:**

**c = mesocortical pathway:**

**d = tuberoinfundibular pathway**

# Substance Dep and Schizophrenia

½ Schizo = SUD

Dopaminergic pathways are shared

MesoLimbic DA pathway is implicated not only in the rewarding mechanism and positive symptoms in Schizo.

MesoCortical (DA deficits in PFC) and contributor to negative symptoms.

One additional proposal (for Schizo using) is that there may be an imbalance of hippocampal-prefrontal regulation of DA release in the NAcc may contribute to both psychosis and the vulnerability to drug abuse in Schizo.

# Dopamine Pathways Explored

## Mesolimbic pathway

- Hyperactivity on this pathway is associated with positive symptoms of schizophrenia

## Mesocortical pathway

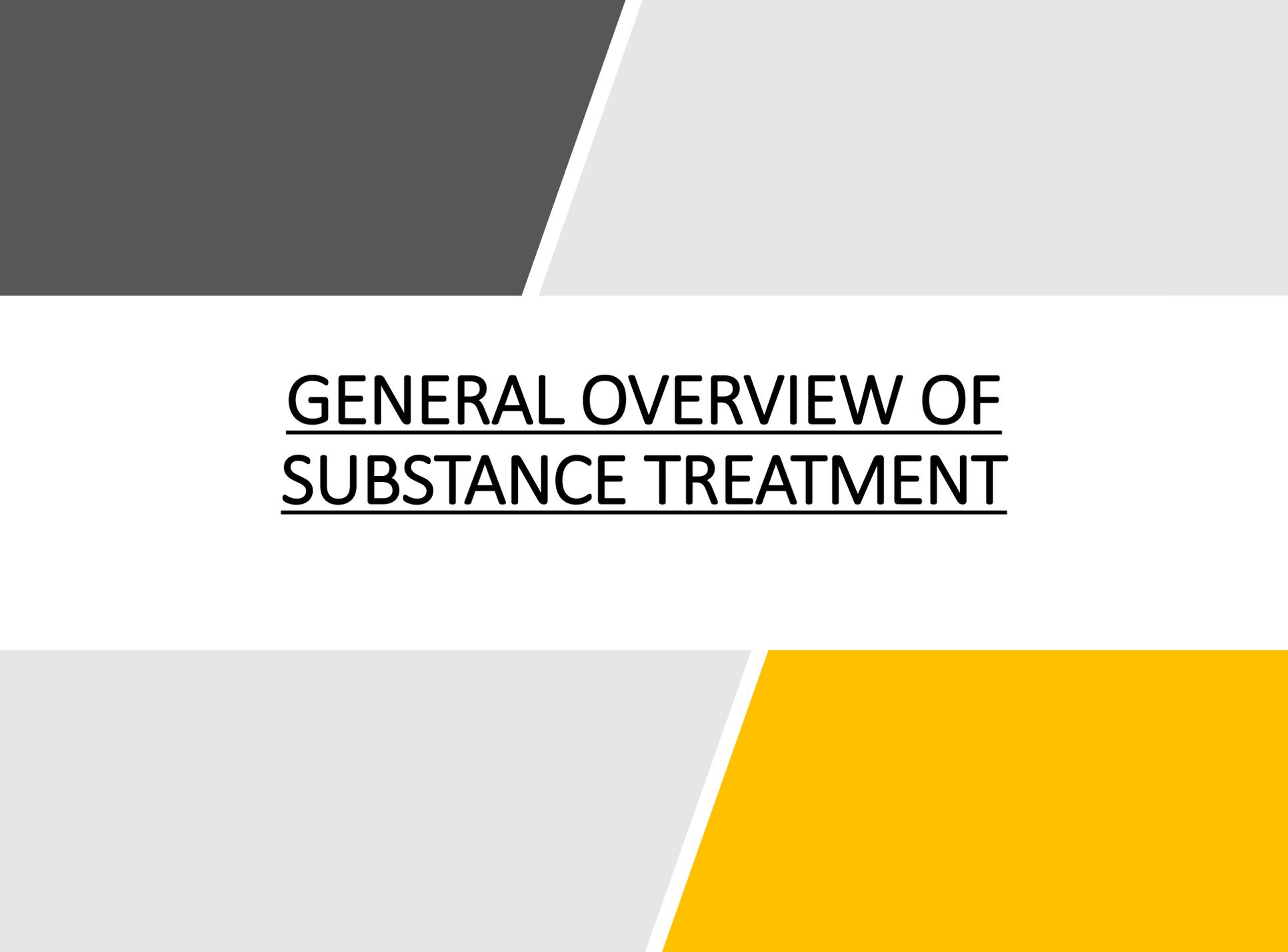
- Deficit in dopamine in this pathway is associated with negative and cognitive symptoms of schizophrenia

## Nigrostriatal pathway

- Part of extrapyramidal system and controls motor movement
- Blockade of D2 receptors causes:
  - --deficiency in dopamine in this pathway and thus movement
  - --disorder such as Parkinson's disease
  - hyperkinetic movement such as tardive dyskinesia

## Tuberoinfundibular pathway

- Increased neuronal activity of this pathway inhibits prolactin release
- Blockade of D2 receptor increases prolactin release and causes:
  - -- galactorrhea
  - -- amenorrhea



# GENERAL OVERVIEW OF SUBSTANCE TREATMENT

# General Considerations SUD Treatment

Screening for Opioid  
Induced  
**Hypogonadism** (low  
testosterone)

Screening for  
**Hypercortisolism** (low  
cortisol-Not Common)

General **Medical Labs**

General screening for  
**STD's** such as HIV,  
Hepatitis, etc

General **Psychiatric  
Assessment**

Explore **Pain Pathology**  
and consider **Opioid  
Induced Hyperalgesia**

Individual, Group and  
Family Counseling.

All Adolescent and  
Adult **Immunizations**  
should also be  
screened and updated.

# General Pharmacological Considerations SUD Treatment

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If the Client is on **Bezo's**, it is important to get the Client off first before starting Suboxone, as the combination together has proven fatal in some studies.

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**Psychiatric Treatment** may wait for at least 30-60 days after they have started the program UNLESS they have a documented history of psychiatric illness prior to drug use or their substance induced psychiatric illness is interfering with active treatment.

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**Consider using Zofran** 8mg TID prior to coming OFF the narcotics, as some research (Dr. Clark, Stanford University) shows that Zofran ameliorates opioid withdrawal effects.

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**Clonidine** is still useful but can be limited with clients with low blood pressure.

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**CNS Depressants** are used to help with anxiety, withdrawal agitation, and insomnia, such as Gabapentin and Tegretal.

# Non-Pharm Rx of SUD

**Therapy (CBT):** Cognitive behavioral therapy (CBT) is a psychotherapeutic approach, a talking therapy, that aims to solve problems concerning dysfunctional emotions, behaviors and cognitions through a goal-oriented, systematic procedure.

**Motivational Interviewing:** A client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence.

**12-STEP:** A twelve-step program is a set of guiding principles outlining a course of action for recovery from addiction, compulsion, or other behavioral problems.

**Nutrition** (next slide)

**Exercise** (next slide)

# Therapy Explored

## CBT:

Diary of significant events and associated feelings, thoughts and behaviors.

Questioning and Testing Cognitions, Assumptions, Evaluations and Beliefs that may be unhelpful and/or unrealistic.

Gradually facing activities which may have been avoided

Trying out new ways of behaving and reacting.

Relaxation, Mindfulness and Distraction Techniques are commonly included.

## Motivational Interviewing: (OARS)

**Open Ended Questions:** Do Not Give Advice (i.e. If I were you this is what I would do) No Yes or Not Questions

**Affirm:** “Pat on the back” (i.e. Sounds like you are doing well.)

**Reflective Listening:** Repeat back to them what they are saying so they know you are listening while allowing them a chance to correct you.

