MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Implementing Antagonist-Based Relapse Prevention Treatment for Buprenorphine-Treated Individuals

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Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Describe the evolution of antagonist-based treatment for opioid dependence
  - State guidelines to select most appropriate patients for treatment with naltrexone
  - Determine pharmacological strategies to initiate treatment with naltrexone
  - Identify clinical challenges encountered during treatment with naltrexone
  - Implement naltrexone in addiction practice competently

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

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Outline

- Agonist vs. antagonist-based treatment of opioid dependence
- Early experiences with opiate blockers
- Strategies to improve effectiveness of naltrexone
  - Long-acting preparation
- Selection of candidates for naltrexone
- Methods for initiating treatment with naltrexone
  - Naltrexone induction algorithms
  - Adjunctive medications
  - Managing ‘naltrexone flu’
- Clinical challenges and controversies with naltrexone treatment
  - Testing the blockade
  - Concerns about overdose risk

Opioid Dependence Treatment Goals

- Help patients to stop using opiates
- Provide protection against the risk of overdose and death
- Teach skills necessary to cope with cravings and life stressors without drugs
- Medications, most likely given over an extended period of time, perhaps indefinitely, should be the mainstay of opioid dependence treatment
- Treatment should be focused on recovery, and many ways it could be reached

The Role of Medication in Treatment of Opioid Dependence

- Detoxification from opioids without pharmacological support afterwards remains the dominant model of treatment
  - Despite decades of experience and evidence to the contrary
- Medications to prevent relapse are not routinely offered after detoxification
  - Result of an emphasis on being opiate- (medication-) free as the treatment goal rather than on the treatment as protection against negative consequences
- First weeks following detoxification are the most dangerous phases of opioid dependence, with a significant risk of overdose and death
  - Pharmacological assistance to prevent overdose is essential during this period
  - It is imperative that either agonist or antagonist is offered to individuals who want to stop using opiates
  - Individuals who decide to undergo detoxification are in an ideal position to have a trial of antagonist to prevent relapse

Choosing Agonist vs. Antagonist Based Treatment

	AGONIST	ANTAGONIST
Maintain physiological dependence and potential for withdrawal	+	-
Potential for tolerance development	+/-	-
Euphoric effects/abuse/diversion	++	-
Compatible with ongoing illicit opioid use	++	-
May alter use of other drugs	+/-	++
Extinction of heroin-reinforced behaviors/reversal of underlying neurobiology	+	++
Duration of treatment	Indefinite?	?
Cultural/ideological barriers to availability	++	-
Professional/public opposition	++	+

Not offering medication after they stop drug use puts patients at increased risk of overdose and death

Using Blockers to Treat Opiate Dependence

- The concept developed in parallel to methadone, in part fueled by the controversies in response to methadone
- In 1960s studies by Martin on various opiates in humans discovered opiate blockers, naltrexone was well tolerated and had a long duration of action
  - Subjects maintained on the blocker did not feel effects of morphine and it was impossible to induce physical dependence
- Wikler suggested that opiate blockers are used for treatment of heroin addiction
  - Based on the behavioral/learning model of addiction, attempts at re-addiction while on the blocker will lead to the extinction of drug seeking

Why There Are Very Few Patients on Naltrexone

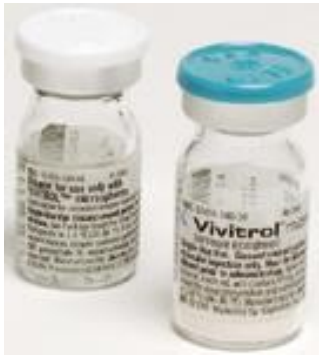
- When heroin epidemic reached panic proportions in 1970s, NIDA had a very active portfolio of naltrexone grants (21 grants 1973-74)
- Results of first years of studies with oral preparations were disappointing
  - Low patient acceptability and poor compliance
  - It became clear that to have more patients benefit from naltrexone, better methods of induction and long-term maintenance needed to be developed
- Meta-analytic studies (e.g., Cochrane Review) concluded that studies to adequately assess the effectiveness of oral naltrexone are lacking which might have discouraged its clinical use

