

Opioids and Pain Pathways

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Opioids and Pain Pathways

- I. Neurophysiology of Pain
- II. Opioids as Analgesics
- III. Clinical Issues

Neurophysiology of Pain

- Processes of pain perception
 1. Nociception (transduction)
 2. central processing (transmission)
 3. central modulation
- Role of inflammation
 - common source of noxious stimulus
 - secondary to the release of prostaglandins and autocoids

Types of Pain

- Prior to 1990, pain was categorized on the basis of duration and prognosis:

- **Acute** trauma or injury,
- **Chronic** conditions for which cures were unknown,
- **Malignant** processes (cancer)

- Now differentiated into two types of pain based on etiology:

Nociceptive
Neuropathic



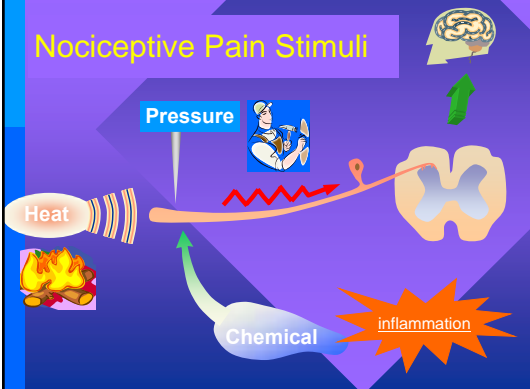
Nociceptive Pain:

- Result of activation of sensory (afferent) receptors (nociceptors) by mechanical, thermal or chemical stimuli
- Functional, physiologic or “normal” pain

Neuropathic Pain:

- Pain resulting from damage to peripheral nervous or central nervous system tissue or from altered processing of pain in the central nervous system

Nociceptive Pain Stimuli



Peripheral nerves involved in pain transmission

C fibers:

- Slow, unmyelinated
- large receptive field, long-lasting, burning
- G-protein receptors

A-δ fibers:

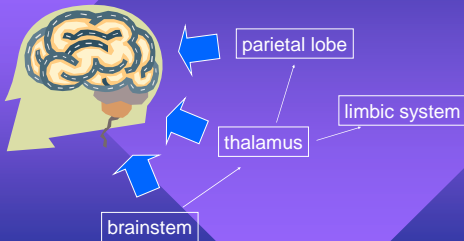
- Fast, myelinated
- well-localized, sharp
- ion-channel receptors



Central transmission of pain



Higher processing of pain



“No Brain, No Pain”

(Allen Basbaum, UCSF)

Central Modulation

- Inhibitory or facilitatory processes on pain
 - Spinal cord (**ascending**)
 - Brain (**descending**)
- Analgesics:
 - ↑ inhibitory processes
 - ↓ facilitatory processes



Ascending Pain Control Mechanisms

A- α and A- β fibers

- Competitive activation of non-nociceptive fibers (Gate Control Theory)

- Close pain "gate" (i.e., TENS, acupuncture)

Dorsal horn receptors

– Excitatory

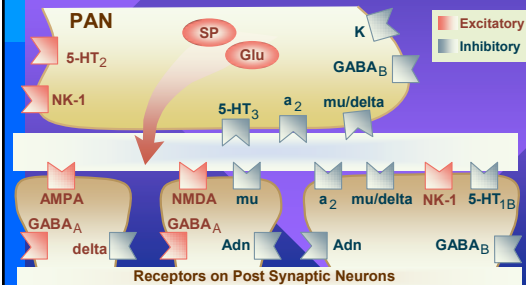
- glutamate, SP, 5HT₂, GABA_A, NMDA

– Inhibitory

- 5HT_{1b}, GABA_B, 5HT₃, Alpha₂, mu-opiate



Dorsal Horn Receptors



Descending Pain Control Mechanisms



cortex

- Music/TV/distraction
- Placebo
- Systemic Opioids
- Hypnosis / Imagery

brainstem

- Endogenous opioids
 - endorphin, enkephalin
- 'tonically active' opioid system mediated by monoamines:
 - 5HT, NE

descending inhibition

Neuropathophysiologic Consequences of Pain

- Neuronal Plasticity
 - Primary Hyperalgesia
 - Secondary Hyperalgesia
 - Enabled NMDA receptors
- Results in:
 - Aberrant communication among PNS and CNS neurons (neuropathic pain)



Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

“The Board recognizes that controlled substances, including opioid analgesics, may be essential in the treatment of acute pain due to trauma or surgery and chronic pain, whether due to cancer or non-cancer origins”

Federation of State Medical Boards, 1998

Opioid Analgesics

Opioid - any ligand which binds to an opioid receptor

- may be endogenous or synthetic, agonist or antagonist
- ≠ "narcotic"
- receptor binding initiates second-messenger cascade

Opioid Mechanisms of Analgesia

1. μ -receptors on **peripheral afferent nerves**; inhibit the release of pain-promoting neurotransmitters (i.e., substance P, bradykinin)
2. μ -receptors in **spinothalamic tract**; inhibitory post-synaptic potential on neurons carrying pain input to brain
3. μ -receptors in **midbrain**; excitatory post-synaptic potential (EPSP) in descending inhibitory pain pathways

μ -opioid analgesia

- limited to perception of nociceptive stimuli
- no ceiling effect
- effective for the relief of nociceptive and neuropathic pain
- development of tolerance & physical dependence

Side-Effects of opiate administration

- Constipation
- Sedation
- Pruritus

Effects of opiate administration with implications for pain management:

- Opioid-Induced Hyperalgesia
- Opioid Addiction
- Effect of Pain on Opioid Effects

Hyperalgesia

- A state of the sensory nervous system in which a previously noxious stimulus is perceived as more noxious
- Molecular, peripheral, and central nervous system mechanisms contribute to the phenomenon
- Symptom of *neuropathic* injury

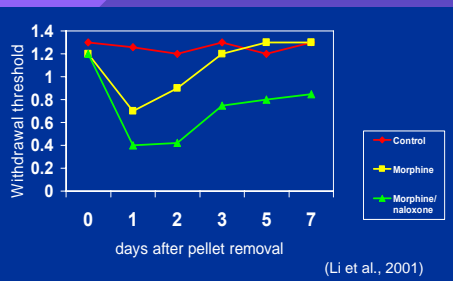
Opioid Withdrawal Hyperalgesia

- A multimodal hyperalgesia
- Follows single or chronic opioid dosing
- Intensity proportionate to opioid dose
- Severity increases with intermittent or naloxone-interrupted opiate dosing
- Can be decreased with NMDA receptor antagonism
 - involves excitatory amino acid, as well as opioid, receptors

DSM- IV Criteria for Opioid Withdrawal

- Dysphoric mood
- Nausea and vomiting
- **Muscle aches**
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

Opioid-induced hyperalgesia



Opioid-induced hyperalgesia:

- Opiates, in addition to providing analgesia, set in motion *anti-analgesic* or *hyperalgesic* processes
- Demonstrated to have neuroplastic as well as conditioned components
- Opioid withdrawal hyperalgesia \approx opioid-induced hyperalgesia

"On the abuse of hypodermic injections of morphia,"
Clifford Albutt, (1870) *Practitioner* 3, 327-330.

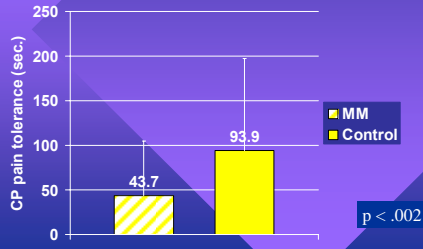
"At such times I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphia, which may be an evil. Here experience is needed. Does morphia tend to *encourage the very pain it pretends to relieve?*"

"...in the cases in question, I have much reason to suspect that a reliance upon hypodermic morphia only ended in *that curious state of perpetuated pain*"

From "What is the morphine disease?"
Charles W. Carter (1908) *Journal of Inebriety* 30, 28-33.

