MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Module 8: Clinical Uses of Buprenorphine

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Clinical Uses of Buprenorphine

- Induction
- Stabilization
- Maintenance
- Withdrawal

Buprenorphine Induction

- Before getting started with treatment: Make goals of treatment and expectations clear to patients
- Use Treatment Agreements that outline terms of treatment; i.e.: what the patient can expect from you and what you will expect/require from the patient, information for patients about buprenorphine and its safe use, informed consent (see Clinical Tools at www.pcss-mat.org)
- Know referral sources in your community so that you can expeditiously refer someone who is not able to follow the treatment agreement and needs more than your practice can offer (e.g. OTPs)

Preparing for Buprenorphine Induction

- Do not induct a patient on the first meeting
  - You must undertake an assessment to determine:
    - Is the patient opioid-dependent? (history, records, physical findings, review of controlled substances records (Prescription Drug Monitoring Program records in your state), urine toxicology screening (including an expanded panel for opioid analgesics (including methadone and buprenorphine and check ethyl glucuronide (alcohol use)), check clinical labs including liver, kidney function, CBC, HIV/HCV status
    - Is the patient a good candidate for buprenorphine/naloxone treatment?
    - Can he/she safely handle medication?
    - Are there other substance use or mental disorders that may place the patient at greater risk for adverse events with office-based treatment?

Preparing for Buprenorphine Induction

- First meeting/assessment can also be used to give the individual information about buprenorphine/naloxone and treatment:
  - Appropriate use of the medication; no sharing or diversion
  - The need to avoid continued drug and alcohol abuse
  - The need to inform physician if other medications are prescribed for any purpose
  - The need to store the medication safely; how will the patient do that?
  - How they must prepare to be inducted (i.e.: need to be in mild-moderate withdrawal)

Buprenorphine Induction

- Goals of Induction
  - Discontinue or markedly reduce use of other opioids
  - Decrease cravings
  - Decrease withdrawal symptoms
  - Minimal/no side effects

Buprenorphine/Naloxone Formulations

- Buprenorphine/naloxone should be used for treatment of opioid dependence
- Naloxone is not well absorbed sublingually or by oral ingestion—if injected it will precipitate withdrawal in an opioid-dependent person. Naloxone is included to decrease injected abuse of the medication.
- Three formulations:
  - Sublingual film (buprenorphine/naloxone; 8/2 mg)
  - Sublingual tablet (buprenorphine/naloxone; 5.7/1.4 mg)
  - Buprenorphine/naloxone tablets (generic)

Buprenorphine/Naloxone Formulations

- The films are a patented formulation considered better tasting than tablets and safer because they are unit-dosed in child-protective foil pouches.
- Other clinical advantages is that the films dissolve more rapidly than tablets and have lower diversion rates
- Tablets are now available as generic medications likely to be less expensive than films
- Choice of formulations is based on:
  - Patient choice
  - Children in home-may want to consider film use
  - Third party payer considerations

Induction

- Patient to fill prescription and bring to office:
  - Enough medication for 2 days of dosing
    - Can give up to 8 mg Day 1; to 16 mg Day 2
    - E.g.: Prescribe Film or Tablets: 2/0.5 mg: 4 for Day 1 and 8 for Day 2; or
    - 4/1 mg Films: 2 for Day 1 and 4 for Day 2
- Some may dislike waiting to start the induction due to need to complete assessment and to fill prescription, but this is generally good practice; opioid addiction not an emergency; induction does not need to occur the first time an individual is evaluated

Buprenorphine Induction – Day 1

Patients dependent on short-acting opioids

- Patients dependent on short-acting opioids (e.g.: heroin/ oxycodone/hydrocodone)
  - Instruct patients to abstain from any opioid use for 12 hours prior to induction visit (so they are in mild-moderate withdrawal at induction visit)
  - Use opioid withdrawal scale (COWS>8) to avoid any risk of precipitated withdrawal. Document and assess severity of withdrawal and track the patient's response to first day's dose.

Clinical Opiate Withdrawal Scale (COWS)

Patient's Name:_____ Date: _____

Enter scores at time zero, 30min after first dose, 2 h after first dose, etc.

