

Pain and Addiction

Diagnostic and Therapeutic Strategies for Diagnosing and Treating Both Conditions

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Educational Objectives

- Apply understanding of neurotransmission of pain to identify therapeutic interventions
- Increase identification of addictive behavior in patients on chronic pain medications
- Develop clinical strategies to minimize risk of addiction when prescribing opioids
- Improve understanding of set points of self administration to monitor for the development of tolerance and physical dependence
- Review pharmacology of opioid medications with emphasis on use of buprenorphine for management of concurrent pain and addiction



Epidemiology of Pain

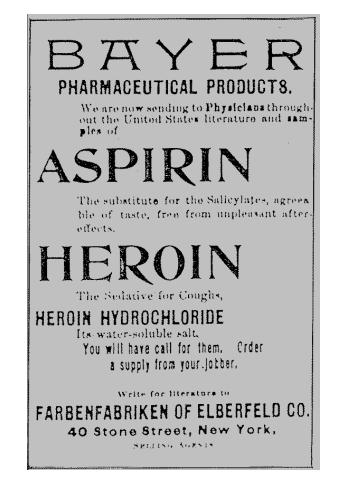
- Pain > 4 billion work days lost per year.
- Causes more disability than cancer and heart disease combined.
- Up to 34 million Americans suffer from pain.
- Aging population will make the problem worse.
- Pain is the most common complaint for which individuals seek medical attention

× Brian Goldman, M.D., FACEP ASAM Pain and Addiction, Common Threads II



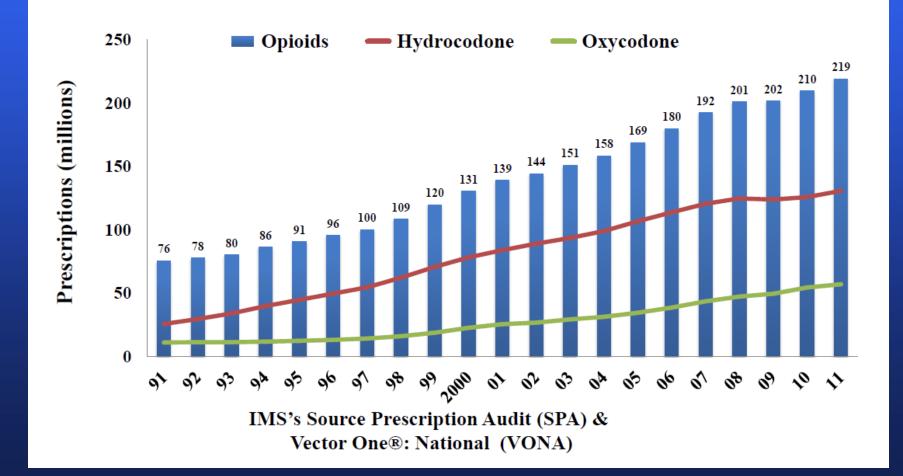
Physician, 1894

"We have an army of women in America dying from the opiate habit - larger than our standing army. The profession (medicine) is wholly responsible for the loose and indiscriminate use of the drug."



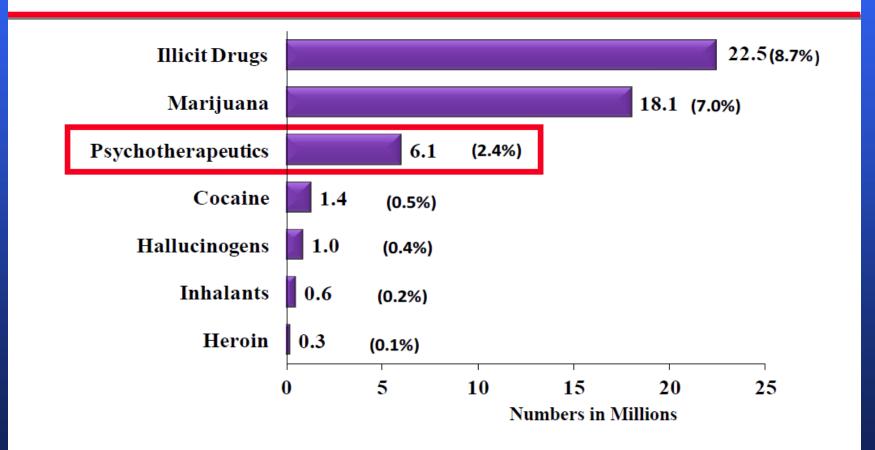
Opioid Prescriptions 1991-2012

Number of Opioid Prescriptions Dispensed by U.S. Retail Pharmacies, Years 1991-2011



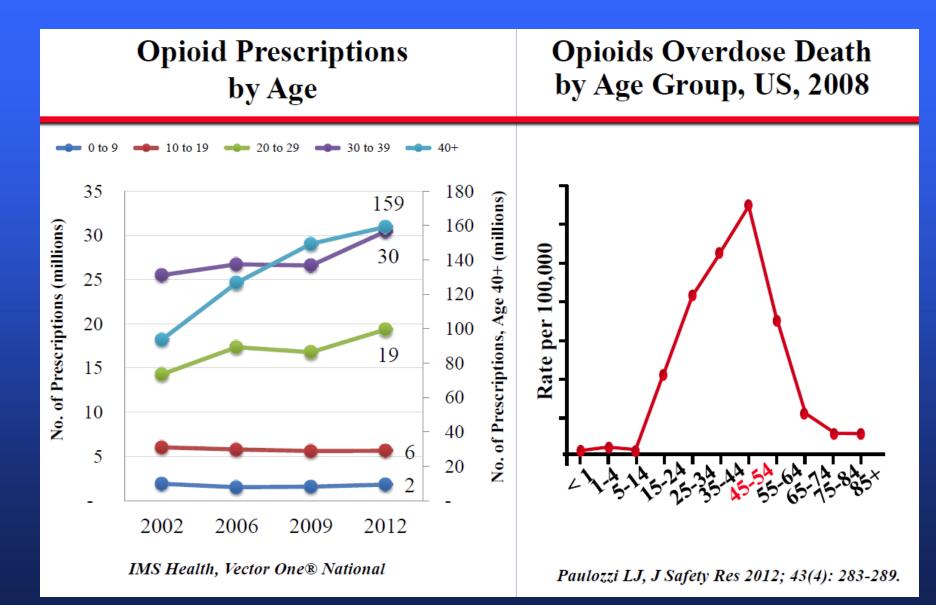
Rates of Misuse / Abuse

Prescription Drug Misuse/Abuse is aMajor Problem in the US Current Drug Use Rates in Persons Ages 12+