**Summarize and Elicit Change Talk:** Summarize and Deflect self negative statements or image.

## Important Tools

- **Develop Discrepancy:** Change is motivated by a perceived discrepancy between present behavior and important goals and values.
- **Roll with Resistance:** Avoid arguing for change
- **Support Self-Efficacy:** Encourage a person's belief in her/his ability to carry out change.

## 12-STEP

# Motivations Interviewing (The 5 R's)

Motivational interviewing is a tactic that can be used when a tobacco user indicates that he or she is not ready to quit.

- Smoking cessation is **Relevant** to the patient's health problems.
- The second R, **Risk**, involves getting the patient to acknowledge specific risks associated with continued tobacco use.
- The patient should also be encouraged to list potential **Rewards** that might be associated with smoking cessation.
- The patient should also be encouraged to identify potential **Roadblocks** that may make quitting more difficult. She may have concerns over weight gain or she may worry that an attempt to quit will be unsuccessful anyway.
- Finally, **Repetition** is important. If the patient does not quit smoking, the clinician should continue to provide

- 
- *Relevance*
  - *Rewards*
  - *Risks*
  - *Roadblocks*
  - *Repetition*

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Consider Amino Acid Therapy, some studies show that amino acid deficiency may contribute to cravings.

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Consider starting Multivitamins and Omega-3-FA for increase energy, nutrition, and mental sharpness.

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3 Balanced meals a day, with a good breakfast...discuss the obvious.

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Inadequate diet from poor eating habits.

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Drugs and ETOH interfere with the absorption of food.

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Many Clients have GI dysfunction

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***Conclusion:*** Many Clients have special and frequently unique food and nutritional requirements.

## Nutritional Considerations

# Exercise

Nearly all Clients have detrimental physical changes.

Lasting psychological effects such as diminished self-worth, self-esteem and self-respect.

Reversing physical effects of addiction

Exercise and Nutrition play a crucial role in achieving the mental and physical fitness for successful recovery.

Exercise regimen needs to be started about 1 week after induction.

Exercise has been shown to be equal to drug treatment for Depression

# Triggers for Relapse

Re-Exposure to Drugs

Exposure to Stress

Exposure to Environmental CUES

(sight, smells, people), it is important to avoid old Social Geography

SALIENCE: Refers to stimuli or environmental changes that are arousing or that elicit an attentional behavior switch.

Saliency affects the motivation to seek anticipated reward

# OPIOID SIDE EFFECTS AND DANGERS



Opium Poppies in Northern Thailand  
photo by John W. Allen



## Risks of Chronic Opioid Therapy (Discussion for Patient)

### **Brain Physiological Brain Changes (Neuroplasticity)**

**CardioVascular Event:** (SCD, MI or Long QT) generally related to Methadone. Do not prescribe Methadone and Valium or drugs that could potentiate possible Long QT

**Constipation and Abdominal Pain:** Chronic Opioids can cause constipation. If this happens consider prescribing Relistor (an opioid-receptor antagonist that does not cross the blood brain barrier and can reverse opioid induced constipation with causing withdrawal or increasing pain.

**Depression:** Treat with antidepressants and/or therapy and encourage therapy

**Hormonal Dysregulation** (increase Prolactin, decreased Cortisol, Test, Estrogen, LH and FSH), Consider using HRT when indicated, consider Suboxone or Methadone or simply slowly taper the patient off Opioid Therapy

**Opioid Induced Hyperalgesia:** Taper the dosage and see if pain improves, remind the patient that opioid withdrawal in and of itself can be associated with pain and physical pain, and does not necessarily represent progression of the underlying disease. Reassess pain about 1 month after withdrawal is complete

**Suppressed Breathing, Brady and Hypotension:** Consider Sleep Study for Apnea. Try not to prescribe Benzo. Monitor for concurrent ETOH consumption.

# General Concepts

The VTA-NAc pathway is one perhaps the important area of the brain for acute rewarding effects of all drugs of abuse. **The VTA-NAc pathway is also involved in “natural addictions”** such as pathological overeating, pathological gambling and sexual addictions, although the pathway for natural reward systems is not as well understood.

Natural Addictions and Negative Emotional Symptoms: THE " HIJACKED" BRAIN HYPOTHESIS: Addictive drugs act on the same brain-reward substrates and mechanisms as do natural biologically essential rewards (e.g. food, sex), in fact addictive drugs derive much of their addictive power by activating these brain-reward substrates and mechanisms more powerfully than natural rewards.

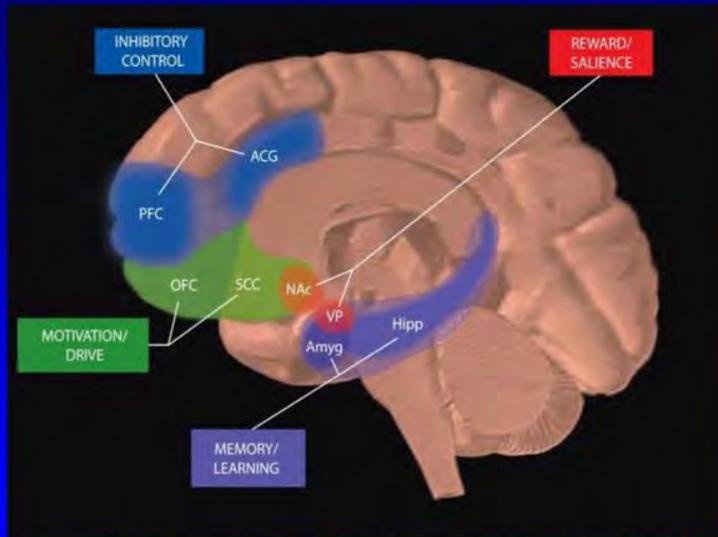
Chronic exposure to any drugs of abuse **impairs the dopamine system**, baseline levels of dopamine function are reduced, and normal rewarding stimuli may be less effective. IT IS THESE CHANGES THAT MAY CONTRIBUTE TO THE NEGATIVE EMOTIONAL SYMPTOMS that occurs in drug exposure. Prolonged drug exposure leads to reduction in the reinforcing effects of natural rewards, reduce motivation and promoting depression.

All drugs of abuse converge on a common circuitry in the brains limbic system, the mesolimbic dopamine pathway which include VTA and the NAc. Chronic exposure to several drugs of abuse can create changes in the **frontal cortical regions** and their glutamatergic outputs, which are implicated **in impulsivity and compulsivity** that characterizes a state of addiction.

Additionally, other drugs activate the brains endogenous opioid and cannabinoid systems within the VTA-NAc.

# Limbic and Frontal Areas

## *Circuits Involved In Drug Abuse and Addiction*



All of these brain regions must be considered in developing strategies to effectively treat addiction

NIDA

## Limbic System

- Several additional brain areas also interact with VTA and NAc are also important, which includes the Amygdala, Hippocampus, Hypothalamus and several areas of the frontal cortex, these structures are associated with the Limbic System and are essential not only **for learning and memory but also for the emotional context** and the affective response to learned associations. This leads to **EMOTIONAL MEMORIES**.