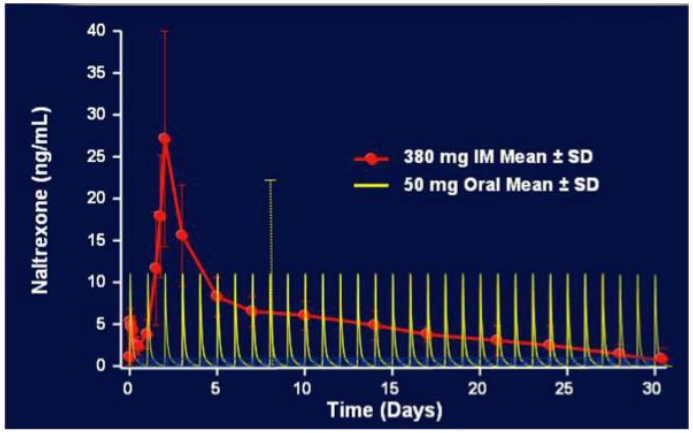
Improving Effectiveness of Naltrexone (1980s -)

- Development of novel methods of detoxification
  - Clonidine become available to treat withdrawal (Gold et al., 1978)
  - Rapid Detox: detoxification was accelerated by administering antagonist and emerging symptoms are treated with clonidine (Riordan & Kleber 1980)
  - General anesthesia and an Ultra-Rapid Detox (1-day detox) was introduced (Loimer 1988)
  - Buprenorphine was introduced as a step-down from methadone during detoxification (Kosten et al., 1992)
- Using antagonists during detox became an opportunity to start naltrexone as a relapse prevention agent: **Rapid Naltrexone Induction** (Brewer)
- Work continued on **improving adherence to oral preparations** using tailored behavioral therapy (BNT: Sullivan et al., 2006)
- Several **long-acting preparations** of naltrexone become available to deal with compliance issue

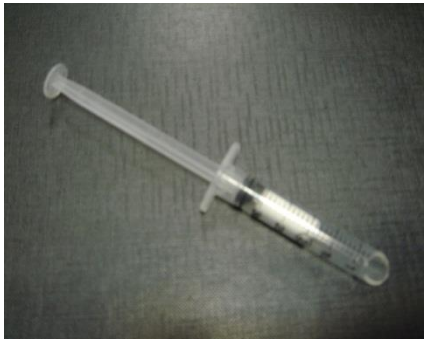
Improving Treatment Retention Using Long-Acting Preparations

- Injections
  - 1st gen: oil suspension (Wedgewood)
  - 2nd gen: microspheres with NTX in suspension Vivitrol licensed in 2007





- Implants
  - 1st gen: compressed NTX c. 1996, now licensed in Russia (Prodetoxone)
  - 2nd gen: NTX mixed with polymer matrix c.2001, Australia)



Efficacy of Extended-Release (XR) Naltrexone

- In research studies comparing oral vs. XR (injections, implants) naltrexone, treatment retention rate in the XR group is twice that of the oral group, approximating 50-70% at 6 months (Hulse et al., 2009; Krupitsky et al., 2012, Kunoe et al., 2009; Brooks et al., 2011)
- Blinded trials comparing injectable naltrexone with injection of placebo show that patients receiving active naltrexone are successful in treatment, and this effect is dose related (Comer et al., 2006; Krupitsky et al., 2011)

Selection of Candidates for Naltrexone

- Patients who are not interested or able to be on agonist maintenance
  - Those with high degree of motivation for abstinence (active in 12-step programs)
  - In professions where treatment with agonist is controversial (healthcare professionals, pilots)
- Patients successful on agonist but who want to try abstinence
- Patients who failed prior treatment with agonist
  - Continued use of heroin, did not improve/dropped out
- Patients who are abstinent but at risk for relapse
  - Moving to old neighborhood, increased stress, worsening psychiatric problems
- Patients for whom relapse would be disastrous (e.g., physicians, pilots, parolees)