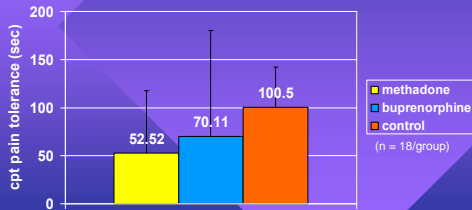
" He is also affected by a *hypersensitiveness to pain*, or a morbid intolerance of any kind of distress, and a degree of mental incompetency probably always more or less present in pronounced auto-toxemias, which render his self-control and his judgment inadequate to a rational course of action. He suffers. *His suffering is actually great. To his astigmatic inner eye it seems even greater than it is.*"

Pain Responses in Methadone-Maintained Opioid Abusers



Compton et al. (2000), J. Pain Symptom Manage., 20:237-245

Pain Intolerance in Opioid-Maintained Patients: Effect of Long-Acting Maintenance Agent

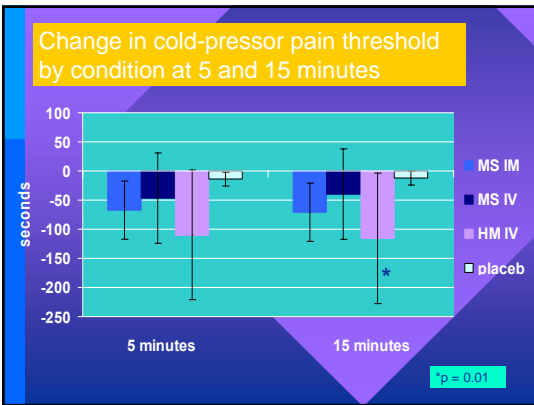


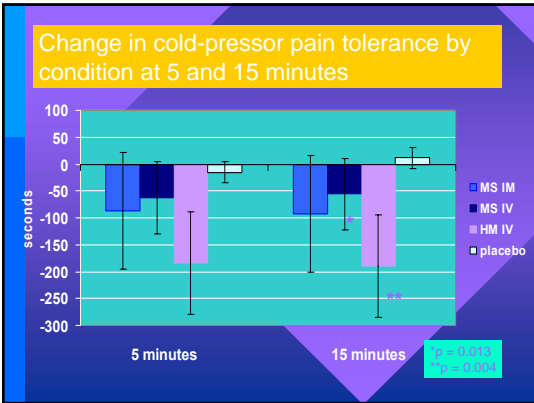
Compton et al., 2001 Drug Alcohol Depend., 63:139-146

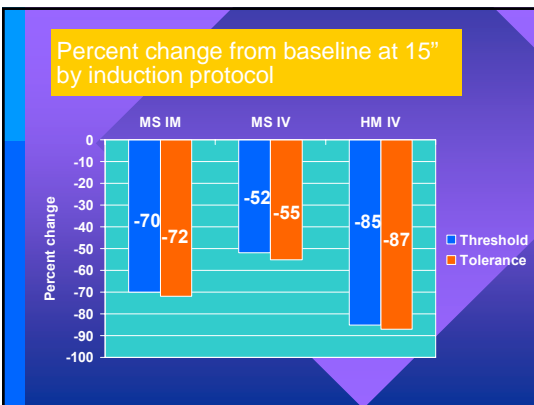
Withdrawal Hyperalgesia After Acute Opioid Physical Dependence in Nonaddicted Humans: A Preliminary Study

- Acute Physical Dependence paradigm
- Four healthy males
- Cross-over design with subjects receiving agonist/antagonist combinations on two separate sessions
- Hyperalgesia – change scores between pre-opiate and post-naloxone on pain responses to standardized cold-pressor pain

Compton et al., 2003, The Journal of Pain, 4(9): 511-519

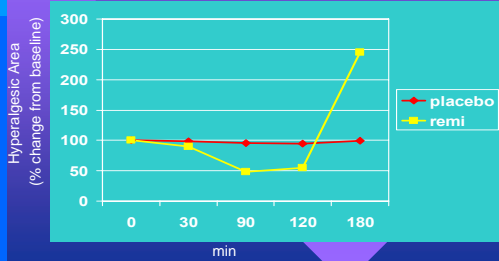




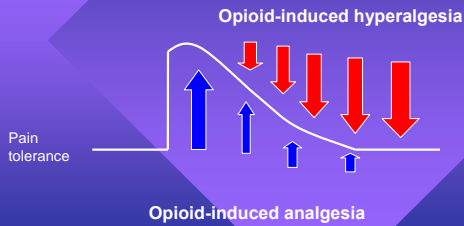


Effects of opiate infusion on mechanical hyperalgesia

(Angst et al., 2003)