## Hypofrontality

- Chronic exposure can also result in “hypofrontality”, reduced baseline activity of several regions of frontal cortex. These areas control executive function, including working memory, attention and behavioral inhibition and are important in **controlling response** to environmental stimuli, in part via glutamatergic projections from these regions to the NAc and VTA.
- MORE ABOUT THE FRONT LOBE →

# Opioid and Hormonal Changes

Hypothalamic-  
Pituitary-Adrenal Axis

Decrease in plasma  
Cortisol

Hypothalamic-Pituitary-  
Gonadal Axis

Increase in Prolactin

Decrease in LH,FSH,  
Testosterone, Estrogen  
and Progesterone

Decreased Libido in  
both Men and Women

Abs R et al. J Clin  
Endocrinol Metab  
2000

# Opioid Induced Hypogonadism

**OPIOID INDUCED HYPOGONASIM:** It is well documented that hormones, such as testosterone become depleted as a direct result of long term narcotics.

Symptoms and signs suggestive of androgen deficiency in men:

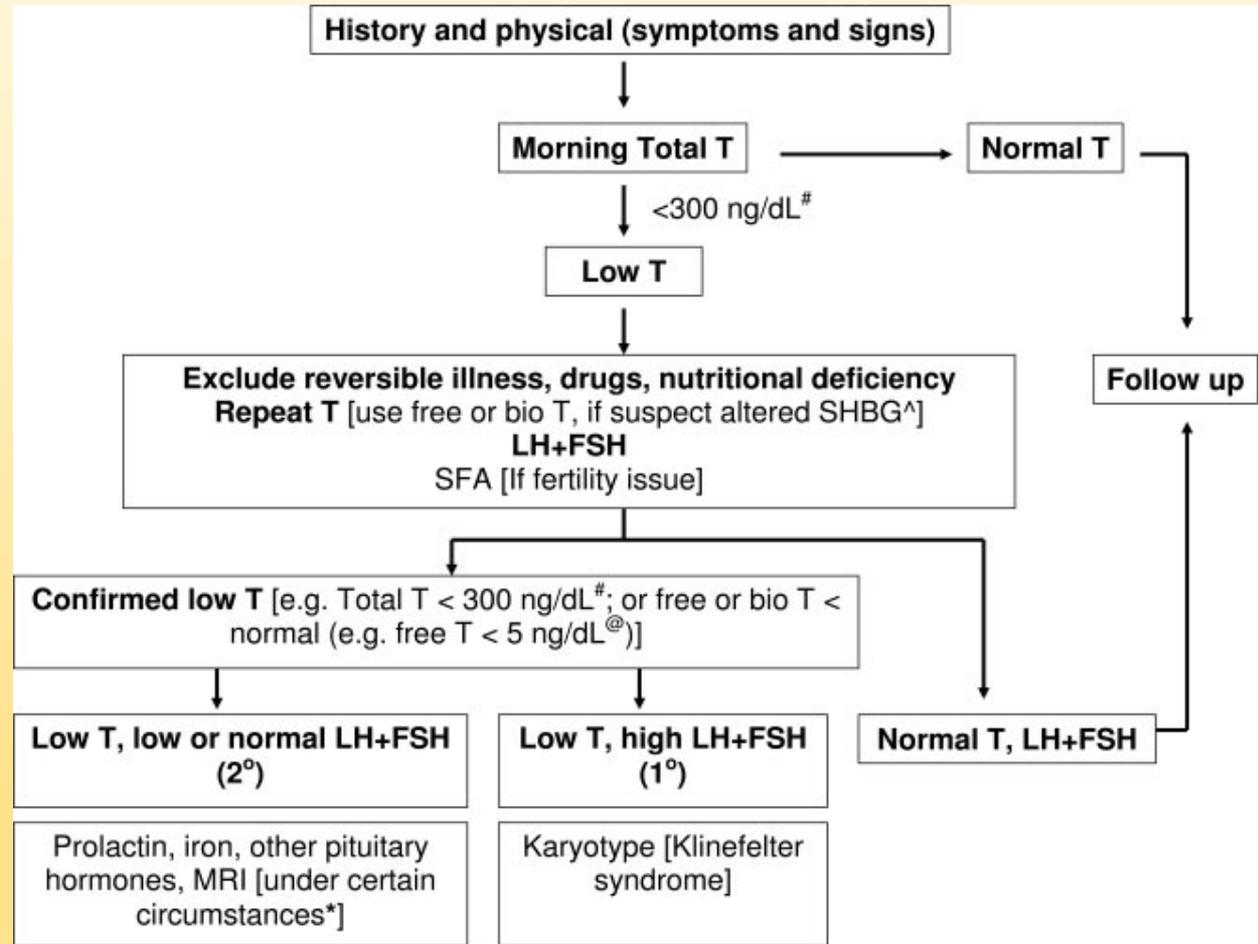
- Incomplete sexual development, eunuchoidism, aspermia
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small or shrinking testes (especially < 5 ml)
- Inability to father children, low or zero sperm counts
- Height loss, low trauma fracture, low bone mineral density
- Reduced muscle bulk and strength
- Hot flushes, sweats

**TABLE 1B. Other symptoms and signs associated with androgen deficiency that are less specific than those in Table 1A above:**

- Decreased energy, motivation, initiative, aggressiveness, self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Increased body fat, body mass index
- Diminished physical or work performance

# Approach to Low Testosterone

Perform pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumor or infiltrative disease, if severe secondary hypogonadism (serum T < 150 ng/dl), panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect, such as headache, visual impairment, or visual field defect, are present.



# Opioid Induced Hyperalgesia



Multiple studies which have concluded that opioid administration can unexpectedly cause:

- Hyperalgesia (enhanced pain response to noxious stimuli)
- Allodynia (pain elicited by innocuous stimuli)
- Witnessed in both acute and chronic opioids use and observed in both animal models and humans.
- The contribution of opioid tolerance versus opioid induced hyperalgesia is not known



Sometimes the best way to see if the patient has OIH is to see where their pain level is after they have been off Opioids for at least several months.



Multiple mechanisms in place that may explain why this occurs but nothing definitive at this time.

**Tolerance involves the NMDA receptor**

**Increase Metabolism of the Opioid**

**Decreased Nociceptive Thresholds may play a role**

TRPV-1 Receptor: Inflammation increases the expression. TRPV-1 plays a role in hyperalgesia

NK-1 neurons play a role in OIH

# Substance Dependency and Low Cortisol

- CRH then increases the pituitary release of adrenocorticotrophic hormone (ACTH). The larger amounts of ACTH released by the pituitary gland would normally induce the adrenal glands to release the necessary amount of cortisol.
- It is not surprising to find that a condition of low cortisol may be one of the driving forces that lead people to alcoholism or substance abuse.
- People with addictions appear to have stress-related hypocortisolemia

## Suggested Protocol for Evaluating Adrenal Dysfunction

1. H & P - look for signs and symptoms of low cortisol (various degrees of an Addison's presentation)
2. Labs: Blood AM (8:00am) and PM (4:00pm) total cortisol PLUS AM (8:00am) and PM (4:00pm) CBG to get the calculated FCI AM and PM
3. If lab results are not consistent with the H&P can order Cosyntropin Stim test but with Cosyntropin 1 mcg (250mcg) and cortisol levels at 30min and 60min. If the levels do not double then quite likely the person is not able to make additional cortisol in response to stress. "A normal response is a final cortisol >18mcg/dl."