Selection of Candidates for Naltrexone

(*continued*)

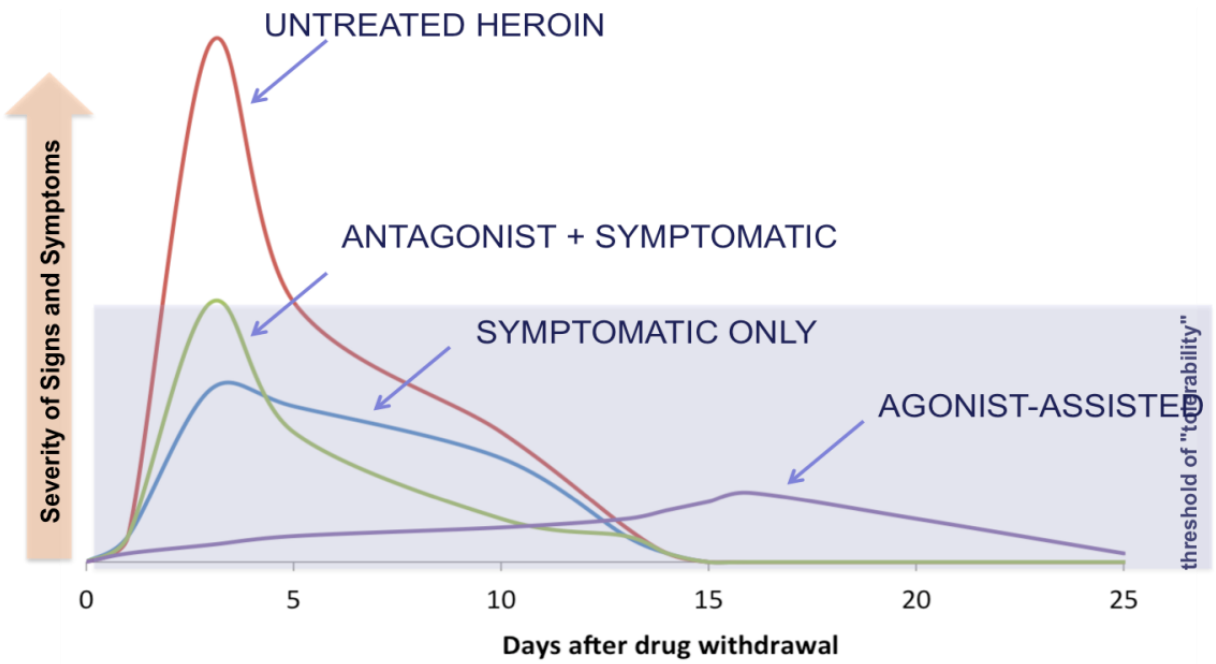
- Patients with less severe form of a disorder
  - Short history of use, lower level of use
- Who is most likely to benefit from naltrexone?
  - Highly motivated patients who are committed to abstinence
  - Older patients with long history of use and multiple relapses
  - Those with longer periods of abstinence between relapses
  - Patients who relapsed and returned to treatment do better

Patients Who are Better Candidates for Agonists

- Patients with history of overdoses, particularly following detoxification
- Patients with serious mental illness, disorganized, homeless
- Patients who have been opiate-free but never felt “normal”
  - Patients in whom psychiatric illness emerged/worsened after previous detoxes (with or w/o naltrexone)
- Patients with chronic pain requiring chronic opioid treatment
- Patients with severe GI disorders exacerbating during withdrawal/abstinence
- Patients with advanced liver disease (Brewer and Wong, 2004)
  - Concerns about hepatotoxicity are not based on the representative data
  - Naltrexone is used for treatment of pruritus in jaundiced patients with severe liver disease