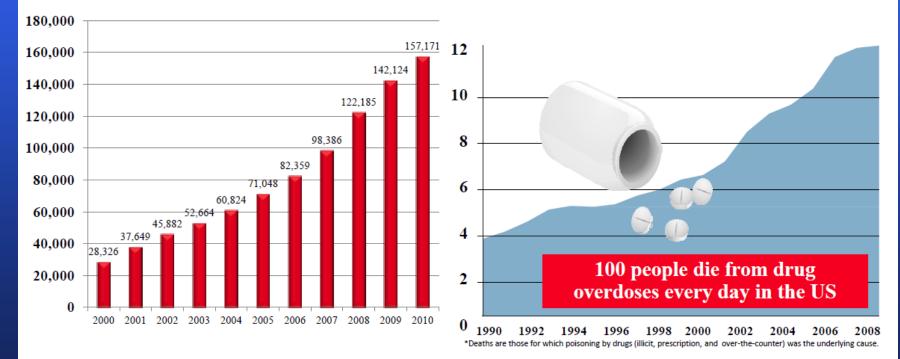
Source: SAMHSA, 2011 National Survey on Drug Use and Health, 2012.

OD and Scripts by Age



Admissions & OD by Year

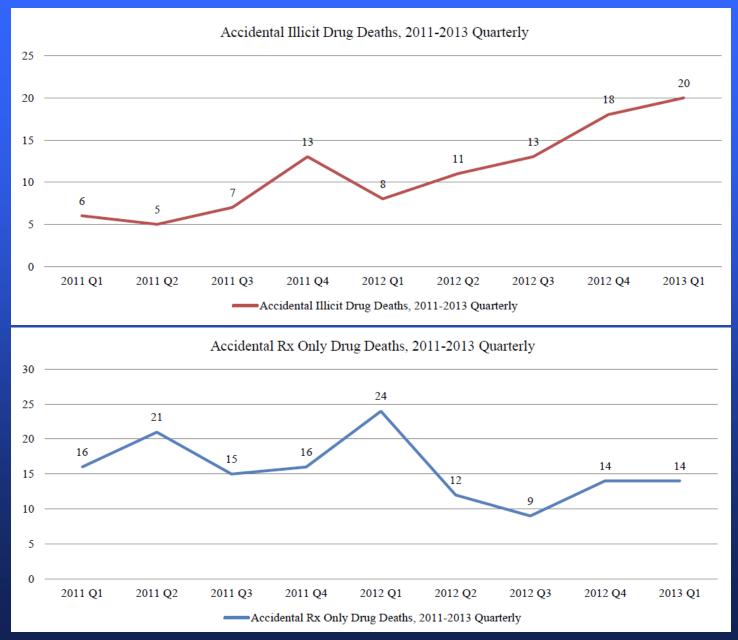
More Than 5-Fold Increase In *Treatment Admissions For Prescription Painkillers* In the Past Decade Drug OD in the US Have More Than Tripled since 1990 and INCREASES Greater for Women (Five-FOLD)



Source: SAMHSA Treatment Episode Data Set (TEDS), 2000-2010 National Vital Statistics System. Drug Overdose Death Rates by State 2008.

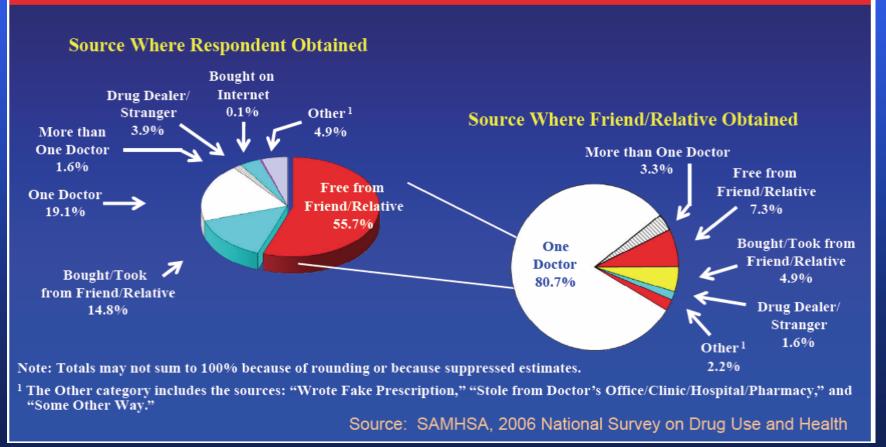
CDC Vital Signs, July 2013.

RI Medical Examiner OD Deaths



Source of Non-Medical Opioid Misuse

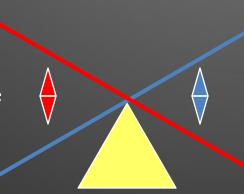
Where are the prescriptionopioids obtained? Source of PrescriptionOpioids for Most Recent NonmedicalUse: Ages12+



Pain Relief & Recovery : Balancing Act

Medical

Pain Relief Improvement in Functioning Monitor adherence + diversion Tolerance + physical dependence Breakthrough pain Drug seeking behavior



Addiction

Withdrawal severity Substance use history Believe pain complaints Preoccupation with supply Detoxification Relapse prevention Distinguish between an addict and a patient with pain?

- Patients with active addictions with painful conditions
- Recovering patients with painful conditions
- Patients who misuse
- Patients who abuse to get high
- Patients who abuse to self-medicate

Tolerance

The need for an increased dosage of a drug to produce the same level of analgesia that previously existed. Tolerance also occurs when a reduced effect is observed with constant dose. Analgesic tolerance is not always evident during opioid treatment and is not addiction.

Pseudotolerance

- The need to increase dosage due to other factors such as:
- Disease progression, new disease, increased physical activity, lack of compliance, change in medication, drug interaction, addiction, and deviant behavior.