ANNALS NEW YORK ACADEMY OF SCIENCES DR SCHUDER

*Stress-Induced Hypocortisolemia Diagnosed as Psychiatric Disorders Responsive to*

*Hydrocortisone Replacement*

SUZIE E. SCHUDER

Hoag Memorial Hospital Presbyterian, Department of Neurology-Psychiatry, Newport Beach, California 92660 USA

# Symptoms of Low Cortisol

- Diarrhea with stress Cravings for: sweets, salty foods, vinegar, pickles, pasta, spicy foods, lemon
- Irritable bowel syndrome
- Sore throat
- Flu-like symptoms
- Achy skin
- Headaches
- Trouble staying hydrated
- Fatigue more in afternoon
- Autoimmune disorders
- Stress-induced fatigue
- Arthritis



- SUNSHINE – DAILY ½ HOUR PER DAY
- FOOD – INCREASES CORTISOL,  
ESPECIALLY PROTEIN
- FRIENDSHIPS
- ROMANCE
- LOVE
- CREATIVITY
- MUSIC
- MEDITATION
- SLEEP REGULARLY
- REGULAR SCHEDULES
- APPRECIATION FOR ALL GOOD THINGS
- LAUGHTER
- EXERCISE

---

## Healthy Ways to Increase Cortisol





GENERAL OPIOID  
PRESCRIBING/PAIN

## Considerations for Providers (Part 1)

- Legitimate pain does not always make prescribing opioids appropriate
- Opioids prescribing is between vilification vs underutilized
- “Trial of Opioid Therapy” should always emphasize Trial
- Pain and Addiction CAN coexist
- Is it doing more to the patient than for the patient
- “A legitimate indication for a drug does not (always) make it’s use appropriate.
- Pain patients and their treatment providers may benefit more from carefully set limits and boundaries
- Do not accept the status quo, and understanding change is a process for the both the patient and the prescriber.

## Considerations for Providers (Part 2)

First, not all patients who struggle to get off opioids are “addicted”

“If they don’t need opioids, they come off them easily” is, for the most part, nonsense

Similarly, not all patients who’s pain gets worse with opioid discontinuation are best served by continuation of opioids (even if they seem to improve somewhat with reintroduction of the class)

Pain often gets better without rather than with opioids

## Considerations in Pre-Opioid Prescribing Strategies

- **SHOULD BE NOTED THAT DOSE OVER 20MG MME CAN PRODUCE OPIOID INDUCED RESP DEPRESSION**
- For acute pain, the **lowest effective dose** of immediate-release opioids should be prescribed in no greater quantity than is needed for severe pain.
- **Risk factors** for opioid-related harms should be evaluated prior to initiation and periodically during treatment. Strategies to mitigate risk should be developed, including offering naloxone to those at increased risk for overdose.
- **A patient's history** of controlled substance prescriptions using a prescription drug monitoring program (PDMP). PDMP data should be reviewed when starting opioid therapy and periodically during treatment.
- **Urine drug testing** may be used prior to initiating opioid therapy and periodically during treatment to assess for controlled prescription medications as well as illicit drugs.
- Evidence-based treatment including **medication-assisted treatment** with buprenorphine or methadone and behavioral therapies should be offered to patients with opioid use disorder.

# Drugs that Cause False-Positive in Immunoassay Testing

**Table 2. Drugs that May Cause False-Positive Results in Immunoassay Testing**

<i>Test drug or drug category</i>	<i>Drugs that may cause false-positive results</i>	<i>Duration of detectability</i>
Amphetamines	Amantadine (Symmetrel), bupropion (Wellbutrin), chlorpromazine, desipramine (Norpramin), fluoxetine (Prozac), L-methamphetamine (in nasal decongestants*), labetalol (Normodyne), methylphenidate (Ritalin), phentermine, phenylephrine, phenylpropanolamine, promethazine (Phenergan), pseudoephedrine, ranitidine (Zantac), thioridazine, trazodone (Desyrel)	Two to three days
Benzodiazepines	Oxaprozin (Daypro), sertraline (Zoloft)	Three days for short-acting agents (e.g., lorazepam [Ativan]) Up to 30 days for long-acting agents (e.g., diazepam [Valium])
Cocaine	Topical anesthetics containing cocaine	Two to three days with occasional use Up to eight days with heavy use
Opiates	Dextromethorphan, diphenhydramine (Benadryl), fluoroquinolones†, poppy seeds, quinine, rifampin, verapamil‡	One to three days
Phencyclidine	Dextromethorphan, diphenhydramine, ibuprofen, imipramine (Tofranil), ketamine (Ketalar), meperidine (Demerol), thioridazine, tramadol (Ultram), venlafaxine (Effexor)	Seven to 14 days
Tetrahydrocannabinol	Dronabinol (Marinol), nonsteroidal anti-inflammatory drugs§, proton pump inhibitors (pantoprazole [Protonix])	Three days with single use Five to seven days with use around four times per week 10 to 15 days with daily use More than 30 days with long-term, heavy use

\*—Current immunoassays have corrected the false-positive result for nasal decongestants containing L-methamphetamine.

†—Notably, ciprofloxacin (Cipro), levofloxacin (Levaquin), and ofloxacin (Floxin).

‡—In methadone assays only.

§—Notably, ibuprofen, naproxen (Naprosyn), and sulindac (Clinoril).

Information from references 10 through 13.

# UA and Adulteration Characteristics

**Table 4. Methods and Criteria for Urine Drug Screening**

**Collection methods and criteria**

Collection of split samples in sealed tamper-resistant containers

Direct observation of specimen collection (when required)

Sample size of 30 mL or more

Temperature between 90°F (32.2°C) and 100°F (37.7°C)

Urine pH of 4.5 to 8.5

Use of an approved chain of custody form to track specimen handling

**Findings suggestive of adulterated, diluted, or substituted specimens\***

General

Temperature < 90°F or > 100°F

Unusual appearance (e.g., bubbly, cloudy, clear, dark)

Adulterated

Nitrite concentration > 500 mg per dL (4.2 mmol per L)

Urine pH < 3 or ≥ 11

Diluted

Creatinine concentration ≥ 2.0 mg per dL but < 20 mg per dL (176.8 mmol per L)

Specific gravity > 1.0010 but < 1.0030

Substituted

Creatinine concentration < 2.0 mg per dL (17.68 mmol per L)

Specific gravity ≤ 1.0010 or ≥ 1.0200

\*—Guidelines from the Substance Abuse and Mental Health Services Administration. Information from references 15 and 17.

## Considerations Regarding Chronic Opioid Therapy

- Consider **Bup** as alternative to other Opioids in patients with increased risk of addiction and overdose
- Pain that progresses despite Chronic Opioid Therapy could be **OIH**.
- When **Opioid Misuse** is detected, do not terminate the patient from the practice, **taper** patient off and refer for treatment of abuse disorder
- Offer **Naloxone** at risk of Opioid Overdose
- Do not Rx **Benzo**
- When decreasing Opioids, decrease the dosage slowly (5-10% every one to four weeks) *Am Fam Phy 2012*