Initiating Naltrexone

- No single best method but rather a set of approaches/tools that can be individualized to individual patient and the treatment team (experience)
- Ability of the team to expect and respond to emerging complications, to maintain enthusiasm and confidence in the method can influence outcome
- Effective method will balance the degree of discomfort and the duration of treatment



Naltrexone Initiation During Detoxification: Rapid Naltrexone Induction Procedure

Columbia Rapid Naltrexone Induction Protocol

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine	admission	4 mg bid					
Naltrexone				3 mg	6 mg	25 mg	50 mg po 380 mg im
Supportive medications	clonidine 0.1-0.2 mg qid, clonazepam 0.5-1.0 mg qid, toradol, ranitidine, zolpidem, trazodone						

- Approximately 70% of patients complete inpatient rapid naltrexone induction procedure and accept long-acting naltrexone (NTX-XR)
- Modification of the algorithm depending on the level of physiological dependence

Rapid Naltrexone Induction Algorithm (Sigmon et al., 2012)

	Severity (physical dependence/anticipated withdrawal)	
	NONE Already abstinent (completed buprenorpine taper and has abstained for 7-10 days, exiting controlled environment)	**MILD** H: 1-2 bags/day; OXY: <50mg/day
Setting	**Outpatient**	**Outpatient or partial hospital**
Buprenorphine Dose	None	None or 4mg, day 1
Clonidine	None	0.1-0.2 mg TID to QID
Clonazepam	None	0.5 mg BID
Ancillary medications	None	Sleep, pain (e.g. NSAID)
Hydration	Routine	Aggressive oral hydration (e.g., sports drinks)
Time to first NTX dose	Day 1	Day 3
Initial oral NTX dose	25-50 mg	12.5 mg QD
Time to Vivitrol injection	Days 1-2	Day 4; (or Day 5-6 after titrating oral naltrexone to 25-50mg QD)

Rapid Naltrexone Induction Algorithm *(continued)*

	Severity (physical dependence/anticipated withdrawal)	
	MODERATE H: 3-6 bags/day; OXY (50-100mg/day); following short-term methadone or buprenorphine taper	**SEVERE** > 6 bags/day; illicit methadone; severe prescription opioid use (>100 mg/day); significant medical problems
Setting	**Partial hospital with with inpatient backup**	**Inpatient or partial hospital with inpatient backup**
Buprenorphine Dose	4-8 mg, day 1 or 2	8 mg, day 1 or 2, or >8 mg as needed
Clonidine	0.2 mg (TID to QID)	0.2-0.3 mg QID
Clonazepam	1.0-2.0 mg (TID to QID)	1.0-2.0 mg QID
Ancillary medications	Sleep, pain, GI distress	Sleep, pain, GI distress
Hydration	Aggressive oral hydration	Aggressive oral or IV hydration
Time to first NTX dose	Days 3-4	Day 4-5 (later if needed)
Initial oral NTX dose	6 mg BID	3-6 mg QD-BID
Time to Vivitrol injection	Days 4-5; or days 5-7 after titrating oral naltrexone to 25-50 mg QD)	Day 5-6; (or Day 6-7 after titrating oral naltrexone to 25-50mg QD)