	Times: ____	____	____	____
Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120				
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face				
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds				
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible				
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort				
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks				
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting				
Tremor *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching				
Yawning *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute				
Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult				
Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection				
Total scores **with observer's initials**				

Score:

5-12 = mild;

13-24 = moderate;

25-36 = moderately severe;

more than 36 = severe withdrawal

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Buprenorphine Induction – Day 1

Patient dependent on short-acting opioids

- Review recent opioid use, including both long- and short-acting opioids. Should reduce methadone to 30-40 mg/ day for at least 1-2 weeks; abstained from methadone for at least 36 hours.
- Before dosing be sure the COWS score is ≥8
- Remind patient of precipitation withdrawal risk if recent use has occurred
- Consider asking patient to return another day; or
- Wait in the office until evidence of withdrawal is seen

Buprenorphine Induction – Day 1

Patients dependent on short-acting opioids

- If withdrawal is observed:
  - Give first dose: 2/0.5-4/1 mg sublingual buprenorphine/ naloxone
  - Note: primary use of buprenorphine alone tablets is in pregnancy
  - Monitor in 1-2 hours after first dose; patient can either wait in clinic, or return, if space is a consideration

Buprenorphine Induction – Day 1

Patients dependent on short-acting opioids

- Buprenorphine plasma concentrations peak at approximately 3 hours after a sublingual dose
- If withdrawal is not relieved after first dose:
  - Give a second dose (8/2 mg is maximum recommended dose on day 1)
  - Determining if second dose is needed can be made in 1-2 hours by evaluating how much withdrawal has been relieved by the first dose and estimating whether the patient is likely to need additional medication

Buprenorphine Induction – Day 1

Patients dependent on short-acting opioids

- E.g.: Pre-induction COWS score of 11 decreases to 6 by one hour after a dose of buprenorphine/naloxone 4/1 was given; this patient is unlikely to get full relief from dose 1 and should be given a second dose
- Once second dose has been given, patient can leave the office

Buprenorphine Induction – Day 1

Patients dependent on short-acting opioids

- If opioid withdrawal appears (worsens) shortly after the first dose:
  - May have precipitated a withdrawal syndrome
  - Greatest severity of buprenorphine-related precipitated withdrawal occurs in the first few hours (1-4 hours) after a dose, with decreasing withdrawal symptoms over subsequent hours

Buprenorphine Induction – Day 1

Patients dependent on short-acting opioids

- If precipitated withdrawal occurs consider:
  - Giving another dose of buprenorphine, attempting to provide enough agonist effect from buprenorphine to suppress the withdrawal; can give mediations for withdrawal symptoms if needed (recommended); or
  - Stopping the induction, providing symptomatic treatments for the withdrawal symptoms, and having patient return the next day

Buprenorphine Induction – Day 2

Patients dependent on short-acting opioids

- On Day 2, have the patient return to the office, if possible, for assessment and Day 2 dosing. If necessary, patient may phone in to speak with prescriber or be directed in dosing via protocol
- Adjust dose according to the patient's experiences on first day
- Many will report that some milder withdrawal symptoms returned in the evening after Day 1 dose(s); those patients will require an increase; generally 12/3-16/4 mg/d maximum dose for Day 2
- Less often patients will complain of opioid side effects (e.g.: sedation) and dose would be lowered in response

Buprenorphine Induction – Day 2

- Assessment of need for a higher dose should include time for attaining steady state (at least 5-7 days at stable dose (e.g.: 5-7 days at 12/3 or 16/4 mg/d before considering increase)
- Package insert recommends upper dose of 24/6 mg daily; most stabilize on a dose of 12/3-16/4 mg/d
- Giving higher doses than needed can provide a source diverted drug
- Some insurance plans will cover only $\leq$ 16 mg per day

Buprenorphine Induction – Day 1

Patients dependent on long-acting opioids

- Patients dependent on long-acting opioids (e.g.: methadone)
  - Patients should have dose decreases until they are down to ≤40 mg/d of methadone
  - Reduce methadone to 30-40 mg/day for at least 1-2 weeks; wait at least 36 hours after last dose of methadone; longer wait may be required, depending on dose and pattern of use. Must monitor patient for emergence of withdrawal.
  - Patients will likely need ancillary medication (e.g. clonidine, clonazepam, zolpidem) in order to abstain for 36+ hours.
  - Give no further methadone once buprenorphine induction is started
  - Procedure is then the same as for short-acting opioids
  - Key is to observe objective withdrawal signs
  - Expect first day's dose to be up to 8/2 mg SL

Buprenorphine Induction

Patients not physically dependent on opioids

- Patients not currently physically dependent on opioids; but good evidence of history of opioid dependence and assessment of a high risk for relapse
  - Examples
    - A patient at high risk for relapse to opioid use, such as an opioid-dependent person who had been incarcerated and was recently released
    - A patient leaving a sober house or halfway house and is at risk for relapse

Buprenorphine Induction

Patients not physically dependent on opioids

- First dose: 2/0.5 mg sublingual buprenorphine/ naloxone
  - Monitor in office after first dose
  - The length of time the patient is monitored in the office can vary depending upon the clinician's familiarity with the patient and with using buprenorphine