Hyperalgesia and Rebound

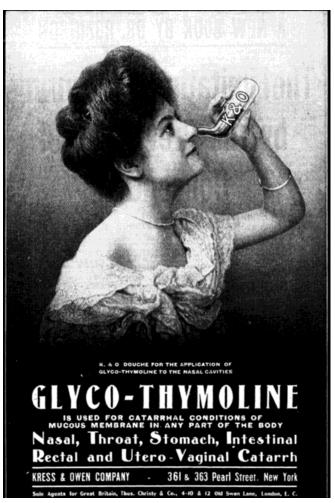
- Common and under recognized in high dose opioid analgesic treatment as well as in opioid maintenance therapy
- Pain-opioid spiral
- Rebound headaches: transformed migraines
- Role of medication withdrawal

Physical dependence

- Indicated by the occurrence of withdrawal symptoms after opioid use is stopped or quickly decreased without titration, or if an antagonist is administered
- Can be avoided by warning patients not to abruptly stop the medication and by using a tapering regimen
- Physical dependence is not addiction

Drug misuse

- Unintentional consumption of a drug in other than the commonly accepted manner.
 - Physician misprescription
 - Patient misunderstanding



Drug abuse

- Deliberate misuse of a drug.
 - Self-medication
 of painful
 feelings and/or
 reality
 To get high



Patient Interviews : CNS Productions

Dr. Darryl Inaba

Co-founder of Haight Ashberry Clinic Research Director, CNS Productions

Excerpts – part one – Beyond Pain

Risk of Addiction

Lifetime prevalence of addiction in general population is 3%-16%.

× Regier, Meyers, & Kramer, 1984

Adapted from Don Kurth, MD-Non Narcotic Pain Management-Common Threads Conference 2002



Hierarchy of Risk to Addiction

Risk to becoming addicted to therapeutic opioids depends upon interaction between personal and family history and environmental stressors

Personal history of opioid addiction

Person history of non-opioid addiction

Family history of addiction

No personal or family history of addiction + stressors

No personal or family history of addiction, no stressors



Low Risk

High Risk

Risk of Addiction When Treating Pain

- Acute Pain Low Risk of Addiction
- Chronic Pain Up to 50-70%

- <u>Living with Pain</u> Richard L. Reilly, D.O.

Adapted from Don Kurth, MD-Non Narcotic Pain Management-Common Threads Conference 2002

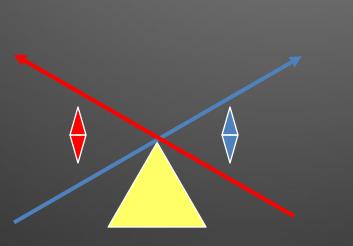


Intoxication & Withdrawal

Opioid See - Saw Effect

Intoxication

OD Nodding High Pain relief Relaxation Pinned pupils Comfortable Drug desire



Withdrawal

Vomiting Diarrhea Cramps Sweats Nausea Chills Bone Aches Restlessness Craving

Same order of appearance & disappearance

As dose increases, withdrawal severity lessens As dose decreases, withdrawal severity worsens

Signs & Symptoms of Opioid Withdrawal

Mild - subjective

Fear of withdrawal

Craving

Anxiety & irritability

Restlessness

Bone aches

Yawning

Hot and cold sensations

Sneezing

Nausea & cramps

Severe - objective

Dilated pupils

Runny nose

Teary eyes

Sweating

Diarrhea

Gooseflesh

Vomiting

Increased blood pressure

Increased pulse



Self Administration Signals

Self administration and medication compliance require:

- Understanding of dosing instruction
- Awareness of dose response
- Timing of appearance and disappearance of pain-relief symptoms
- Availability of drug
- Experience with drug
- Changes over time in dose response



Self Administration Signals

Set points for self administration

• thoughts, feelings and behaviors that occur when:

"On" signal

Pre next dose signal that results in decision to take next dose

"Off" Signal

 Dose that results in undesirable side effects of excessive sedation, mental clouding, nausea, dizziness, etc that result in decision to not take as much next time

"Ah" Signal

 Dose that results in the desirable effect – pain relief, anxiety reduction, sleep, energy, etc



Drug Effect Set Points of Drug Self Administration OD Nodding Off High Pain relief Relaxation Pinned pupils Comfortable Drug desire Craving Restlessness Bone Aches Chills Nausea Sweats Cramps Diarrhea

On

Withdrawal

Vomiting

Self Administration Signals

Set points for self administration

- Use COWS withdrawal assessment scales (may require modification for improved sensitivity) to identify pre-dose signal
- Compare onset of pain to any withdrawal associated symptoms
- If on signal = withdrawal symptoms and expectation of worsening with delay of dosing AND pain severity is mild, then pain generator is really withdrawal mediated and not underlying condition = good candidate for buprenorphine or increasing dosage of medication
- If the on signal is associated with high dose effects (closer to the ah and off signal), then the desired effect is more likely to be addiction related



Changes in Set Points in Addiction

Non Addict in Pain Addict in Pain

On Moderate Pain severity Mild Withdrawal Symptoms

AhFunctional Pain ReliefDesired Side Effect

Off Negative Side Effects

Coma - Death



Addictive behavior vs Medical dependence

- Primary purpose: euphoria
- Rapid dose
 escalation as
 tolerance develops
- Abstinence unlikely to be maintained despite frequent attempts

- Relief of pain
- Constant dose and frequency with slow increases for tolerance Usually able to
 - abruptly stop or if wd develops can be successfully

Addictive behavior vs Medical dependence

- Function:
 frequent
 intoxication
- Behavior: focus on drug-seeking to exclusion of socially productive activities
- Able to function productively; in acute pain states slight sedation may occur
- Able to engage in productive activity due to relief of pain

Addictive behavior vs Medical dependence

- Side effects common due to dose and routes of administration; continued use despite complications
- Polydrug use frequent

- Mild, manageable side effects
- Polydrug use rare unless prescribed by physician

Suspect Addiction Associated with Chronic Opioid Therapy

- Adverse consequences of opioid use.
- Loss of control over medication use.
- Preoccupation with opioids.
- Does not actively participate in an addiction treatment program.

• Savage, 1998.



Adapted from Don Kurth, MD-Non Narcotic Pain Management-Common Threads Conference 2002

Is Patient Using Drugs Addictively?

What is the nature of the relationship between patient and drug?