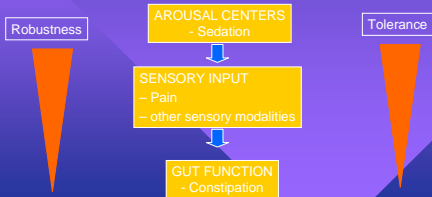
Opponent Process Theory



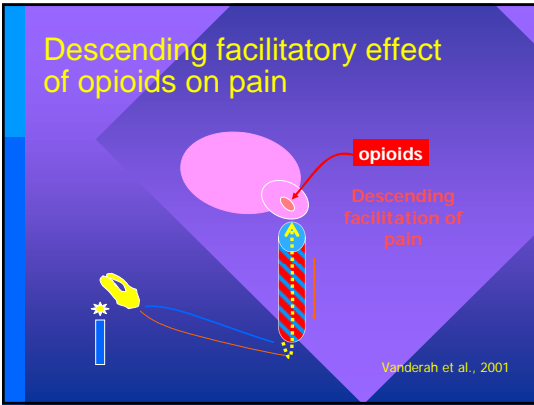
(Solomon, 1980; Koob, 1989)

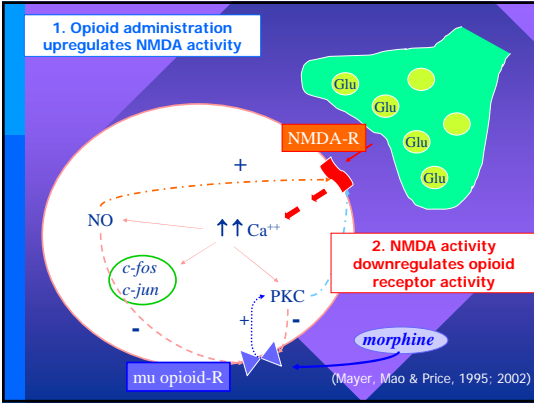
Complex System Theory

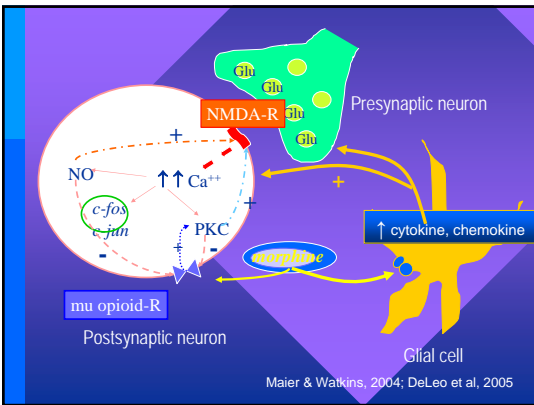
Critical systems are designed to maintain homeostasis

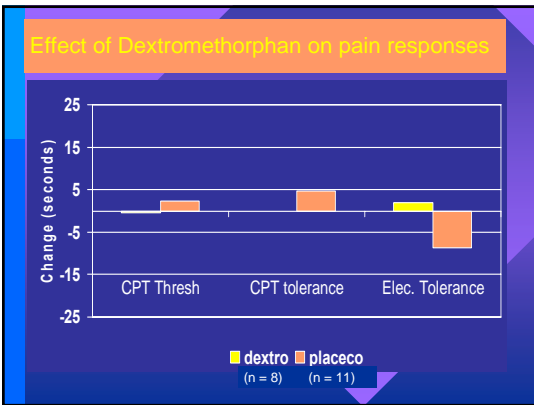


(Palmer, APS 2003)









Analgesic tolerance

Opioid-induced Hyperalgesia

- Is opioid analgesic tolerance actually an organismic expression of an opioid-induced increased sensitivity to pain?
- Opioid tolerance not so much a down-regulation of analgesic systems, but an upregulation of hyperalgesic systems

(Colpaert, 1996; Laulin et al., 1999)

