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Medication-Assisted Treatment for Opioid Dependence: Role for Agonists and Antagonists

Maria A. Sullivan, MD, PhD
Associate Professor of Psychiatry at CUMC
Division on Substance Abuse
Columbia University/ New York State Psychiatric Institute

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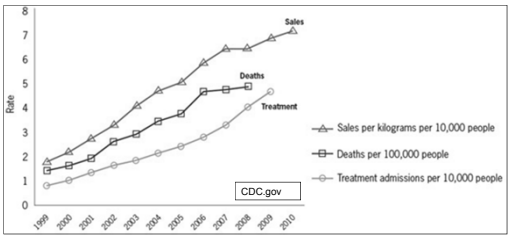
The contents of this activity may include discussion of off-label or investigative drug uses. The faculty is aware that it is their responsibility to disclose this information.

Opioid Addiction: A Public Health Imperative

- Up to 1 million heroin users in need of treatment; most heroin or prescription opioid addicts not in treatment
- While heroin use remains prevalent, prescription opioid abuse has risen dramatically in the past decade (SAMHSA, 2012).
- Prescription opioid abuse: more than 3 times prevalence of heroin dependence
- By 2006, number of new initiates to prescription opioid abuse exceeded those for marijuana and cocaine (NSDUH, SAMHSA)
- Most common sources for misused opioids: free from friend or relative (60%), followed by obtaining Rx from one MD (17%) (NSDUH, 2011)

The Epidemic: Prescription Opioid Morbidity and Mortality



- 40 people die every day of painkiller overdose (300% increase in 10 years)
- Half of ER visits are due to misuse/abuse of painkillers

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Epidemiology of Prescription Opioid Abuse in the United States

- 4.5 million Americans (2.1% of U.S. pop.) used prescription opioids non-medically in past month (USDUH 2013)
- Prevalence: 30.4% chronic pain patients in a large (N=239) general practice reported taking extra narcotic doses (Rosser et al. 2011)
- Prescription opioids are gateway drug: 17.1% of substance abusers cite pain medication as being the first substance they abused (NSDUH 2009)
- Efforts to more aggressively manage pain have resulted in sharp rises in prescribing and misuse of high-potency opioids such as hydrocodone and oxycodone.

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Opioid Dependence: Morbidity and Mortality

- Since 2003, opioid analgesics account for more deaths by overdose than cocaine and heroin combined (CDC, MMWR 2012)
- Overdoses from Rx opioids have more than tripled in the past 20 years, reaching 16,651 deaths in the U.S. in 2010 (Blackburn-Munro 2004)
- Deaths due to opioid analgesics in US (2008): 15,000, surpassing motor vehicle accidents as cause of death in some states (Paulozzi et al. 2008)
- Immunosuppressive effects of opioids may increase morbidity from infectious diseases, autoimmune diseases, and cancer (Pergolizzi et al. 2008)

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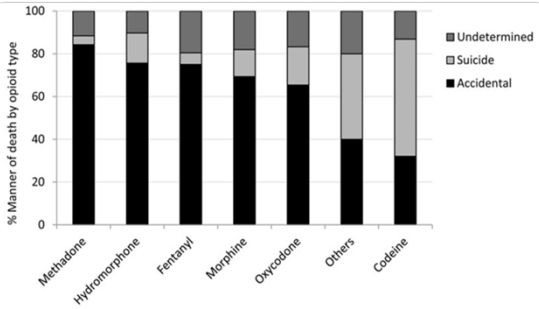
Opioid-related Deaths in Ontario, 2006-2008 (N=1359)



Madadi et al. 2013

Narcotic Addiction: A Treatment Gap

- Most people with opioid dependence are not receiving effective treatment (SAMHSA 2013, Olsen and Sharfstein 2014).
- Reasons for this gap between treatment need and delivery include lack of access to opioid dependence treatment programs and lack of training for providers (Cicero et al., 2007; Knudsen et al., 2007).
- Detoxification, followed by counseling alone without an effective medication, remains the standard of care for opioid dependence, despite evidence of the high relapse rate (Weiss et al. 2011) and risk of death from overdose after detoxification (Kakko et al. 2003, Merrall et al. 2012)
- Thus, expanding available treatment options is an important public health priority (CASA Columbia, 2012).