- Did they want to take more?
 × If one is good, two is better
- Did the thought of stopping increase desire for the drug?
 ×Loss of supply requires awareness of "special relationship"
- Is there awareness of the need to cut down or control use?
 ×Awareness of cutting down or controlling use = problem
- Is the use resulting in negative feelings toward use
 × Feeling guilty about using and continuing to use = use despite consequences
 × Social users and adequately dosed pain patients aren't guilty about use
- Are any family members or friends giving feedback to them about their use?
 × Usually adequate treatment does not result in others worrying about use
 × When someone is annoyed at feedback, then they have a problem

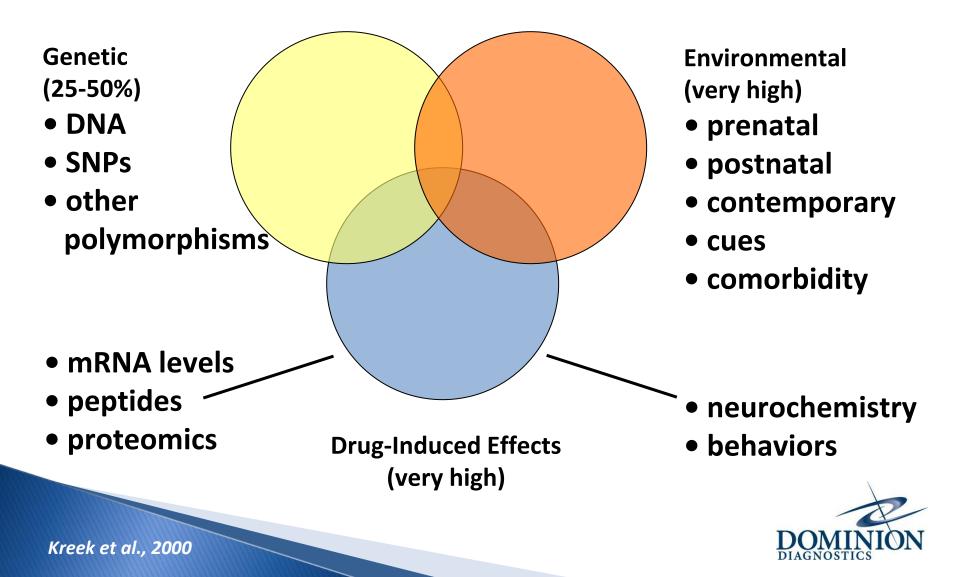


5 Questions : Risk Assessment

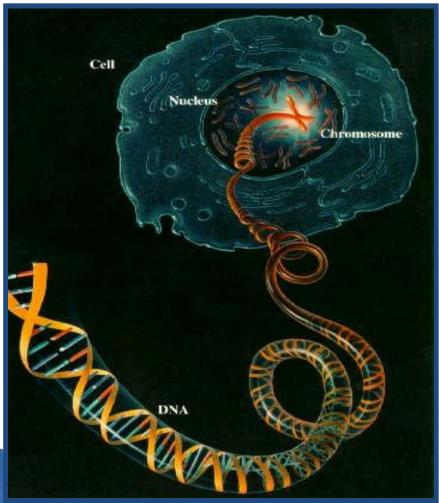
- -Atypical Response
 - "Perc Up" + Motivation opioids
 - Slow down + focus stimulants
- –Hollow Leg inherited tolerance
- -Minimal severity of hangovers
- -Co-occurring ADD, PTSD, Mood, etc
- -Family history of alcohol & drugs



Factors Contributing to Vulnerability to Develop a Specific Addiction



The Human Genome



 In the human genome, there are ~3 billion bases (nucleotides)

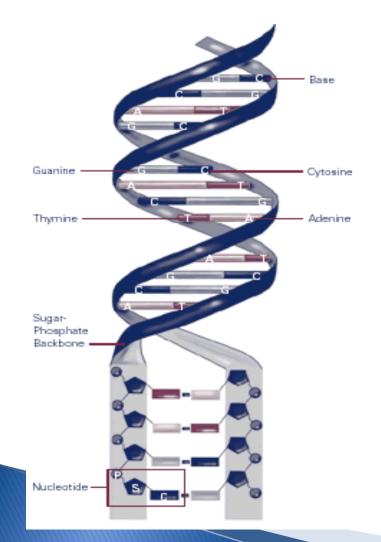
 In humans, there are estimated to be ~30,000 genes (many but not all identified and annotated)

 Each gene is a sequence of bases or nucleotides

Kreek (Rockefeller University) & Hassin (Columbia P&S), 2004



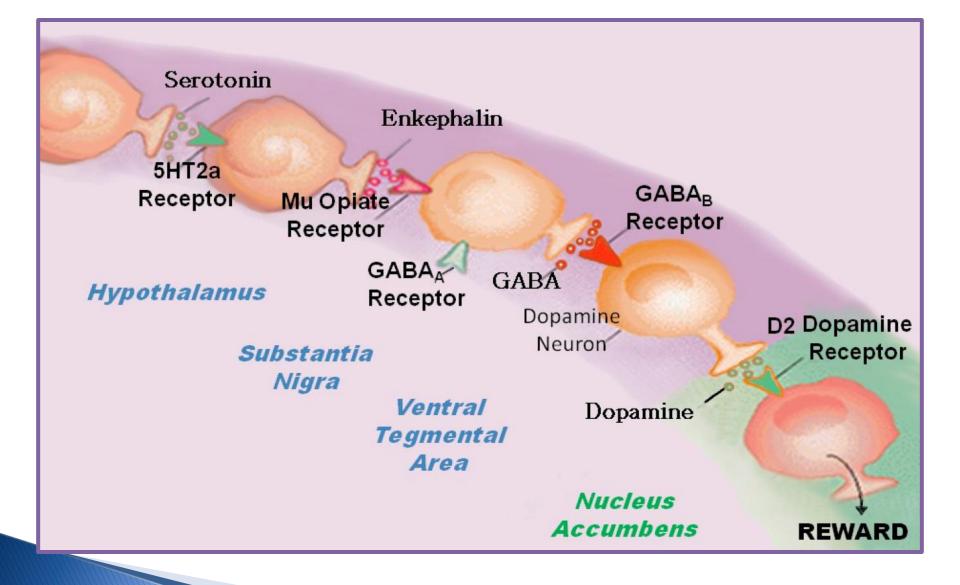
Single Nucleotide Polymorphisms (SNPs) in Genes: Definitions



- SNP a single nucleotide polymorphism, that is, one nucleotide or base of any base pair
- Allelic Frequency:
 - <1% low or rare 1–5% intermediate >5% high, frequent