Opiate Analgesic Addiction

- Published rates of abuse and/or addiction in chronic pain populations are $\leq 10\%$
- Suggests that known risk factors for abuse or addiction in the general population would be good predictors for problematic prescription opioid use
 - History of early substance use
 - Personal/family history of substance abuse
 - Co-morbid psychiatric disorders

Fishbain, 1992, 1996

Annual No. (in millions) of New Nonmedical Users of Pain Relievers aged 12 or Older



National Survey on Drug Use and Health, 2004

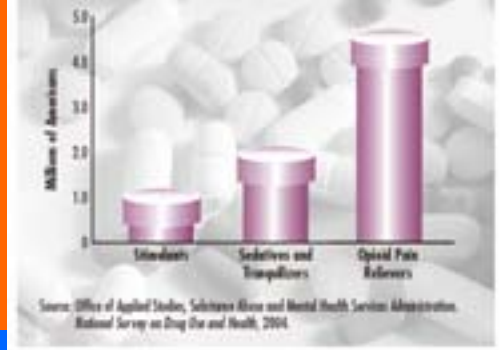
About which "opioid abuse behaviors" are we concerned?

Any non-prescribed use of a drug (NIDA, 2002 & DEA, 1970)

Non-medical use of a substance for psychic effect, dependence, or suicide attempt or gesture (SAMHSA, 2002)

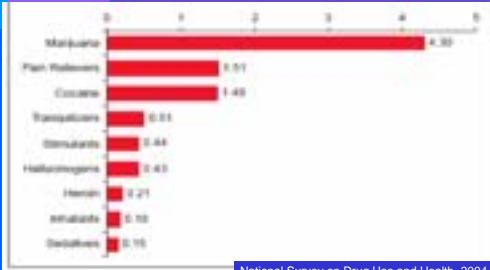
Any harmful use, irrespective of whether the behavior constitutes a "disorder" in the DSM-IV diagnostic nomenclature (IOM, 1996)

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by one or more behaviorally-based criteria (APA, 1994)



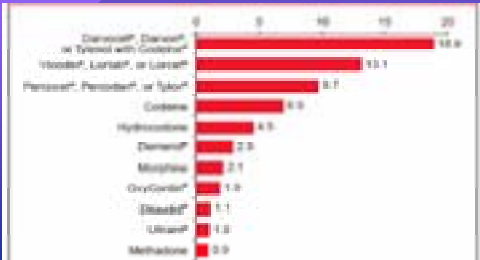
Source: Office of Applied Studies, Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health, 2004.

Estimated Numbers (in millions) of Persons Aged 12 or Older with past year Illicit Drug Dependence or Abuse, by Drug: 2002



National Survey on Drug Use and Health, 2004

Estimated Number (in millions) of Lifetime Nonmedical Use of Selected Pain Relievers among Persons Aged 12 or Older: 2002

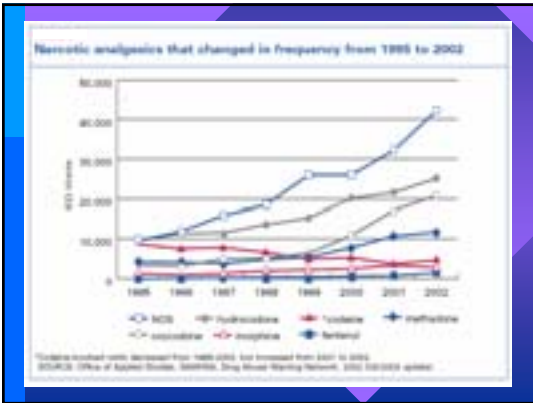


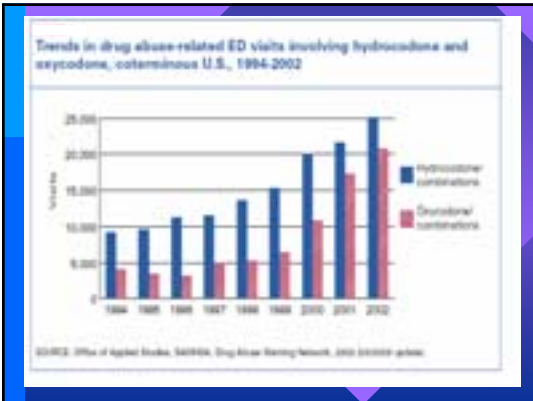
National Survey on Drug Use and Health, 2004