*AAFP 2016 April*

## Opioid Prescribing for Chronic Pain (CDC)

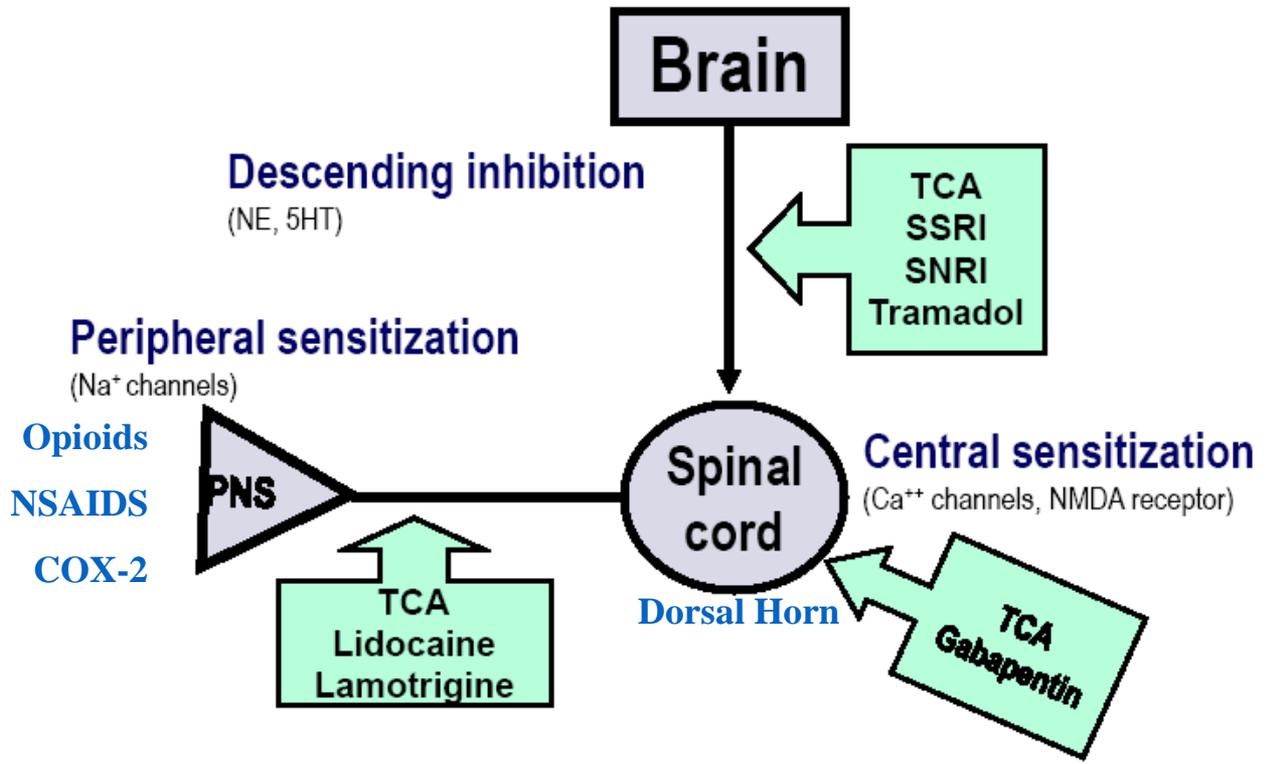
### Key Recommendations:

- Nonpharmacologic and Non-opioid pharmacologic therapies are preferred for chronic pain.
- Benefits and risks should be reassessed when increasing dosages to  $\geq 50$  morphine milligram equivalents (MME)/day. Dosages  $\geq 90$  MME/day should be carefully justified or avoided if possible.
- Opioid therapy should be considered only when benefits for both pain and function are anticipated to outweigh the risks. If opioids are used, they should be combined with non-pharmacologic and non-opioid pharmacologic therapy as appropriate.
- Realistic treatment goals for pain and function should be established before initiation of opioid therapy. Opioid treatment should be continued only if there is meaningful improvement in pain and function that outweighs risk.
- When starting opioid therapy for chronic pain, the lowest effective dose of immediate-release opioids should be prescribed instead of extended-release/long-acting (ER/LA) opioids.

# Mechanism-Specific Pain Management



## Mechanism-Specific Pain Management



# Nutrition and Pain

---

Vitamin D (Mayo, Plotnikoff and Quigley)

---

Vitamin B12

---

Vitamin C

---

Magnesium

---

Calcium

---

Omega 3 Oils

---

## Mitigating Risk for Discontinuation

---

Do not abruptly discontinue chronic therapy (opioid withdrawal)

---

Taper gradually 5-10% per week or month, can take many months

---

Unable to taper off short acting opioids, could switch to equianalgesic doses of longer-acting opioids such as Buprenorphine (keep in MME and Precipitated Withdrawal)

---

Provide withdrawal meds such as Clonidine, Neurontin, Muscle Relaxants, Zofran. However, do not use Soma (Carisoprodol has potentiating effects on opioids and alcohol. It poses a significant overdose risk when combined with alcohol, as both have gabaminergic effects. A considerable proportion of carisoprodol is metabolized to meprobamate, which is a known drug of abuse and dependence.

## How Much is Too Much?

---

- Compared with patients receiving 1-20 mg/d of morphine equivalents, patients receiving 50-99 mg/d had a 3.7-fold increase in overdose risk

---

- Patients receiving 100 mg/d or more had an 8.9-fold increase in overdose risk with a 1.8% annual overdose rate

---

- Morphine equivalent doses over 120 mg/d doubled the risk of alcohol-or drug-related health services utilization encounters (withdrawal, intoxication, overdoses)

# Legal Aspects of Opioid Prescribing



## STATE LAW REQUIRES THE FOLLOWING FOR RECORD KEEPING:

- **Physicians should document pain levels, levels of function, and quality of life. Medical documentation should include both subjective complaints of patient and caregiver and objective findings by the physician. “**
- “The physician and surgeon should keep accurate and complete records according to items above, including the medical history and physical examination, other evaluations and consultations, treatment plan objectives, informed consent, treatments, medications, rationale for changes in the treatment plan or medications, agreements with the patient, and periodic reviews of the treatment plan.
- Physicians should document periodic reviews at least annually or more frequently as warranted.

*Records: STATE OPIOID PRESCRIBING POLICY: CALIFORNIA BY JENNIFER BOLEN, JD*

Consider	Consider Suboxone in order to treat addiction and chronic pain
Initiate	Initiate therapy when the patient is in withdrawal
Refer	Refer to Maintenance Treatment Clinic (MAT) if necessary (i.e. insurance) or Specialized Addiction Treatment Center
Taper	Taper Opioids and consider Naltrexone or Buprenorphine or Tramadol if appropriate
Offer	Offer Naloxone, an opioid receptor antagonist that can reverse overdose if seems appropriate

## OPIOID USE DISORDER: WHAT NEXT?

# MAT (MEDICATION-ASSISTED TREATMENT) Opioid Addiction

- Buprenorphine/Suboxone
- Naltrexone
- Methadone

## MAT (Medication-Assisted Treatment)

1. Induction
2. Stabilization
3. Maintenance

Suboxone  
Methadone  
Naltrexone

---

Half of US Counties do not have a single prescriber of medication to treat Opioid Add

---

MAT: Medical Therapy with Opioid Agonist or Antagonist should be with counseling/recovery support

---

MAT is superior to withdrawal alone (big surprise)

---

MAT decreases rates of infectious disease

---

Cochrane review (2014) showed no difference in retention or suppression of illicit opioid use between Methadone and Buprenorphine

---

# Receptor Affinity Clarification

AFFINITY is the strength with which a drug physically binds to a receptor

Naloxone, naltrexone or buprenorphine show very strong affinity and will displace full agonists like heroin and methadone

Note receptor binding strength (strong or weak), is NOT the same as receptor activation (agonist or antagonist)

This is clinically important in overdose rescue (naloxone), and in timing of first dose (buprenorphine, naltrexone).

If receptor activation is less, a drug with strong affinity can precipitate painful withdrawal.