Treatment Options for Opioid Dependence

- Residential and drug-free approaches
- Agonist maintenance
- Antagonist maintenance

Detoxification and "Drug-free" Approach

- Traditional model for opioid dependence involves detoxification without subsequent pharmacological support
- Medication-free approach can be effective for small subgroup of stable patients with high motivation (Flynn et al., 2003; Van den Brink and Haasen, 2006).
- As many as 90% of those detoxified will relapse within first 1-2 months unless treated with medications (Weiss et al. 2011, Smyth et al. 2010)
- Some patients who relapse will die as a result of overdose (Kakko et al., 2003)

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Residential Treatment

- High failure and dropout rates from therapeutic communities (TCs); ; up to 50% dropout during first week after detoxification (Chutuape et al. 2001)
- Requires significant investment of time and financial resources, disruption of other domains of educational, social, or occupational functioning.
- Discharge from controlled environment without agonist or antagonist "on board" is associated with significantly heightened risk for overdose and death.

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The Role of Medication in Treatment of Opioid Dependence

- Detoxification from opioids without pharmacological support afterwards remains the dominant model of treatment
  - Yet decades of experience and evidence have shown lack of effectiveness
- Medications to prevent relapse are not routinely offered after detoxification
  - Misplaced emphasis on being opioid- (medication-) free as the treatment goal rather than on protecting against negative consequences
- First weeks following detoxification carry a significant risk of overdose and death
  - Imperative that either agonist or antagonist pharmacologic support is offered to individuals who want to stop using opiates
  - Individuals who undergo detoxification can initiate antagonist to prevent relapse without experiencing withdrawal

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Agonist Treatments for Opioid Dependence

- Methadone
- Buprenorphine/naloxone

A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine. With this medication, and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. Medical and psychometric tests have disclosed no signs of toxicity, apart from constipation. This treatment requires careful medical supervision and many social services. In our opinion, both the medication and the supporting program are essential.

ough review of evidence available in 1957,[1] concluded that "The advisability of establishing clinics or some equivalent system to dispense opiates to addicts cannot be settled on the basis of objective facts. Any position taken is necessarily based in part on opinion, and on this question opinions are divided." With respect to previous trials of maintenance treatment, the Council found that "Assessment of the operations of the narcotic dispensaries between 1919 and 1923 is difficult because of the paucity of published material. Much of the small amount of data that is available is not sufficiently objective to be of great value in formulating any clear-cut opinion of the purpose of the clinics, the way in which they operated, or the results attained." No new studies bearing on the question

JAMA Classics: Celebrating 125 Years
Methadone Maintenance 4 Decades Later
Thousands of Lives Saved But Still Controversial
Commentary by Herbert D. Kleber, MD
JAMA. 2008;300(19):2303-2305

JAMA. 1965;193(8):646-650

From the Rockefeller Institute, and Manhattan General Division of Beth Israel Hospital, New York.
Reprint requests to Rockefeller Institute, New York 10021 (Dr. Dole).

Methadone

- Studies in 1960s by Dole and Nyswander demonstrated that methadone had highest efficacy at relieving opioid withdrawal
- Has dominated treatment of opioid dependence in U.S. (currently >260,000 patients in MMT programs)
- Advantages to methadone: highest retention rates (80% at 6 months), reduction in HIV and Hep-C infection
- Disadvantages: settings for methadone are restrictive and highly structured, maintains physiological dependence

Stigma of Methadone

- Methadone is perceived by many as “substituting one addiction for another”
- Segregation of methadone maintenance from the rest of healthcare vs. medical model for addiction as an illness.
- Perceptions of institutionalization and social control (Etesam et al. 2014)
- Patients in MMT report secrecy, shame; sometimes leading to dropping out of treatment

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Safety Concerns with Methadone