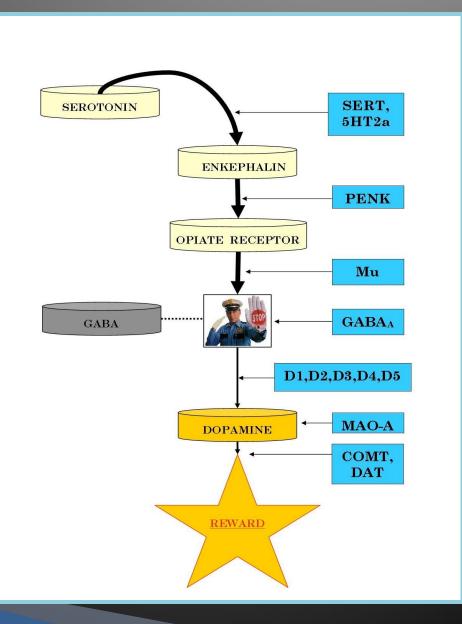
Kreek (Rockefeller University) & Hassin (Columbia P&S), 2004



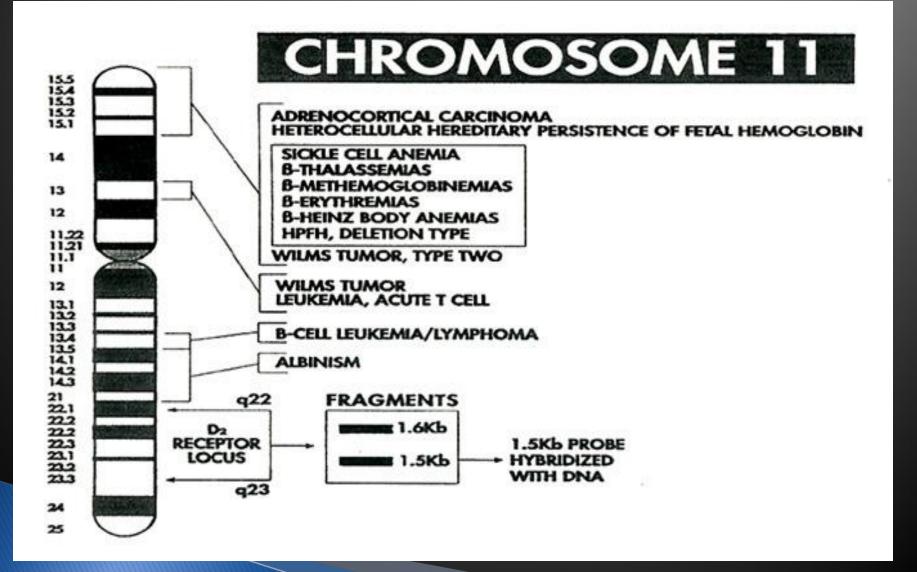


The Brain Reward Cascade

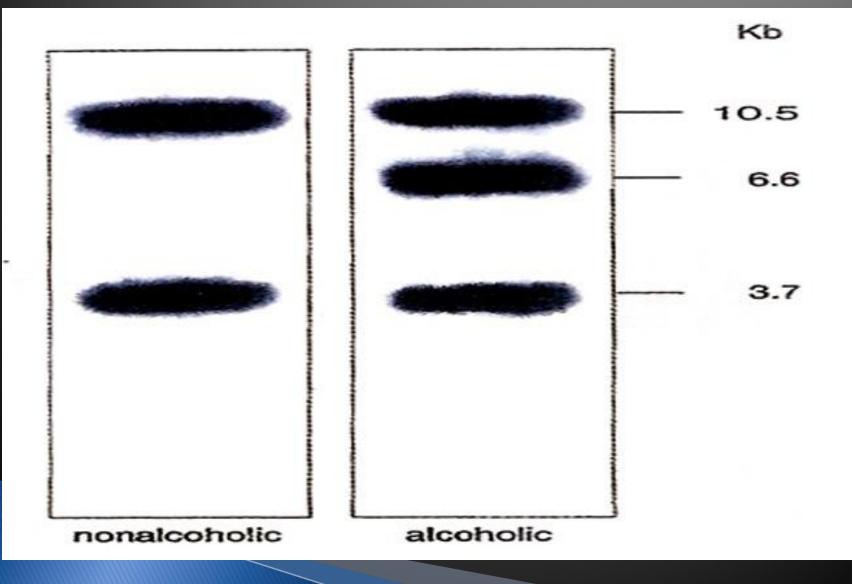
Gene Targets in the Brain Reward Cascade