## **BUP IS PREFERRED: WHY?**

- Lower Risk of Overdose
- More flexible at-home dosing
- Lower Risk of Diversion
- However Methadone should be considered with those with very high daily doses of Opioids and hx of severe withdrawal symptoms

(JAMA July 2016)

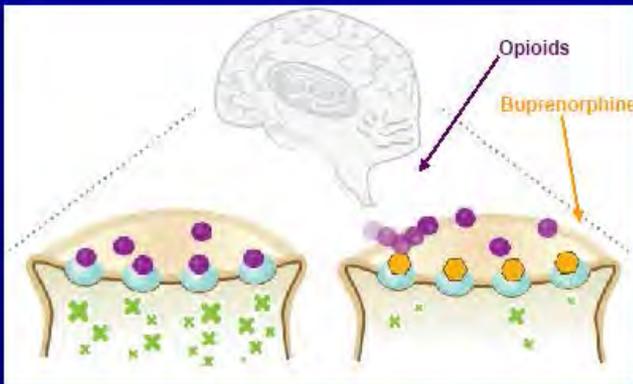
MAT (Medication-Assisted  
Treatment)  
Buprenorphine



# Buprenorphine Characteristics

## Key Properties of Buprenorphine: High Affinity for $\mu$ Receptor

Slow Disassociation Due to Tight Receptor Binding



- Blocks effects of subsequently administered opioid agonists
- Long duration of action

4

## Buprenorphine: Analgesic Profile

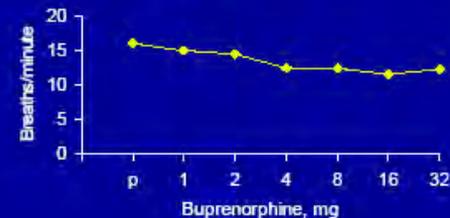
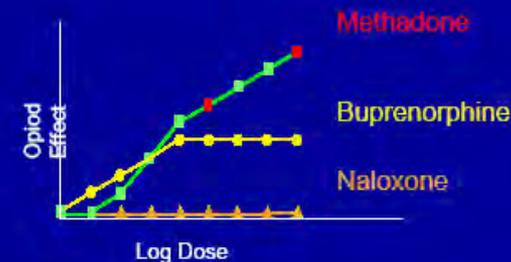
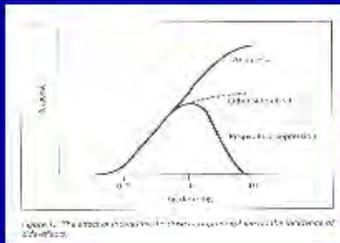
- Rapid onset of action
- Long duration of peak effect (60-120 min)
- Long half life (3.5 hrs)
- Analgesic action up to 8 hrs.
- Low physical dependence profile

*Semisynthetic Opioid  
Partial Agonist Mu Receptor*

# Buprenorphine Characteristics

## Key Properties of Buprenorphine: Ceiling Effect

- Pharmacologic ceiling effect for buprenorphine provides high safety profile
- Ceiling effect on respiratory depression



Partial agonist at mu receptor (hence negating the potential for life-threatening resp depression, unlike Methadone)

Important to note that researchers feel that benzo's may alter the ceiling effect and therefore make Bup more dangerous when taken together.

# Buprenorphine Formulations

Buprenorphine/naloxone tablets



Buprenorphine Product Formulation Comparison - <http://www.buprenorphine.com/portal/12206>

PSYCHOPHARMACOLOGY INSTITUTE

## Monotherapy : 2002: FDA approved for treating opioid dependence, DEA scheduled III narcotic:

- Buprenorphine (generic): Sublingual Tablets: 2 and 8 mg
- Probuphine: 74.2 mg Subdermal Implants (4 implants for 6 months)
  - 4 implants are inserted in the upper arm for 6 months of treatment and removed by the end of the sixth month.
  - Not appropriate for New Entrants, only Maintenance Treatment with about 8mg Buprenorphine containing products

## Combination Medications (Buprenorphine/Naloxone)

- Bunavil: Buccal Films
- Buprenorphine/Naloxone (Generic): Sublingual Tablets (2/0.5 and 8/2mg)
- Suboxone Film: 2,4,8 and 12 mg Sublingual Films
- Zubsolv: 1.4, 5.7, 8.6, and 11.4 Sublingual Tablets

Note: Butrans Patch (preparation for Chronic Pain)

# New Buprenorphine Formulation

## INDICATION AND USAGE:

- SUBLOCADE is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
- SUBLOCADE should be used as part of a complete treatment plan that includes counseling and psychosocial support.

## PRESCRIBING INFO:

- SUBLOCADE should only be prepared and administered by a healthcare provider.
- SUBLOCADE is administered monthly only by subcutaneous injection in the abdominal region.
- The recommended dose of SUBLOCADE is two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses.
- Increasing the maintenance dose to 300 mg monthly may be considered for patients in which the benefits outweigh the risks.



**Sublocade™**  
(buprenorphine extended-release)  
injection for subcutaneous use   
100mg•300mg

## Safety and Interactions of Buprenorphine (not complete)

### Safety

- Hepatic Considerations (screen LFT's, Hepatitis, Liver Dz)
- Perinatal Effects
- Respiratory Depression
- Opioid Withdrawal Effects

### Drug Interactions:

- Anticholinergics
- Benzodiazepines
- Cyto p450 3A4 Inducers (Phenobarbital, Tegretol, Dilantin, Rifampin) may lead to increase clearance of Buprenorphine
- Cyto p450 3A4 Inhibitors (Azoles, Macrolides, Protease Inhibitors, Antidepressants) may lead to decrease clearance of Buprenorphine
- Soma/Flexeril (Increase chances of Resp Depression)
- Other CNS depressants, (i.e. Hypnotics, ETOH)
- Cocaine leads to decrease in Buprenorphine

# Buprenorphine Treatment Considerations

Please do not drink water while you have the pill dissolving in your mouth. The drug will not well absorbed in the stomach and as such must be given time to be absorbed from the under the tongue.

Please do not lie. Do not take “one for the road”, doing this will set you up for very bad withdrawal (precipitated withdrawal) and you could up be hospitalized and spending a lot of money unnecessarily not to mention putting your life at risk.

Please give adequate time for the pill to be absorbed. It is important to have the pill to be FULLY dissolved underneath your tongue. Spit saliva out if nauseated.

You should take some time off of work during the time you are in Acute Withdrawal. This usually is around 2-5 days.

You should also NOT drive while you are in withdrawal.

**How do you assess Opioid Withdrawal?**

# Opioid Withdrawal Syndrome

## Spontaneous Opioid Withdrawal Syndrome

- Develops spontaneously if a physically dependent person suddenly stops, or markedly decreases, the opioid use
- Severity is usually less with longer half-life drugs
- Duration depends on half-life of opioids person uses

	Onset	Peak	Duration
Heroin	4 - 6 hours	~3 days	4 - 5 days
Methadone	1 - 2 days	~7 days	12 - 14 days

**(COWS) Clinical Opiate Withdrawal Scale: Pulse, Sweating, Restlessness, Anxiety, Pupil Size, Aches, Runny Nose & Tearing, GI Sx, Tremor, Yawning, Gooseflesh**

**SCORE: Mild (5-12), Mod (13-24), Mod Severe (25-36), Severe (36-48)**

## INDUCTION STAGE

**Induction Stage:** In general, induction procedures used for each patient depend on the unique properties of each medication, prevailing regulatory requirements, patient preferences, and safety.

- **Day 1:** 4mg (½ 8mg) IS GIVEN, FOLLOWED AFTER 4 HOURS WITH UP TO 4mg if needed, but the total on day 1 should NOT exceed 8mg. Most cases first dose should be given when the COWS scores is 10 or above
- All opiate clients will be assessed utilizing COWS and be administered Buprenorphine during the “Induction Phase of Treatment.”
- COWS assessment will be done at the start of Induction and every 2-3 hours during the day until the COWS Score is less than 5, at that point discontinue doing COWS, unless symptoms worsen.
- The first Buprenorphine Dose will be 4mg {1/2 8mg pill} and should be ONLY given if the client’s COWS score is above 10 to 15.
- The client will then be reassessed every 3-4 hours. The client will continue to receive 4mg Buprenorphine one time after 4 hours evaluation for total of 8mg in 24 hours. There are rare cases where clients may need more.
- **Buprenorphine will not be give more than 8mg Max Suboxone the first day (TIP 43)**
- However, there may be times when the dosing amounts may change depending on individual needs and in some instances like switching to Buprenorphine from Methadone.