- Risk of cardiac arrhythmias, including QTc prolongation and Torsades de Pointes (Chou et al. 2014)
- In a large study (N=2112) of fatal unintentional prescription opioid overdoses, methadone was associated with the highest number of deaths per equi-analgesic dose sold (23.3) (Piercefield et al. 2010)
- Combining methadone with benzodiazepine abuse carries risk of unintentional overdose

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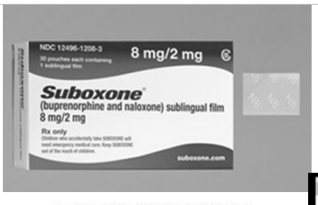
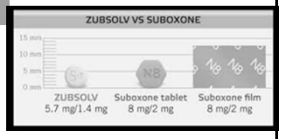
Buprenorphine/naloxone (Suboxone, Zubsolv)





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Buprenorphine

- Buprenorpine/naloxone, a thebaine derivative, is a long-acting partial opioid agonist, became available for office-based prescribing in 2002.
- Currently two formulations: Suboxone 8/2 and 2/0.5 mg films; Zubsolv 5.7/1.4 and 1.4/0.36 tablets
- Buprenorphine retains 40-55% of patients over 3 to 6 months of treatment in clinical trials (Mattick et al. 2014, Haddad et al. 2013, Schottenfeld et al. 2008).
- Induction is a modest barrier; patients must wait 12-18 hours after last use of a short-acting opioid

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Advantages of Buprenorphine

- Less restrictive prescribing rules
- Less risk of overdose because of its partial agonist ceiling effects
- Lower risk of ventricular arrhythmias
- Milder withdrawal effects
- Like methadone, normalizes cortisol stress response (vs. fluctuating levels with oral naltrexone), which decreases relapse risk (Nava et al. 2006, Lorenzetti et al. 2010)

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Challenges with Buprenorphine

- Risk of diversion and abuse (film: lower liability)
- Withdrawal symptoms will occur if more than one dose is missed; opioid dependence persists
- Bup-maintained patients are frequently diagnosed with anxiety (23-42%), and benzodiazepine prescriptions are filled at high rates (47-56%) in this population (Mark et al, 2013)
- Optimum duration of maintenance unclear; high (80-90%) relapse when discontinued after $\leq$ 5 months (Nielsen et al. 2013)
- Slower tapers (4+ weeks) are more successful (Katz et al. 2009, Sigmon et al. 2013) than brief tapers
- Provider availability: requires special training, DEA waiver.
- Medication availability: As of May 2013, 11 states have lifetime limits on bup prescriptions for opioid dependence, ranging 12-36 months (Rinaldo et al. 2013)

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Antagonist Treatment

- Oral naltrexone
- Long-acting injectable naltrexone (XR-NTX)

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Naltrexone: Formulations and Inductions

- Approved by FDA in 1984 (oral) and 2010 (long-acting injectable Vivitrol)
- Blocks opioids without agonist effects; incompatible with ongoing illicit opioid abuse. No tolerance or withdrawal develops.
- Induction requires abstinence for 5-7 days from heroin, 7-10 days from methadone
- Oral form taken daily (50 mg) vs. monthly (380 mg) IM injection;
- Serum level of 2 ng/ml provides effective blockade against 25 mg IV heroin effects
- Only 15.8 % of treatment facilities in U.S. report using naltrexone.*

*SAMHSA. National Survey of Substance Abuse Treatment Services. Data on Substance Abuse Treatment Facilities. 2009. Rockville MD: US Department of Health and Human Services; DHHS publication SMA 05-4112.