Drug abuse-related ED visits involving narcotic analgesics: 1995-2002



SOURCE: Office of Applied Studies, SAMHSA Drug Abuse Warning Network, 2002 (2A2001-0200)





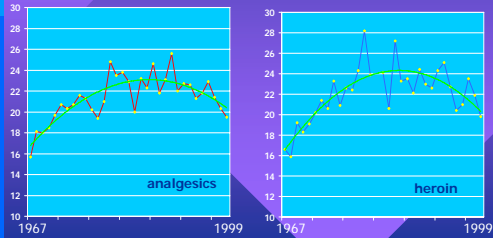
Prescription of opioids vs. indicators of analgesic abuse

Between 1996 and 2001:

	Medical use	ER mentions
morphine	↑ 75%	↑ 294%
fentanyl	↑ 218%	↑ 1988%
oxycodone	↑ 108%	↑ 477%
hydrocodone	↑ 72%	↑ 89%

(Zacny et al., 2003)

Mean Age at First Prescription Opioid Use and First Heroin Use, 1967-1999



(NHSDA, 2000)

Opioid Addiction

- ≠ tolerance and physical dependence
 - degree to which these develop in persons with pain unclear
- ≠ drug-seeking
 - therapeutic dependence
 - pseudoaddiction
- not an inevitable outcome of regular opioid exposure

Addiction in the presence of pain

- Adverse consequences associated with opioid use
- Loss of control over the use of opioids
- Preoccupation with obtaining opioids despite the presence of adequate analgesia

A Consensus Statement from ASAM, American Academy of Pain Medicine and American Pain Society (2001)

"Currently, no validated measure exists that is useful in predicting opioid abuse in persons with chronic pain. The "gold standard" assessment is a comprehensive evaluation by a psychologist or psychiatrist ... unfortunately, not all caregivers have access to this There has been a call for screening tools to assess addiction in persons with organic pathology who are considered candidates for opioid therapy."

Nedeljkovic, Wasan, & Jamison. (2002). *Clin J Pain*, 18: S39-51.

Pain and Substance Use Questionnaire (PSUQ)

- Developed for use in pain patients with "problematic" substance use
- Administered to 52 opioid-treated CNMP pts; concurrently evaluated by addiction medicine specialist for presence of addictive disease
- Items predictive of addictive disease*
 - Pt believes he/she is addicted
 - Increases analgesic dose/frequency
 - Preferred route of administration

(*correctly classified 92.9% of subjects)

Miotto & Compton, 1996, 1998

Additional Findings

- Up to 20% of non-addicted patients evidenced "drug-seeking" behaviors
- Illegal activities (prescription forgery, buying on street) rare in addicted sub-sample
- Of non-addicted pts, 27% had previous substance abuse history (60% of whom received drug abuse treatment), and 50% had positive family history

Correlates of analgesic abuse in chronic pain patients with a history of addiction

- Absence of family support
- Lack of 12-step involvement
- Recent history of polysubstance abuse (not alcohol abuse alone)
- Previous history of chronic opioid therapy
- Failure in improvement of pain symptoms

(Dunbar & Katz, 1996)

Barriers to the development of a screening tool to predict which pain patients will develop opioid addiction

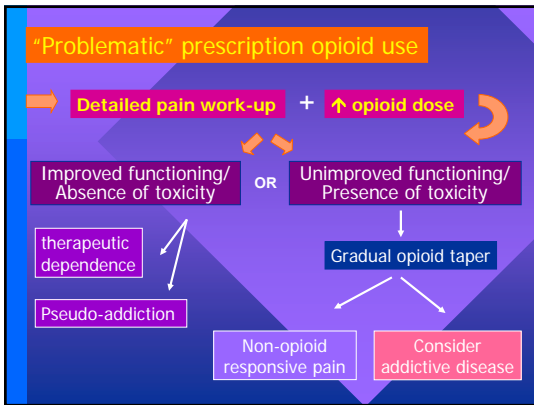
- Imprecision/inconsistencies in measurement and/or identifying cases of abuse/addiction
- Important concerns about false positives and false negatives
- Exposure rate to opioid therapy in pain patients is severely truncated, such that base-rate risk estimates are difficult to ascertain