Adjunctive Medication Used During Detox/NTX Induction

Symptoms	Drug Class	Medication (dosage)
Autonomic arousal (sympathetic)	A_2-adrenergic agonists	• Clonidine (0.1–0.3 mg PO q 6–8 h) • Lofexidine (0.6–2 mg/d in 2–3 div doses)
Anxiety/restlessness	Benzodiazepines Antihistamines	• Clonazepam (0.5–2 mg PO q 4–8 h) • Oxazepam (15–30 mg PO q 4–6 h) • Lorazepam if parenteral (IM, IV) dosing needed • Diphenhydramine (50–100 mg PO q 4–6 h) • Hydroxyzine (100–150 mg PO q 6 h)
Insomnia	Sedating antidepressants Non-benzodiazepine hypnotics Sedating atypical neuroleptics	• Trazodone (50–150 mg PO at hs) • Doxepin (50–100 mg at hs) • Zolpidem (10 mg PO at hs) • Eszopiclone (3 mg PO at hs) • Quetiapine (50–200 mg PO at hs)
Musculoskeletal pain	NSAIDs Aniline analgesics Antispasmodics	• Ibuprofen (400 mg PO q 4–6 h) • Aspirin (650 mg PO q 4–6 h, max 4 g/d) • Ketorolac (30 mg IM q 6 h, max 120 mg/d for 5d) • Acetaminophen (650–1000 mg PO q 4–6 h) • Cyclobenzaprine (5–10 mg PO q 4–6 h); others include baclofen, tizanide, methocarbamol)
GI Distress (nausea, vomiting, diarrhea)	Oral hydration Antiemetics $5HT_3$ antagonist Miscellaneous	• Sports drinks (contain electrolytes), diluted fruit juice, bouillon • IV fluids as backup if needed • Prochlorperazine (5–10 mg PO or IM q 3–4 h) • Promethazine (25 mg PO or IM q 4–6 h) • Ondansetron (8–16 mg PO or IM q 8–12 h) • Bismuth subsalicylate (2 tablets PO q 1 h) • Loperamide (2 mg PO after each BM

Transition from Buprenorphine Maintenance to Naltrexone

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine	2 mg qd						
Naltrexone				1-3 mg	6 mg	25 mg	50 mg po 380 mg im
Supportive medications	clonidine 0.1-0.2 mg qid, clonazepam 0.5-1.0 mg qid, toradol, ranitidine, zolpidem, trazodone, d-amphetamine						

- Many people who are unable to taper off buprenorphine have anxiety disorder, which can benefit from SSRI or an anticonvulsant (gabapentin, pregabalin)
- People who stop buprenorphine maintenance are either anxious or sedated, treat symptomatically accordingly (e.g., clonazepam, stimulant)

Protracted Withdrawal: Naltrexone Flu

- Patients who start naltrexone right after detoxification commonly experience a “flu-like” sign and symptoms
  - Somatic complaints: insomnia, GI distress, hyperalgesia, anergia
  - Anxiety, irritability, dysphoria, anhedonia
  - Severity may be lower if naltrexone is started 10-14 days after completion of detoxification (but many relapse by then)
- Partially alleviated with aggressive symptomatic treatment,
  - Insomnia (v. frequent, often severe): zolpidem, trazodone, quetiapine
  - GI distress: H2 blockers
  - Anxiety/hyperarousal: clonazepam, clonidine
- Most of these symptoms remit by 2-4 weeks
  - True prolonged symptoms are rare and likely reflect additional psychopathology
- Persistent/protracted withdrawal vs. acute effects of naltrexone (?)
  - Negative mood and vegetative symptoms are significantly higher in participants who are receiving higher dose of naltrexone

Clinical Challenges: Testing the Blockade

- It is expected that approximately 50% of patients will ‘test’ blockade often same day as discharge
  - Make sure sufficient levels of naltrexone are present on discharge (oral supplementation if NTX-XR is given on the day of discharge)
- Most commonly patients will test 1-3 times with low doses of opioid during the first few days after discharge, after which they are reassured blockade works and do not return to use
- Some patients will use large amounts, for 1-3 weeks, trying to get high
- Very few patients will continue using, often IV, even though they are blocked, but are interested staying on naltrexone
- Rarely, NTX is quickly metabolized, blood levels are low and patients may become re-dependent while receiving NTX as recommended

Clinical Challenges: Managing Relapse

- Some patients have increased craving and may use in weeks 3-4, in those more frequent injection or oral supplementation is needed
- Most commonly, the first sign of relapse is missing doses/injections. The blockade wears off 2-3 days after oral and 5-6 weeks after injectable doses
  - Additional therapy, involving network members is useful to improve adherence
  - Inpatient stabilization and another attempt at antagonist treatment
  - Residential treatment/sober house
  - Transition onto agonist

Safety Concerns: Overdose

- Risk of overdose is significant if patient decides to stop taking naltrexone, stop attending treatment and resumes opiate use
  - Provide detailed description of risks (signed consent for treatment), continue discussing risks in patients who continue use:

    "I understand that after I stop naltrexone I may be more sensitive to the effects of heroin and any other narcotics. The amount of heroin or narcotics I may have been using on a routine basis before I started naltrexone, might now cause overdose and death. I fully understand the nature and seriousness of this possible consequence.