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Candidates for Naltrexone

- Who is most likely to benefit from naltrexone?
- Individuals not interested in agonist maintenance (high degree of motivation, professions in which agonist use is controversial)
- Those who have successfully used agonist but wish to taper off maintenance without risking relapse
- Patients who have failed prior agonist treatment
- Individuals who are already abstinent but at high risk for relapse (e.g. acute psychiatric status)
- Those with less severe form of the disorder; shorter history of opioid dependence, perhaps adolescents

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Barriers to Naltrexone

- Oral naltrexone did not live up to its pharmacological potential. Poor adherence and retention caused clinicians to lose confidence in antagonist treatment.
- Induction is labor-intensive for the clinician (assessment of withdrawal, observation over time) and for the patient (must tolerate distress of moderate opioid withdrawal)
- Many practitioners are uncomfortable with IM gluteal injections.
- Lack of experience and training in antagonist treatment

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Strategies to Improve Efficacy of Naltrexone

- Behavioral therapy to support adherence
- Use of naltrexone during detoxification as relapse prevention agent
- Development of long-acting preparations that eliminated need for daily pill-taking
- Newer induction methods to minimize opioid withdrawal and permit outpatient detoxification

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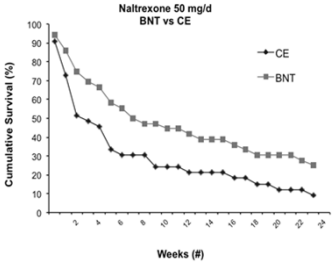
Improving Treatment Retention on Oral NTX Using Behavioral Therapy

- Behavioral naltrexone therapy (BNT) was developed to:
  - Promote adherence to oral naltrexone and encourage lifestyle changes supporting abstinence
  - Includes components from empirically validated treatments: Network Therapy, Community Reinforcement Approach, Voucher Incentives, and Relapse Prevention



Sullivan et al., 2006

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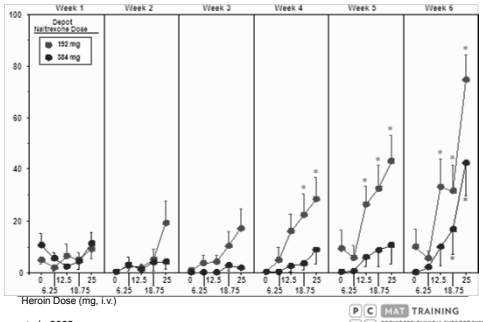
VAS Ratings of "I Feel High" in Non-treatment Seeking IV Heroin Users on Depot Naltrexone in Self-Administration Paradigm



Comer et al., 2002

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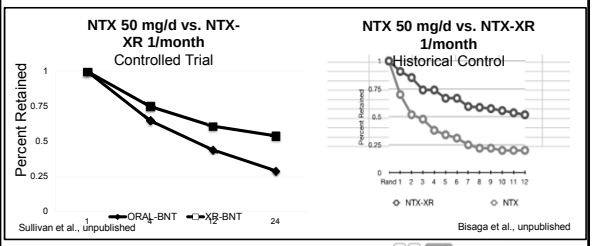
Retention in Treatment: Oral vs. XR-Naltrexone

- The retention rate in the XR group is twice that of the oral group, approximating 50% at 6 months



Sullivan et al., unpublished

Bisaga et al., unpublished

(Sullivan et al., ,unp

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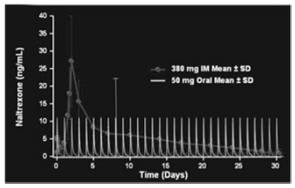
Improving Treatment Retention Using Long-Acting Injectable Naltrexone

Microspheres with naltrexone in suspension licensed in 2007



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Naltrexone-assisted Opioid Detoxification

- *Day 1* – Ancillary meds: clonidine, clonazepam, compazine, zolpidem, trazodone
- *Day 2* – Buprenorphine 4 mg BID
- *Day 3* – Washout Day
- *Day 4* – Naltrexone 3 mg
- *Day 5* – Naltrexone 6 mg
- *Day 6* – Naltrexone 25 mg
- *Day 7* – Naltrexone 50 mg, followed by 380 mg IM (Vivitrol)
  - Alpha-2 adrenergic agents (clonidine), benzodiazepines, and sleeping agents can ameliorate withdrawal symptoms
  - Approximately 70% of patients complete inpatient induction and accept long-acting naltrexone (NTX-XR)