## STABILIZATION STAGE

**STABILIZATION STAGE:** The goal is to eliminate the patient's drug-seeking behavior, craving, and illicit opioid use or prescription opioid abuse. Optimal dosage should be determined by patient response, but some guidelines exist for the following medications

- **Buprenorphine.** For most patients, the stabilization dosage is 12–16 mg per day, although some patients may need up to 32 mg per day. Increasing the dosage to 24 mg or more per day is usually necessary for every-other-day dosing schedules.
- **Day 2:** Give total Day 2 dose in 4 divided doses (i.e. Total Day 2 16mg, then give 4mg qid)
- **Day 3:** Move toward once or twice daily dose. (i.e. Total Day 3 16mg, then give 8mg bid)

## MAINTENANCE STAGE

**MAINTENANCE STAGE:** The goal is for the patient to resume normal functioning while continuing to receive regular medication dosages, without the need for routine dosage adjustments.

- Patients in this stage
- Are responding well to treatment and dosage
- Have stopped substance abuse
- Have resumed productive lifestyles
- Typically have received take-home medication privileges
- May remain at the same dosage for many months or years

# MAT Supportive Medications to be Considered

Zofran: 8mg TID 2-3 days prior to stopping Opioids. (This research is based from Dr. Clark's research at Stanford University.)

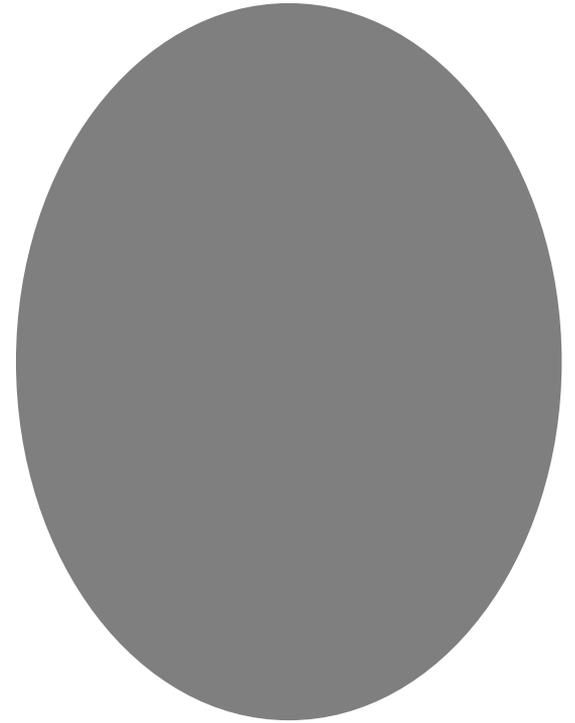
Clonidine and CNS Depressants may also have some help in decreasing agitation, insomnia and anxiety

Neurontin 300mg 1-2 pills po qhs

Various PRN medications can also be considered

# Methadone Characteristics

- Constipation
  - Slight QTc prolongation on ECG
  - Sweating
  - Methadone Drug Interactions
- 
- Naturally long acting
  - Bioavailability 80%
  - Metabolized by cytochrome P450 system
  - No active metabolites
  - Methadone Drug Interaction



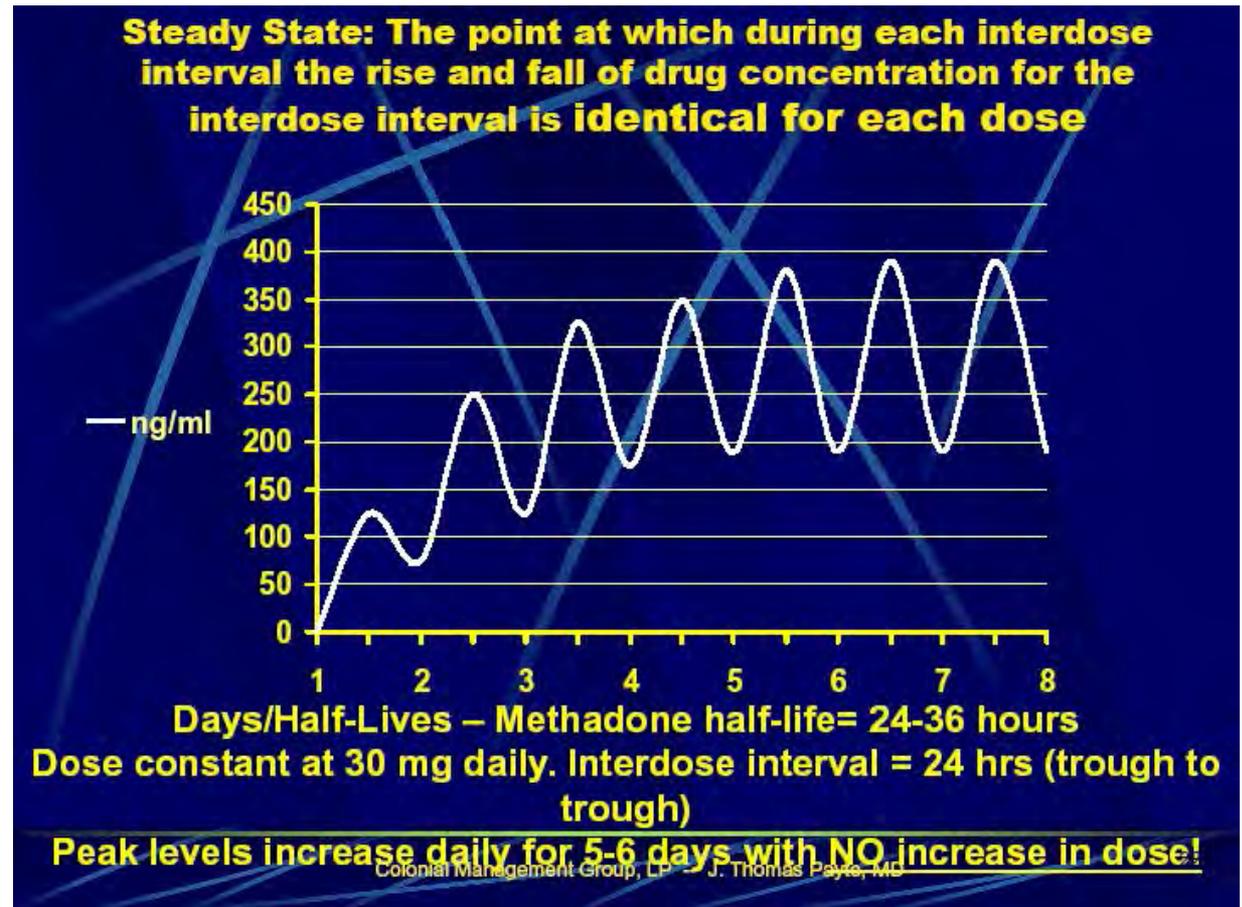
# MMT: Steady State

## Induction: 3-7 days

- First Dose Regulated to 30mg, 40mg/24hr
- Peak levels increase daily for 5-6 days with no increase in dose 1/2 life is 24-36 hrs.