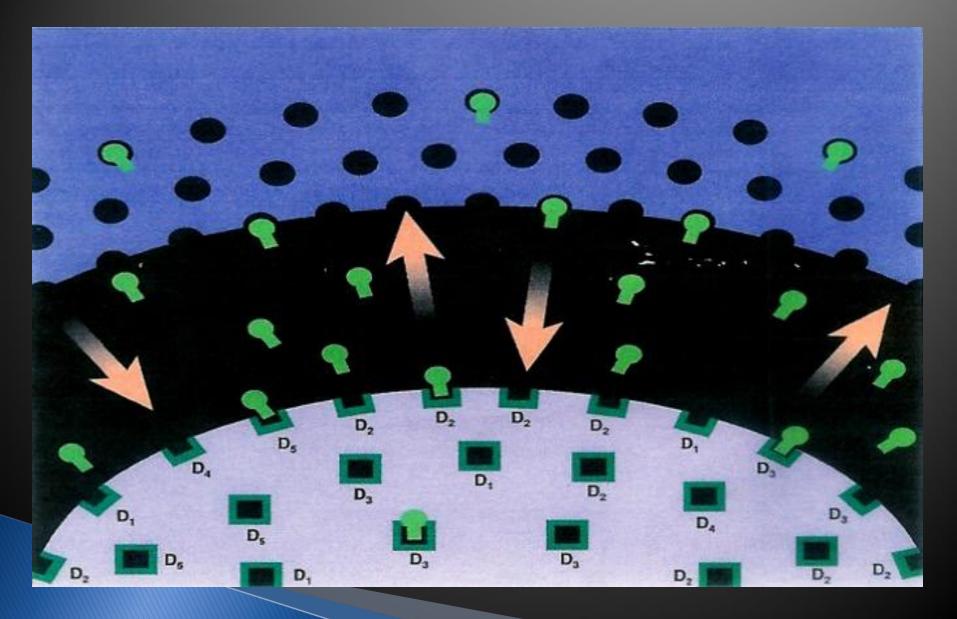
The Dopamine D₂ Receptor Gene



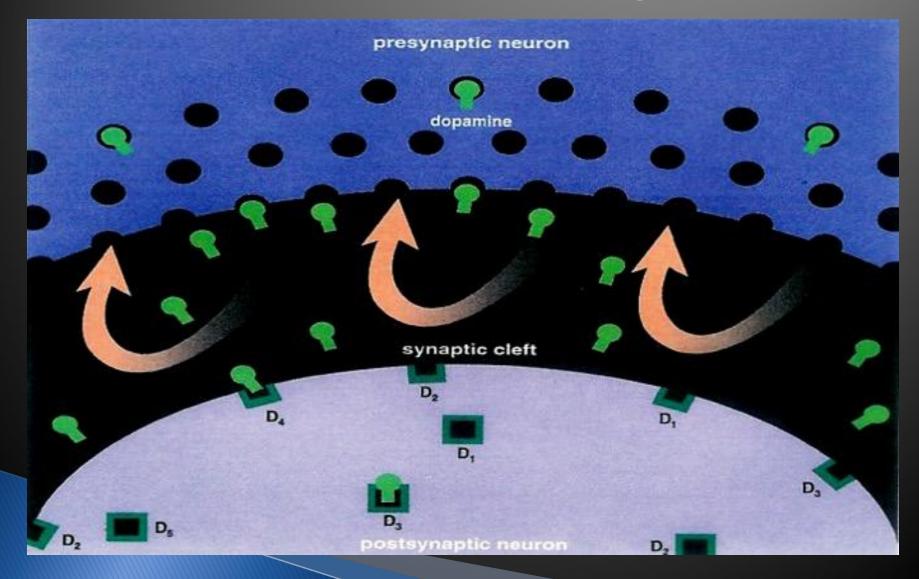
The Reward Gene



A_2 Gene = Normal D_2 Receptors



A_1 Gene = 1/3 Lower D_2 Receptors Equates to 100,000,000 people living in the USA



>1/3 OF THE Total US Population Carries the DRD2 A1

(Over 100,000,000 people)

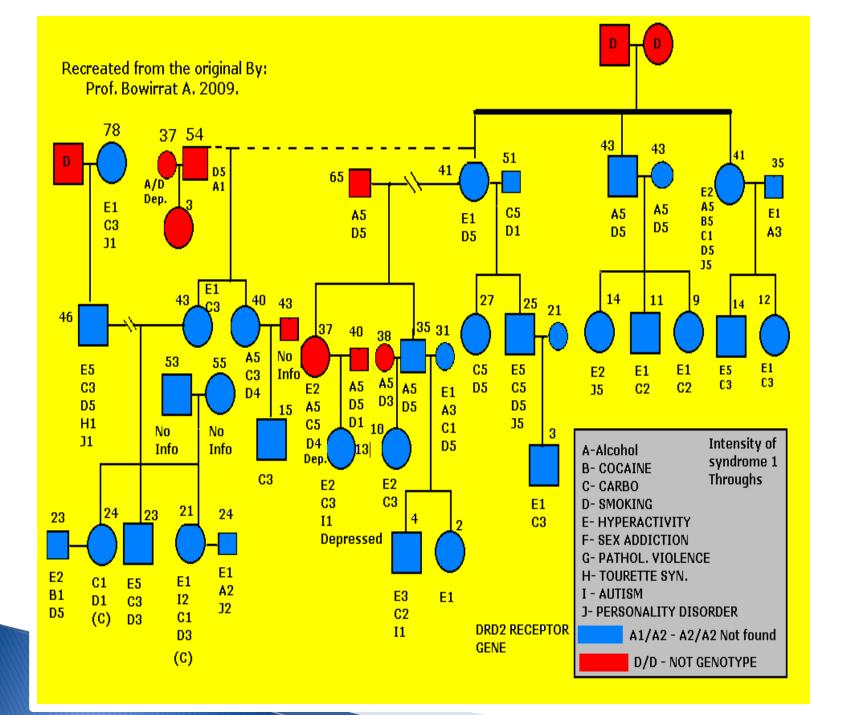
50% of African Americans carry the DRD2 A1 gene 58% of Hispanics carry the DRD2 A1 gene



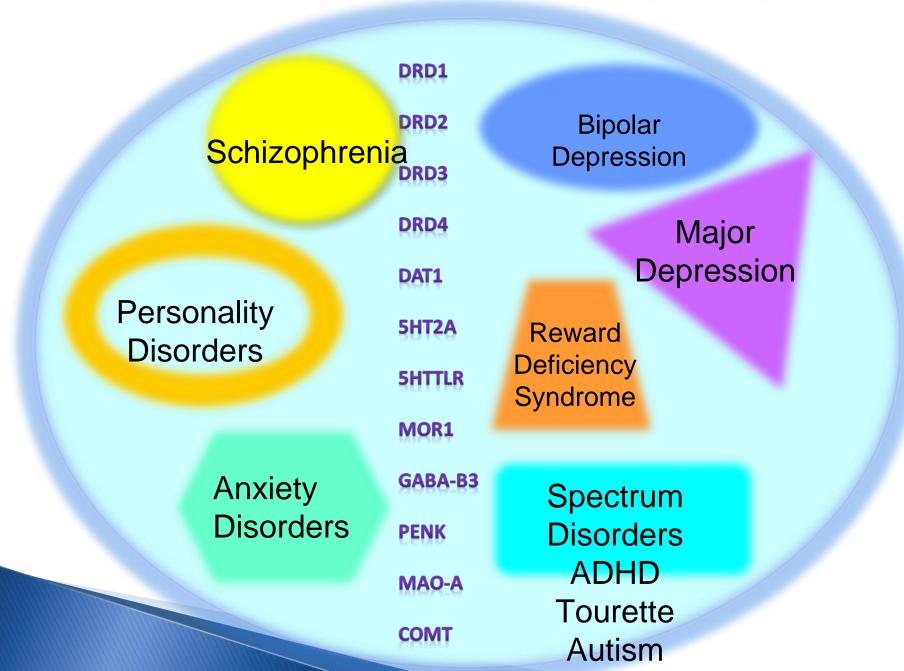
72% of Asians carry the DRD2 A1 gene 85% of Native Americans carry the DRD2 A1 gene

Reward Deficiency Syndrome

reward deficiency syndrome			
addictive behavior	impulsive behavior	compulsive behavior	personality disorder
severe alcoholism	attention-deficit disorder, hyperactivity	aberrant sexual behavior	conduct disorder
polysubstance abuse	Tourette		antisocial
smoking	syndrome		personality
obesity	autism		aggressive behavior