Sigmon, Bisaga et al., 2012

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XR-NTX Induction: Outpatient Opioid Detoxification with Naltrexone vs. Buprenorphine

- ***Sample:*** 140 opioid-dependent patients
- ***Randomized to one of two outpatient detoxification strategies:***
  - (1) 7-day buprenorphine induction/taper (8 mg to 0 mg)
  - (2) 7-day naltrexone induction (1 mg to 25 mg) + adjunct medications (clonidine, clonazepam, prochlorperazine, zolpidem)
- Administration of Vivitrol given on Day 8 (naltrexone group) and on Day 15 (buprenorphine group)
- ***Aim:*** Compare injectable naltrexone induction rates between the naltrexone and buprenorphine detoxification arms

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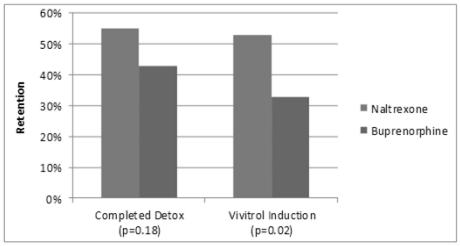
Completion of Detox & Vivitrol Induction



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Naltrexone Maintenance Therapy: Conclusions

- Injectable naltrexone (XR-NTX) is an effective medication-assisted treatment for patients in primary care and psychiatric treatment settings.
- Behavioral therapy strategies improve adherence to oral and injectable naltrexone
- Several trials of oral naltrexone maintenance found ceiling of ~30% retention at 6 months (Preston et al. 1999; Carroll et al. 2001, 2002, Sullivan et al. 2006)
- Long-acting NTX formulations (injections, implants) double retention rate, compared to oral naltrexone; protect against relapse and overdose.
- Depot naltrexone achieves 6-month retention rates of 50%-70%, comparable to buprenorphine maintenance (Hulse et al. 2009; Krupitsky et al. 2012, Kunoe et al. 2009; Brooks et al. 2011).

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MAT for Opioid Dependence: Summary

- Both agonists (methadone, buprenorphine) and antagonists (injection naltrexone) protect against relapse and overdose
- Methadone has highest treatment retention, but low acceptability to many patients
- Buprenorphine can be prescribed in office setting and carries less risk of cardiac effects or overdose, but no guidelines on length of maintenance; difficulty tapering off
- Naltrexone (XR-NTX) is least utilized pharmacotherapy but gaining acceptance; not compatible with ongoing opioid use
- All Medication-assisted Treatments for Opioid Dependence are compatible with 12-step work, behavioral therapies (e.g. Motivational Interviewing, Relapse Prevention, CBT)
- Optimum duration of treatment has not been established

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Psychiatric Co-morbidities in Opioid Dependence

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Prevalence of Psychiatric Disorders in Opioid Dependence

- Lifetime prevalence of affective disorders is 85.4% in women and 70.0% in men (Rounsaville 1982), with current prevalence of major depression of 15.8% (Brooner 1997).
- Major depression is most prevalent mood disorder (19% current, 24% past) among patients seeking primary care office-based buprenorphine/naloxone.
- In NESARC waves 1,2, lifetime non-medical prescription opioid use was found to be associated with generalized anxiety disorder (Martins et al. 2012)
- Post-traumatic stress disorder (PTSD) is also common, though patients may deny a PTSD history until they feel confident in their treating clinician.

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Psychiatric Co-morbidities in Chronic Pain

- Depression (37%), anxiety (25%), substance use disorders (12%) (Knaster et al. 2012), somatization, borderline personality disorder (McWilliams et al. 2013).
- Prevalence of drug or alcohol abuse in chronic pain patients: 3-19% (Fishbain et al. 1992, Chabal et al. 1997).
- Patients with significant psychiatric co-morbidity and substance abuse are more likely to stay on opioids and to receive higher doses (Krashin et al. 2013).
- Patients with pain are prone to a more chronic course of depressive and anxiety disorders *(Gerrits et al. 2012)*, and depression significantly predicts onset of chronic pain (Tunks 2008).