## Stabilization: 2-8 weeks dose titration

## Maintenance: Steady Dose



# Methadone Interactions (incomplete)

- **Decreases methadone levels**

1. *Phenytoin*
2. *Phenobarbital*
3. *Carbamazepine*

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- **Increases Methadone levels (CYP4503A4)**

1. *Fluoxetine*
2. *Paroxetine*
3. *Tricyclics.. May increase tricyclic levels*

*NOTE: Sertraline has no interaction with CYP4503A4*

# Buprenorphine vs Methadone

**Table 2. Comparison of Buprenorphine or Buprenorphine–Naloxone and Methadone for the Treatment of Opioid Dependence**

Characteristic	Buprenorphine or Buprenorphine–Naloxone	Methadone
Pharmacologic action at $\mu$ opioid receptor	Buprenorphine (partial agonist) and naloxone (full antagonist)	Full agonist
Clinical indication	Pharmacologic withdrawal, maintenance therapy	Pharmacologic withdrawal, maintenance therapy
Route of administration	Sublingual*	Oral
Dose	Buprenorphine, 2–32 mg† (20); naloxone, 0.5–8 mg*	20–120 mg†
Frequency of administration	Daily or 3 times weekly	Daily
Primary side effects (unrelated to withdrawal syndrome)	Headache, nausea, sweating, constipation, rhinitis (21–23)	Cardiac dysrhythmia, hypotension, diaphoresis, constipation, nausea, vomiting, asthenia, dizziness, lightheadedness (24), sedation
Contraindications	Need for ongoing full opioid agonist medications to obtain pain relief; hypersensitivity to either compound	Hypersensitivity
Use in pregnancy	Category C: Buprenorphine–naloxone is not recommended in pregnancy and should be replaced with methadone or buprenorphine alone	Category C: Methadone is considered current standard of care for treatment in pregnancy because there are more data on its safety in pregnant patients
Location of prescribing and dispensing treatment of opioid dependence	A physician's office or opioid treatment programs	Opioid treatment programs
Regulations on prescribing and dispensing treatment	Physicians can prescribe only with a special registration certificate code issued from the Drug Enforcement Administration; 30-patient census per prescriber in first year and 100-patient census thereafter; pharmacies can dispense up to a 30-day supply on the basis of schedule III	Physicians can prescribe methadone only to patients with opioid dependence for up to 72 hours as a bridge to treatment entry; only licensed opioid treatment programs can dispense methadone; federal regulations govern frequency of medication dispensing (e.g., daily, 3 times weekly, weekly)
Insurance coverage	Variable, depending on insurance plan	Variable, depending on insurance plan

\* Naloxone is not well absorbed sublingually, resulting in a primary buprenorphine effect. Naloxone is added to discourage injection misuse.

† Lower doses typically reflect dose initiation or dose tapering in stabilized patients.

# Naltrexone

- Pure opioid antagonist
- Oral naltrexone
  - Well tolerated, safe
  - Duration of action 24-48 hours
  - FDA approved 1984
- Injectable naltrexone (Vivitrol®)
  - IM injection (w/ customized needle) once/month
  - FDA approved Oct 12, 2010
  - patients must be opioid free for a minimum of 7-10 days before treatment

## Naltrexone Induction/Stabilization

### **Induction**

- Patients should be abstinent from short-acting opioids for 7 days and long-acting opioids for 10 days.
- Initial dosing is 25 mg followed by 50 mg on day 2 if no withdrawal symptoms occur, then 50 mg per day up to 350 mg per week.

### **Stabilization**

- A daily 50 mg a day or the weekly equivalent three times a week.
- For example, if the patient is taking 50mg a day, you can switch the patient to 100mg three times a week (300mg).

# Naloxone

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Provided to Health Professionals

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Dispensed directly to Non-Professionals as part of a drug overdose prevention

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Prescribed by Physicians and Dispensed via retail pharmacies

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2014, FDA fast-tracked approval of a new delivery device for Naloxone that can be used by Lay-Person with little or no training

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California Law



## California Law and Naloxone

- AB635 in effect since 1 January 2014
- Designed to encourage CA healthcare providers and community programs to widely distribute naloxone

Expands previous naloxone legislation in CA:

- **Allows for prescription and distribution throughout the state.**
- **Protects licensed health care professionals** from civil & criminal liability when they prescribe, dispense, or oversee distribution via a standing order of naloxone via an overdose prevention program or standard medical practice.
- **Permits individuals to possess and administer naloxone in an emergency** and protects these individuals from civil or criminal prosecution for practicing medicine without a license.
- Clarifies **that licensed prescribers are encouraged to prescribe naloxone to individual patients** on chronic opioid pain medications to address prescription drug overdose.

# Naloxone

1

The most common used Opioid Antagonist used in treatment of Opioid Overdose

2

Acts quickly, non-addictive

3

Dispensed by Injection (IM) or Nasal

4

Prompt Action by non-professional who observe someone experiencing opioid overdose increase survival

# Naloxone Forms



## How to Prescribe Naloxone

### Two Formulations (Older and **Newer**):

- Injectable

- Naloxone 0.4mg/1ml single dose vial, inject 1 ml IM if overdose. Call 911. Repeat if necessary. IM syringes (3ml 25 g 1" syringes are recommended)

- Autoinjector (Evzio): 0.4mg/injection carton of 2

- Intranasal

- Naloxone 2mg/2mL prefilled syringe, spray ½ into each nostril if overdose. Call 911. Repeat if necessary. MAD (Mucosal Atomization Device) nasal adapter.

- Nasal Spray: 4mg/0.1ml, two blister packages of one dose each

Recipient need not be the person to whom naloxone is administered

*SBIRT codes cover education in 15 minute intervals*

- Medicare – G0396

- MediCal – H0050

- Commercial – CPT 99408

# **NARCAN<sup>®</sup>** (naloxone HCl) **NASAL SPRAY**

## **QUICK START GUIDE** Opioid Overdose Response Instructions

Use NARCAN<sup>®</sup> (naloxone hydrochloride) Nasal Spray for known or suspected opioid overdose in adults and children.

**Important:** For use in the nose only.

Do not remove or test the NARCAN Nasal Spray until ready to use.

### **1** Identify Opioid Overdose and Check for Response

**Ask** person if he or she is okay and shout name.

**Shake** shoulders and firmly rub the middle of their chest.

**Check for signs of an opioid overdose:**

- Will not wake up or respond to your voice or touch
- Breathing is very slow, irregular, or has stopped
- Center part of their eye is very small, sometimes called "pinpoint pupils"

Lay the person on their back to receive a dose of NARCAN Nasal Spray.



### **2** Give NARCAN Nasal Spray

**REMOVE** NARCAN Nasal Spray from the box.  
Peel back the tab with the circle to open the NARCAN Nasal Spray.

**Hold** the NARCAN Nasal Spray with your thumb on the bottom of the plunger and your first and middle fingers on either side of the nozzle.

**Gently insert the tip of the nozzle into either nostril.**

• Tilt the person's head back and provide support under the neck with your hand. Gently insert the tip of the nozzle into one nostril, until your fingers on either side of the nozzle are against the bottom of the person's nose.

**Press the plunger firmly** to give the dose of NARCAN Nasal Spray.  
• Remove the NARCAN Nasal Spray from the nostril after giving the dose.



### **3** Call for emergency medical help, Evaluate, and Support

**Get emergency medical help right away.**

**Move the person on their side (recovery position)** after giving NARCAN Nasal Spray.

**Watch the person closely.**

**If the person does not respond** by waking up, to voice or touch, or breathing normally another dose may be given. NARCAN Nasal Spray may be dosed every 2 to 3 minutes, if available.

**Repeat Step 2 using a new NARCAN Nasal Spray to give another dose in the other nostril.** If additional NARCAN Nasal Sprays are available, repeat step 2 every 2 to 3 minutes until the person responds or emergency medical help is received.



# Naloxone Safety Profile

**Short-acting (30--60 minutes), highly specific, high affinity mu opioid receptor antagonist**

The only element of the coma cocktail that can be safely administered alone

Only contraindication is a known allergy to naloxone

Opioid withdrawal symptoms generally mild at lay-distributed doses

Opioid effect will return, a significant concern mostly for long-acting opioids, so call 911

Essentially no effects if opioids not present

QUESTIONS?