- Little evidence to suggest that a patient with CNMP who **is responsive to opioid therapy** is at increased risk for patterns of “problematic” prescription opioid use
- An individual with chronic pain AND untreated addictive disease **WILL NOT get better** with opioid prescription

Goal: Functional Restoration

- physical capabilities
- psychological intactness
- family and social interactions
- degree of health care utilization
- drug use for symptom control





Addiction results in a "Syndrome of Pain Facilitation"

Discomfort augmented by:

- subtle withdrawal syndromes
- intoxication or withdrawal-related sympathetic arousal, muscular tension
- sleep disturbance
- affective changes
- functional changes

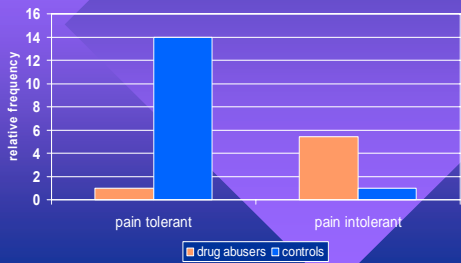
Savage & Schofferman, 1995

Deleterious effects of addiction in advanced cancer patients

- Increased patient suffering
 - Poor pain and symptom management
 - Impeded diagnosis of psychiatric problems
 - Tension in social support network/caregivers
- Increased stress and frustration of family/caregivers
- Masking of symptoms important to care
- Family concern over misuse of medication
- Reluctance of providers to give adequate analgesics
- Poor patient compliance with medical regime
- Decreased quality of life

Passik & Theobald, 2000

Cold-pressor Pain Tolerance: drug abusers vs. controls



Compton, 1994

What we know:



What we don't know:



Does pain modify opioid addiction responses?

Under acute pain conditions:

- Significantly less morphine analgesic tolerance in pain assays (Brown et al., 2002, Vaccarino et al., 1993)
- Significantly less morphine physical withdrawal symptoms (Brown et al., 2002, Vaccarino et al., 1993)
- Significantly less opioid reward or euphoria (Zacny et al., 1996)

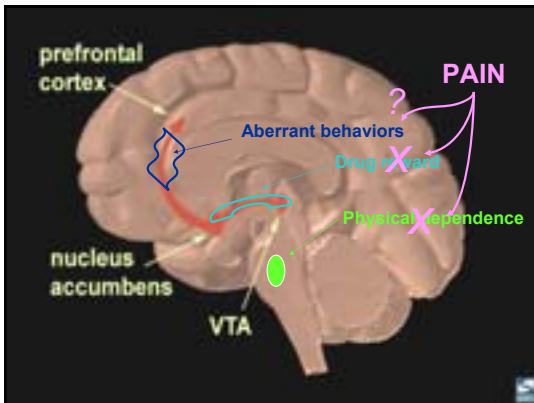
Opioid systems are tonically active

- Rate of basal firing is altered by opioid administration
 - i.e., naloxone does nothing in absence of morphine-pretreatment.
- Effects of opioids can be different depending on state of basal firing



- Could presence of pain alter basal firing?
 - Such that opioids administered are less "addictive"?





Related clinical questions with respect to opioids and pain

- Does the presence of pain protect chronic pain patients from developing addictive disease?
 - Evidence that chronic pain patients with history of addiction can use opioids appropriately
- Could chronic opioid therapy for pain induce hyperalgesia and contribute to pain experience?
 - Anecdotal evidence that opioid detoxification improves chronic pain or functionality

opioid addiction and hyperalgesia: a syndrome?

- A distinct sub-population of patients who suffer a syndrome that includes both opioid addiction and CNMP
 - Appear treatment resistant
 - High rates of psychiatric morbidity
 - Low functioning
 - Chronic pain “syndrome”
- Require syndrome-oriented treatment interventions?