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Assessment and Treatment of Opioid Abuse in Chronic Pain Patients

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Overlapping Neural Circuitry: Pain and Addiction

Chronic pain serves as pathway for problematic opioid use/addiction:

- Several brain regions involved in both pain processing and opioid addiction: NA, amygdala, ACC, hypothalamus
- fMRI studies suggest shared neural system for evaluating aversive and rewarding stimuli (Becerra et al. 2001)
- Chronic pain down-regulates amygdala GABAergic function, priming for opioid reward effects (Zhang et al. 2014)

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Cognitive Deficits in Pain and Opioid Addiction

Chronic pain patients demonstrate:

- Decision-making abnormalities *(Apkarian et al. 2004)*
- Impaired prospective short-term memory *(Ling et al. 2007)*
- Reduced hippocampal volume; observed learning and emotional deficits *(Mutso et al. 2012)*

Opiate users demonstrate:

- Diminished error-related activation in anterior cingulate cortex *(Lee et al. 2005, Yucel et al. 2007)*
- Prolonged deliberation times in making risky decisions *(Fishbein et al. 2007)*
- Among patients with chronic back pain, those on opioid therapy (vs. no opioids) had significantly slower information processing, reduced spatial memory, and impaired performance in working memory *(Schiltenwolf et al. 2014)*

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Implications for Treatment

- Psychiatric co-morbidity is risk factor for non-medical prescription opioid use and abuse/dependence (Katz et al. 2013).
- Most chronic pain patients (CPPs) (52%) are treated by PCPs without specialized training in identifying either psychiatric conditions or opioid misuse.
- Since opioids exert brief anxiolytic and antidepressant effects, they are used by patients to "self-medicate" emotional and physical pain (Howe et al. 2014).
- Prescription opioid epidemic reflects a serious need for better recognition and treatment of psychiatric conditions in CPPs.

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Alternatives to Opioid Analgesics for Chronic Pain

- World Health Organization (WHO) and American Pain Society guidelines recommend that non-opioid analgesics should be first-line agents for management of chronic pain.
- Many patients will experience a good therapeutic response to non-opioid analgesics, without the need for opioid therapy.
- While opioids can be effective for short-term pain relief, the evidence is mixed concerning their effectiveness in chronic pain lasting >6 months (Trescot et al. 2008).

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Non-Opioid Analgesics

- **NSAIDS** – inhibit synthesis of prostaglandins and **thromboxane via COX-1 and COX-2**
- **Autonomic nervous system agents** – clonidine, baclofen
- **Tricyclic antidepressants** – inhibit 5HT and NE reuptake, relieve sleep disorder, treat depression
- **SNRI** - duloxetine (Cymbalta)
- **Anticonvulsants** – effective in neuropathic pain states, stabilize sodium channels, suppress firing (e.g. gabapentin, carbamazepine)
- **Behavioral techniques** – CBT, deep relaxation, exercise, physical therapy
- **Invasive procedures** – nerve blocks

NSAIDs = non-steroidal anti-inflammatory drugs; 5HT = hydroxytryptamine receptors; NE = norepinephrine; CBT = cognitive behavioral therapy.

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How Can Chronic Pain Patients Benefit from XR-NTX?

- Many "chronic pain" patients abusing prescription opioids may receive effective pain management from non-opioid analgesics.
- Complaints of chronic pain can be idiom of distress for patients with opioid abuse and other co-morbid psychiatric conditions.
- Inter-dose withdrawal and hyperalgesia can be mistaken for chronic pain in some cases.
- Requests by "chronic pain" patients to detox. from opioids should be seriously considered.
- Naltrexone decreases risk of relapse following opioid analgesic use when latter is determined to be medically unnecessary; can support abstinence.