Comorbid Reward Genes in Psychiatry



DRD2 and Defense Style

Defense Style Questionaire given to 3 populations: 123 Addiction treatment unit 42 Tourette syndrome 49 controls

Addiction and Tourettes

Decrease in mature defense

Increase in immature defenses compared to

Antolin, Noble, et al: D2 dopamine receptor (DRD2) gene, P300 and personality in children of alcoholics: Psychiatry Res 2009 Apr 30:166



Genetics, P300 & Personality

100 Adolescent COA – 39 A1 + 62 A2

A1 had higher IQ and Self directedness A1 had lower harm avoidence and novelty seeking – Tridimensional Personality Questionaire (TPQ) Worry, pessismism, shyness, alientation A2 had P300 peak and Cooperativeness

At risk adolescents had lower % P300 and higher % A1 – low dopamergic

Antolin, Noble, et al: D2 dopamine receptor (DRD2) gene, P300 and personality in children of alcoholics: Psychiatry Res 2009 Apr 30:166



Genetic Addiction Risk Score (GARS)

GENE/ALLELE	Function and Risk
Caspi MAOA uVNTR	Increased mitochondrial metabolism of dopamine
DRD4	High risk for novelty seeking
DAT	Increased reuptake of dopamine – increased ADD risk
5HTTLLR dialletic	5HTTLLR dialletic
COMT	Enhanced synaptic catabolism of dopamine
DRD2	Reduced number of dopamine receptors
DRD3	Increased risk for cocaine addiction
OPRM1	Carriers of G Allele hypofunction opioids+dopamine
GABRA3	Defective hypofunctioning GABA: Increased anxiety



ASAM New Definition of Addiction

Addiction is a primary, chronic disease of brain reward, motivation, memory, and related circuitry. Dysfunction in these circuits leads to characteristic biological psychological social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.

August 15,2011



Essential components of pain

- Pain experience
 - Nociceptive physical pathways of pain
- Subjective nature
 - No pain meter patient is own control
- Emotional component
 - Other emotional problems color pain experience severity and interpretation
- Occurs with and without injurious stimuli
- Functional limitations most important in development of coping patterns



Components of Pain

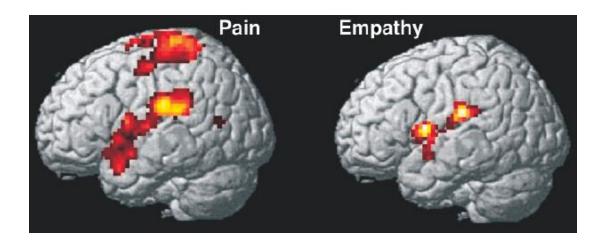
- Pain Nociceptor pain generator treat the cause to produce the effect
- Suffering Modulation within emotional and expectation circuits with addictive disease are at special risk for suffering due to inadequate management of their pain. (Savage, 1998)



Cortical pain processing

- Sensory aspects of pain seem to be processed in the Somatosensory cortex.
- Emotional distress associated with pain seems to be processed in the Anterior Cingulate Cortex (ACC).
- Subjects with lesions in ACC could still accurately judge the intensity of pain.
 But they were not in the least bothered by it.

• On the other hand, subjects empathy for the pain of others only elicits activity in ACC, not Somatosensory cortex.



Concurrent Emotional States

- Depression and anxiety augment pain
 - Opioids allow for emotional escape and distancing
- Hyperventilation and panic
- Continued use of substances masking pain
- Functional limitations secondary to chronic pain overlap with dysfunctional addictive behaviors augmenting pain and disability



Chronic Pain Causes Secondary Problems

Bodily functional impairments

- Sleep disturbance
- Physical deconditioning
- Sex dysfunction
- Affective disturbances depression, anxiety

Behavioral functional impairments

• Interference of work

× Financial problems, free time, lack of distraction × Disability payments tied to inability to work

• Interference with home and family roles

- Acute illness sick role creates stress on others over time
 Excuses from daily roles burdensome to others
 Interference of family rituals
- × Family dysfunction may continue pain syndrome
 - × Communication occurs through language of pain
 - × Anger from family members unexpressed
 - × Enabling behaviors



Clinical Management to Minimize Risk of Addiction

- Encourage integrated pain management
 - Active patient role
 - Physical conditioning
 - Self awareness
 - Non-medication therapies
 - Functional rehabilitation
 - Family involvement
 - Therapeutic drug monitoring
 - Withdrawal severity and pain scales



Pain Management : Treatment Approach

- What type of pain problem?
- What was the drug of choice?
- Is the patient stable?
- What agonist is involved?
 - Special concerns regarding dose, agent or other medications
 - Can the maintenance drug be used for pain?
- Is the addictive disorder dominant?
 - Never dismiss or minimize the pain component
- Is the pain opioid responsive?
 - Mechanical and structural, neuritic and intermittent
- Do you have the resources to manage the patient?
 - Methadone program but no pain specialist and no on-site evaluation
 - Detox program with return of pain as dose is dropped?
 Withdrawal based changes in pain sensitivity
 - × Masking on underlying condition and need for re-evaluation for acute pain
 - Use of withdrawal assessment scales and pain scales



Pain Management: Clinical Concerns

Altered pain threshold and sensitivity

- Addicts may need higher dosages of medication to control pain
- Addicts may interpret withdrawal symptoms as need for medication

Surgical procedures

- Speak with surgeon prior to surgery to discuss pain management
 Ask what usual dosage and duration of opioid requirements for usual patient
 Explain that you will help them with pain management or arrange for pain consultation rather than "dumping" problem patient upon surgical staff
 Demand adequate dosage to achieve pain relief to estimate size of tolerance "filling the tank"
- Inadequate pain control is more risk to relapse than drugs prescribed
 × If you do not prescribe enough pain medication or don't know what you are doing, then patient will take over control since they know how to do it well



Pain Management : Dosing Schedules

Avoid PRN

- For an opioid addict, PRN = per request of narcotic addict
- Indication for next dose in addict will most likely be subjective

Use time contingent rather than symptom contingent dosing

Avoids reinforcement of pain-relief cycle
 Addict not longer has to prove need for drug based upon severity of complaints
 Patient does not have to ask for meds
 Patient requests are less likely to be interpreted as drug-seeking behavior

Scheduled dosing

- Indication for next dose = time not symptoms
 Careful attention to induction of tolerance and fast metabolizers
- Consider "reverse PRN"