    If I am not sure that I can avoid opiate use, I understand that I can be referred to alternative treatment programs, such as a methadone maintenance, which is an effective treatment for heroin dependence and has a reduced risk of fatal overdose."
  - Consider transition onto agonist to decrease risk of overdose if unable to comply with NTX
- Fear of overdose applies to any completed detoxification or discontinuation of agonist maintenance. Naltrexone, especially long-acting, actually PROTECTS against overdose

Managing Severe Pain

- First try full doses of NSAIDs (e.g., ketorolac injection)
- For persistent or intolerable pain try regional nerve blocks
- High potency opiates (fentanyl or buprenorphine) can override blockade but buprenorphine is safer, anesthesiology involvement is advisable
- Patients should wear medical bracelet or wallet card with a 24-hr contact number

Controversies Surrounding Antagonist Based Treatment Approaches

- Concerns about safety of this treatment: whether treatment with naltrexone increases risk of depression, suicidality, and overdose post-treatment
  - No convincing evidence that NTX may increase depression (not well studied)
  - There may be higher risk of an overdose compared to patients on agonist, but such risk is low, lower than in untreated individuals, and likely similar to risk in those who stop agonists
  - The long "tail" on the serum naltrexone curve with LA preparation may provide protection during early experience of the drug-free lifestyle, which was previously marked by an elevated mortality
- Concerns about inadequate efficacy (as compared to agonists)
  - Is naltrexone inferior to methadone/buprenorphine? On what outcomes (retention vs. continuing use), in what samples?
  - Recent studies with buprenorphine show comparable treatment retention and lower rates of opiate use
  - Controlled, direct comparison trials have not been done

Naltrexone in Clinical Practice

- Naltrexone can be offered to:
  - Patients coming out of rehab who can be easily started on extended release preparation
  - Patients who had some abstinent time after detox/rehab but struggle, have intense cravings, and started using, though are not dependent yet (naloxone challenge needed)
  - Patients who requested brief buprenorphine taper and want to be protected from relapse
  - Young patients with a brief episode of Rx opiate use and involved parents
  - Patients who were stable on buprenorphine but would like not to be dependent and take medication daily

Naltrexone in Clinical Practice

(*continued*)

- Naltrexone complements treatment with buprenorphine offered in private addictions practice
  - Experienced buprenorphine providers should try offering naltrexone, a lot of fears will dissipate
  - Treatment matching is more important than proving superiority of any one method

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Case Vignette
57 y.o. Male, Using 5 Bags of Heroin Daily, Seeking Treatment

Adam Bisaga M.D.
Maria Sullivan M.D., Ph.D.

Case Presentation: History

- 57-year-old opioid-dependent male using 5 bags/day (IN)
- Using heroin regularly for 22 years
- Had a 5-year period of abstinence before relapsing 6 months earlier
- Patient is smoking marijuana daily and uses cocaine 2-3 times/month
- Patient seeks injectable naltrexone treatment as he is not interested in agonist maintenance

Presentation on Evaluation

- Physical examination: hypertension
- Psychiatric evaluation: substance-induced mood disorder (depressed mood, moderate anhedonia, decreased sleep)
- Urine toxicology: positive for heroin, cocaine, and THC

Treatment: What can be offered?

- Polysubstance dependence is present, so patient cannot undertake treatment for opioid dependence without first addressing daily MJ use and cocaine abuse
- Presence of a mood disorder makes opioid dependence treatment unlikely to succeed; depression must be treated first
- Opioid dependence can be treated, despite depression and other concurrent substance dependence

How would you proceed at this point?