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Agonist Treatments for Concurrent Opioid Dependence and Chronic Pain

- **Methadone:**
  - Less acceptable for prescription opioid abusers in clinic setting, and office-based prescribing carries high risks for patient safety.
- **Buprenorphine:**
  - Superior safety profile, but analgesic effects wear off in 6-9 hours; pain management requires divided daily dosing

NSAIDs = non-steroidal anti-inflammatory drugs; 5HT = hydroxytryptamine receptors; NE = norepinephrine; CBT = cognitive behavioral therapy.

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Disadvantages to Methadone for Pain Management

- Maintains and increases physiological dependence; discontinuation is difficult
- Considerable individual differences in metabolism based on genetic polymorphisms of cytochrome P450 enzymes
- Accumulation possible because of long T1/2 and high fat solubility; increased risk of overdose
- Not a first-line agent for opioid analgesic therapy. Should not be used in opioid-naïve patients.
- Potential cardiac arrhythmias led to black-box warning in 2006:
- QT prolongation – prevalence 9.2% (Fonseca et al. 2009)
- Torsades de Pointes (Mayet et al. 2010), more likely at doses of >120 mg/day

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Buprenorphine/naloxone: Role in chronic pain management?

- Although use for pain management is currently off-label, bup/nx is FDA-approved for treatment of opioid dependence.
- For chronic pain patients seeking opioid dependence treatment, 2/3 experience clinically meaningful reduction in pain (Weiss et al. 2010, POATS study). May exert anti-hyperalgesic effect.
- Bup/nx is effective in divided daily dosing in individuals with concurrent pain and opioid abuse (Jones et al. 2010; Roux, Sullivan et al. 2012; Davis 2012; Neumann et al. 2013) – esp. in those maintained on less than 200 mg morphine equivalents at baseline (Daitch et al. 2012, Rosenblum et al. 2012).
- Importance of flexible dosing, multiple daily doses for optimal pain management
- **Conclusion:** Bup/Nx has potential as an analgesic medication in treating patients with chronic pain who abuse opioids.

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Treatment Approaches to Chronic Pain and Opioid Addiction

- Assessment of Need for Opioid Analgesics
  - Can the patient's pain be managed without opioids?
    - For patients who can be detoxified, antagonist maintenance with NTX-XR (Vivitrol) protects against relapse and overdose.
  - Does a patient requiring opioid analgesics have a history of opioid addiction?
    - Perform baseline testing (urine toxicology, screening for level of risk), medication contract, ongoing monitoring with drug testing and interviews to detect aberrant behaviors, and assessment of functioning.
- Long-acting Opioid Agonists for Chronic Pain
  - Buprenorphine/naloxone in TID divided-dosing for pain
  - Avoid methadone as first-line agent and in opioid-naïve patients

PCSS MAT TRAINING PROVIDERS' CLINICAL SUPPORT SYSTEM For Medication Assisted Treatment

Current Situation of Opioid Dependence Treatment

- Although opioid dependence is the most devastating of addiction, it has the most effective medication-assisted treatments – yet, most patients are not receiving MAT (<20%)
- Most programs offer a single treatment: "one size fits all"; where you enter treatment determines what you are offered
- Detoxification, followed by psychosocial treatment alone remains dominant model across US -- despite ineffectiveness (> 90% relapse) and possibly increased risk of death.
- Training in clinical uses of naltrexone and buprenorphine will enable providers to offer treatments which can reduce the risk of overdose or relapse.

PCSS MAT TRAINING PROVIDERS' CLINICAL SUPPORT SYSTEM For Medication Assisted Treatment

Best Practice Plan: Guidelines

- The treatment delivery system for OUD needs to become more flexible in tailoring treatments (agonist vs. antagonist vs. therapy alone) to replace the "silo" approach (where treatment is site-specific; based on convenience, beliefs or tradition).
- Currently available scientific evidence recommends pharmacologic support with either agonist or antagonist treatment following detox from opioid dependence, to prevent relapse and reduce the risk of overdose.
- Treatment guidelines are needed for community programs and practice, to enhance patient outcome while improving utilization of scarce resources.

PCSS MAT TRAINING PROVIDERS' CLINICAL SUPPORT SYSTEM For Medication Assisted Treatment

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- **Collaborators:**

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