×RN asks patient if need drug based upon time schedule and patient refuse if not needed

can



Pain Management : Methadone Maintenance

Meet baseline opioid requirements for prevention of withdrawal + add dose to cover pain requirements

× Determine average daily dose of opioids

× Calculate equianalgesic dose (see dosing table)

× Decide whether to maintain patient on methadone or switch to equianalgesic dose

• "Methadone on methadone"

× Take one per day dosing and split into three/four

× Use low dose (5-10 mg) methadone for breakthrough

× Advantages

× Urine drug screens remain interpretable

× Cost effective, well tolerated and familiar, easy to return to QD dosing

• "Methadone plus mu agonist"

× Maintain daily dose of methadone for withdrawal prevention and add short acting mu opioid agonist for pain control

× Use immediate release opioid (orally or parenterally) for pain relief

× Do **NOT** use partial mu agonist or antagonist (may precipitate withdrawal)



Pain Management : Suboxone

Dose of Suboxone will determine extent of opioid blockade

- > 16 mg / day of buprenorphine majority of opioid receptors blocked
- Low dose buprenorphine < 4 mg/day may allow for reversal of blockade
- Stickiness to opioid receptor prevents binding of opioid antagonist
 - May need 8-10 amps of narcan to overpower affinity for receptor
 - Pain control requires high dose of high affinity opioid
 × Fentanyl or Dilaudid IV is usually needed to overpower opioid blockade
 × Short duration of action of opioid antagonist may result in return of opioid blockade
- Slow dissociation from receptor = long duration of blockade
 - Duration of blockade may continue 2-3 days after stopping buprenorphine
 - Rapidly changing rate of reversal of opioid tolerance may result in oversedation
 - Resetting of opioid receptor tolerance may allow for reversal of tolerance and lower than expected opioid dosage



Pain Management : Suboxone

Overpower buprenorphine blockade

- Use of high affinity pure mu agonist
 - × Dilaudid and Fentanyl IV

× May require much higher doses than usual

- × Needs careful monitoring for oversedation and respiratory depression × Short duration of action of agonist may cause wearing off of effectiveness
- Bypass opioid system for pain relief
 - General anesthesia with non-opioid agents
 × Propofol, Benzodiazepines, paralytics, inhalable anesthetics
 - Regional anesthesia locally acting nerve blockade

Discontinue buprenorphine and restart pure mu agonist

Pay attention to duration of action of buprenorhine – slow dissociation
 × Blunted analgesic effect secondary to continued blockade

Continue Buprenorphine with regional anesthesia or non opioid treatments

 Increase dose of buprenorphine for pain on top of maintenance dose
 I mg sublingual buprenorphine = 5-10 mg of hydrocodone, oxycodone, morphine
 Split dosing of buprenorphine to TID to QID dose schedule
 Add non steroidal antiinflammatories, Ice, TENS, PT



Pain Management : Dosing of Non Drug Therapies

Increase "dose of recovery" and relapse prevention activities during increased pain

Increase frequency of addiction treatment Increase AA/NA meetings and one to one support from sponsor Increase frequency of counseling appointments or higher level of care Increase frequency of urine toxicology testing Therapeutic drug monitoring Decrease temptation to abuse if know levels are monitoring Know if patient relapses to other non-prescribed drugs

Increase frequency of non-drug therapeutic activities Increase PT appointments, office visits or other follow up treatment activities

Measure "dose equivalency" of recovery activity by objective pain scale How much pain relief is obtained by "talking and doing therapy"

Monitor recovery attitude and recovery behavior "What's below the surface of the iceberg is what sinks ships" what's not said is sometimes more important and predictive of relapse Monitor frequency of utilization of recovery skills - "the 500 pound phone"



Recovery Skill Development

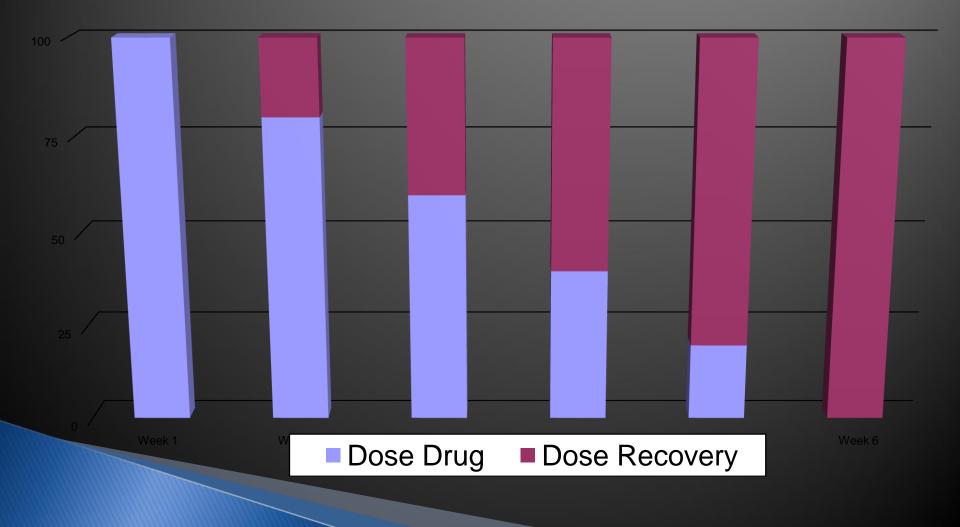
Concept of "dose equivalent" = reduction of withdrawal symptoms by non-drug techniques = social setting detoxification, supportive care

- Need to try non-pharmacological approaches
 - × Change setting go for a walk, exit strategies, re-arrange living environment
 - ×Asking for help
 - × Calling sponsor
 - × Speaking about feelings
 - × Exercise
 - × Attending meetings
 - × HALT techniques
 - × Hot baths / showers
 - × Massage
 - × Meditation, visualization
- Other pharmacotherapies
 - × NSAID
 - × Mood stabilizers
 - × Antidepressants
 - × Sleeping aids (often unnecessary when buprenorphine dose is adequate)



Detox Schedule

Rate Dosage Adjustment + Recovery Skill Acquistion



Chronic Pain & Addiction Program



Comprehensive Pain Evaluation Physical and Mental Status Exam Opioid Withdrawal Severity Assessment Buprenorphine Pain Management Medication Monitoring & Adherence Program

Chronic Pain Coping Evaluation Osteopathic Manipulation Neuropsychological Evaluation Medication Assisted Therapy Pain Support and Skills Group Therapy Cognitive Behavioral and Mindfulness Groups