1. Inpatient detoxification (1-2 days of buprenorphine, 3-4 days of washout) followed by naloxone challenge and injection of XR-naltrexone
2. Outpatient detoxification over 7 days: rapid naltrexone induction (1-day buprenorphine followed by increasing doses of oral NTX, and administration of injectable naltrexone)
3. Weeklong buprenorphine taper followed by a weeklong washout, and then injectable naltrexone administration
4. Induction onto buprenorphine maintenance
5. Advise patient to abstain from using heroin for 14 days and, once negative, to come in for injectable naltrexone injection

Treatment Considerations

- Patient is unable to go inpatient due to familial and occupational responsibilities
- Increased risk of resuming opioid use during the washout week
- Patient does not want to be on buprenorphine maintenance
- Patient has previously had a 5-year period of sustained abstinence

Outpatient Induction onto injectable naltrexone

- Patient presents in mild withdrawal after his last use of heroin (1 bag) 14 hours previously
- Administered 2 mg of buprenorphine, followed by a second 2mg dose 1 hour later
- Sent home with 4 mg of buprenorphine to take over the course of the evening
- Reported using methadone upon arriving home, followed by 4 mg of buprenorphine, causing the precipitation of opioid withdrawal

How would you proceed at this point?

- Abandon outpatient induction and insist on admission to inpatient unit for completion of the naltrexone induction process
- Referral to agonist maintenance
- Continue with outpatient induction procedure, adjusting regimen to clinical presentation

Continuation of outpatient naltrexone induction

- Buprenorphine washout was extended for additional 2 days
- Higher doses of ancillary medications (clonidine, clonazepam, prochlorperazine, and zolpidem) were administered
- Daily monitoring, medication dosing/adjustment was conducted at the clinic

Response

- Reported moderate intensity symptoms of insomnia, anxiety, runny nose, and back pain
- The patient continued to receive ancillary medications and oral naltrexone induction was initiated
- Patient tolerated increased doses of oral naltrexone (Day 1: 1mg x 3; Day 2: 6mg x 2; Day 3: 25mg)
- Once the patient was able to tolerate 25mg oral naltrexone, injectable naltrexone was administered 1 hour later
- Was inducted onto injectable naltrexone but during the first week complained of **severe insomnia**; also anxiety, depression, and decreased appetite

Insomnia: Differential diagnosis

- Persisting/protracted opioid withdrawal
- Naltrexone-induced withdrawal syndrome (“naltrexone flu”)
- Naltrexone-induced mood disorder
- Underlying mood/anxiety disorder that reemerged during opioid abstinence

Acute Intervention: Goals

- Treatment retention; if we don't treat distressing symptoms, he will not come back for another injection and likely will resume heroin use
- Regardless of the etiology, insomnia should be aggressively managed to maximize comfort and treatment engagement
- Patient was treated with zolpidem 10 mg/HS, trazodone 100 mg/HS and clonazepam 2 mg/d for two weeks post-injection
- Weekly psychotherapy aimed at developing strategies to deal with limited sleep and physical distress and motivating to remain in treatment and on medication

Patient Response/Outcome

- Patient reported no use of opioids, but continued to smoke marijuana daily
- Insomnia, mood, and decreased appetite improved and resolved by the 3rd week of treatment
- Accepted 2nd and 3rd injection of naltrexone, and has not used any opioids since the first day of induction
- Patient is interested in remaining on injectable naltrexone, for 1 year, as recommended

Case Discussion

- Patients using during the first week of induction are at high risk of not completing procedure, and the protocol needs to be flexible to accommodate them
- Once on the injectable naltrexone, as many as 50% of patients will use opioids, but most will test the blockade 2-5 times and then stop
- Persisting with naltrexone induction can be effective in a majority of cases to help patients enter stable abstinence
- During early opioid abstinence on XR-NTX, other substance abuse may need to be tolerated initially; can be addressed in behavioral therapy sessions

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