Buprenorphine Induction

Patients not physically dependent on opioids

- Gradually increase dose over days:
  - Day 1: 2 mg
  - Day 2: 4 mg
  - Day 3: 6 mg then wait 5 days
  - These patients will not have withdrawal when they present since they are not currently opioid-dependent and they may show evidence of opioid effects which need to be monitored in the office

Buprenorphine Stabilization/ Maintenance

- Stabilize on one daily sublingual dose
- Usual administration of buprenorphine/naloxone dosing is BID or daily, given by prescription
- Expect average dose will be somewhere between 4/1-16/4 of buprenorphine/naloxone daily
- Higher daily doses more tolerable if films/tablets are taken sequentially rather than all at once
- Maximum FDA-approved daily dose is 24/6 mg

Buprenorphine Stabilization/ Maintenance

- Give dose daily until stabilized (induction can be completed in 2 days in most cases)
- Usual administration of buprenorphine/naloxone dosing is daily and is given by prescription
- Once stabilized on a maintenance dose, dose changes are not frequently needed

How Long Should Buprenorphine Maintenance Be?

- No data to provide guidance on how long to treat a patient with buprenorphine/naloxone maintenance
- Studies as long as 16 weeks show high relapse rates with medical withdrawal (Weiss et al., 2011)
- Patients can be retained long term; Kakko et al., 2003 showed approximately 75% retention at one year with maintenance
- Continue maintenance as long as patient is benefitting from treatment (opioid/other drug use, employment, educational goals pursued, improvement in relationships, improvement in medical/mental illnesses, engaged in psychosocial treatment)

Withdrawal Using Buprenorphine

- Buprenorphine suppresses opioid withdrawal symptoms
- Long-term efficacy of medical withdrawal with buprenorphine is not known
- Studies of other withdrawal treatments have shown that brief withdrawal periods are unlikely to result in long-term abstinence

Withdrawal Using Buprenorphine

- Withdrawal can be primary treatment or termination of period of maintenance therapy
- Many regimens can be used based on clinical practice and patient needs
- Example: Withdrawal over 3 days:
  - First day: 8/2-12/3 mg s.l.
  - Third (last) day: 6/1.5 mg s.l.
- Can extend taper by 2-3 days if patient has trouble tolerating the procedure; offer reassurance and treat emerging insomnia, anxiety, and/or myalgias
- Withdrawal symptoms may not occur until completely off drug for 2-3 days
- Ancillary medications to treat withdrawal include clonidine, clonazepam, zolpidem or trazodone

Example of a Buprenorphine Withdrawal Protocol Developed by NIDA Clinical Trials Network

Study Day	Buprenorphine-Naloxone Dose mg
1	4 + additional 4 as needed
2	8
3	16
4	14
5	12
6	10
7	8
8	6
9	4
10	2
11	2

Withdrawal over 4-30 days is common in clinical practice. Buprenorphine is very flexible and withdrawal can be achieved rapidly or slowly, depending on treatment issues.

Selection of Candidates for Naltrexone

Antagonist Treatment with Injectable Naltrexone

- Patients who are not interested in, 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

Selection of Candidates for Naltrexone

Antagonist Treatment with Injectable Naltrexone

- Patients for whom relapse would be disastrous (e.g., physicians, pilots, parolees)
- Patients with less severe form of opioid use disorder
  - Short history of use, lower level of use
- Who is most likely to benefit from naltrexone (XR-NTX)?
  - 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 have 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 without naltrexone)
- Patients with chronic pain requiring chronic opioid treatment

Patients Who are Better Candidates for Agonists

- Patients with severe GI disorders exacerbated 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

Summary

- Buprenorphine is effective and safe for maintenance treatment of opioid dependence
- Buprenorphine/naloxone is preferred formulation for treatment of opioid dependence;
- Buprenorphine mono product has greater risk for diversion
- Monitor patient during induction; best to keep patient at clinic after first dose to gauge response and effectiveness
- Dosing is usually q a.m. or BID, but patients with chronic pain and opioid abuse may benefit from TID dosing.

Summary

- Maintenance is preferred treatment and length should be for as long as the patient benefits
- Withdrawal from buprenorphine may be milder than withdrawal from other opioids; stabilize over 3 days, then can decrease dose by 2 mg daily as one example
- For patients not interested in agonist treatment, or who have failed prior agonist maintenance, induction onto injectable naltrexone can be an effective strategy for relapse prevention and protection against overdose
- Financial issues related to treatment should be discussed before treatment is initiated

References

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PCSSMAT is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA) and American Society of Addiction Medicine (ASAM).

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