Medication-Assisted Treatment (MAT) Management Of The Use Of Multiple Substances: Challenging Comorbidities And Conditions

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Fellow of the American Psychiatric Association
Fellow of the American Society of Addiction Medicine
1. Current consensus for treating OUD

2. Management Of The Use Of Multiple Substances
   • Benzodiazepines
   • Methamphetamines

3. Challenging comorbidities and conditions
   • Pain conditions
   • Methadone—> Buprenorphine transition
Buprenorphine has been used internationally for the treatment of opioid use disorder (OUD) since the 1990s and has been available in the United States for more than a decade. Initial practice recommendations were intentionally conservative, were based on expert opinion, and were influenced by methadone regulations. Since 2003, the American crisis of OUD has dramatically worsened, and much related empirical research has been undertaken. The findings in several important areas conflict with initial clinical practice that is still prevalent. This article reviews research findings in the following 7 areas: location of buprenorphine induction, combining buprenorphine with a benzodiazepine, relapse during buprenorphine treatment, requirements for counseling, uses of drug testing, use of other substances during buprenorphine treatment, and duration of buprenorphine treatment. For each area, evidence for needed updates and modifications in practice is provided. These modifications will facilitate more successful, evidence-based treatment and care for patients with OUD.

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For author affiliations, see end of text.
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# Current consensus for treating OUD

<table>
<thead>
<tr>
<th>Previous Approach</th>
<th>New Findings and Recommendations</th>
</tr>
</thead>
</table>
| A medical setting is needed for induction.  
Benzodiazepine and buprenorphine coprescription is toxic. | Home induction is also safe and effective (6).  
**Buprenorphine should not be withheld from patients taking benzodiazepines** (5). |
| Relapse indicates that the patient is unfit for buprenorphine-based treatment.  
Counseling or participation in a 12-step program is mandatory. | Relapse indicates the need for additional support and resources rather than cessation of buprenorphine treatment (43).  
Behavioral treatments and support are provided as desired by the patient (6). |
| Drug testing is a tool to discharge patients from buprenorphine treatment or compel more intensive settings.  
Use of other substances is a sign of treatment failure and grounds for dismissal from buprenorphine treatment.  
Buprenorphine is a short-term treatment, prescribed with tapered dosages or for weeks to months. | Drug testing is a tool to better support recovery and address relapse (56).  
**Buprenorphine treatment does not directly affect other substance use, and such use should be addressed in this context** (43).  
Buprenorphine is prescribed as long as it continues to benefit the patient (6). |
Management Of The Use Of Multiple Substances
## Benzodiazepines

Many of the most commonly prescribed benzos are those which are most readily abused, including:

<table>
<thead>
<tr>
<th></th>
<th>ALPRAZOLAM (Xanax)</th>
<th>CLONAZEPAM (Klonopin)</th>
<th>CHLORDIAZEPoxide (Librium)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIAZEPAM</strong></td>
<td><img src="image" alt="Diazepam" /></td>
<td><img src="image" alt="Clonazepam" /></td>
<td><img src="image" alt="Chlordiazepoxide" /></td>
</tr>
<tr>
<td>(Valium)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LORAZEPAM</strong></td>
<td><img src="image" alt="Lorazepam" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ativan)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TEMAZEPAM</strong></td>
<td><img src="image" alt="Temazepam" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Restoril)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TRIAZOLAM</strong></td>
<td><img src="image" alt="Triazolam" /></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Halcion)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Benzodiazepines

• Do not stop MAT for OUD (FDA 2017)

• Individualized taper has best evidence
  
  • Ashton Method (https://benzo.org.uk/manual/)
  
  • Canadian Deprescribing Guidelines (https://www.deprescribingnetwork.ca/)
  
  • VA National Center for PTSD Benzo Taper Recommendations (See references section)
Benzodiazepines—Know your Immunoassay

• Standard assays detect
  • Nordiazepam & Oxazepam

• Immunoassays may not detect
  • Clonazepam
  • Alprazolam
    • Lorazepam
    • Temazepam

Figure 1: Illustrations of benzodiazepine metabolism.
Arrows indicate metabolic pathways
*Nordiazepam is also a metabolite of halazepam, medazepam, prazepam, and tetrazepam
Benzodiazepines

• Pharmacologic Tapering Strategies
  • Gradual Taper of same Benzo taken by patient
  • Substitution of long-acting Benzo
    • *Exception*: Older patients already on short-acting, taper this first
  • Set clear goals with patients
  • Frequent follow up visits
  • Chronic users = slow taper over MONTHS
  • Scheduled, not PRN dosing

*It does not matter how slowly you go as long as you do not stop.*
–Confucius

**THM**: No clear evidence-based guidelines on taper rates
Benzodiazepines

- Potency Equivalents

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Half-life (hrs) (^1) [active metabolite]</th>
<th>Approximately Equivalent Oral dosages (mg) (^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>6-12</td>
<td>0.5</td>
</tr>
<tr>
<td>Bromazepam (Lexotan, Lexomil)</td>
<td>10-20</td>
<td>5-6</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>5-30 [36-200]</td>
<td>25</td>
</tr>
<tr>
<td>Clobazam (Frisium)</td>
<td>12-60</td>
<td>20</td>
</tr>
<tr>
<td>Clonazepam (Klonopin, Rivotril)</td>
<td>18-50</td>
<td>0.5</td>
</tr>
<tr>
<td>Clorazepate (Tranxene)</td>
<td>[36-200]</td>
<td>15</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>20-100 [36-200]</td>
<td>10</td>
</tr>
<tr>
<td>Estazolam (ProSom)</td>
<td>10-24</td>
<td>1-2</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol)</td>
<td>18-26 [36-200]</td>
<td>1</td>
</tr>
<tr>
<td>Flurazepam (Dalmene)</td>
<td>[40-250]</td>
<td>15-30</td>
</tr>
<tr>
<td>Halazepam (Paxipam)</td>
<td>[30-100]</td>
<td>20</td>
</tr>
<tr>
<td>Ketazolam (Anxone)</td>
<td>30-100 [36-200]</td>
<td>15-30</td>
</tr>
<tr>
<td>Loprazolam (Dormonoc)</td>
<td>6-12</td>
<td>1-2</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>10-20</td>
<td>1</td>
</tr>
<tr>
<td>Lorazepam (Lorazepam)</td>
<td>10-12</td>
<td>1-2</td>
</tr>
<tr>
<td>Medazepam (Nobrium)</td>
<td>36-200</td>
<td>10</td>
</tr>
<tr>
<td>Nitrazepam (Mogadon)</td>
<td>15-38</td>
<td>10</td>
</tr>
<tr>
<td>Nordazepam (Nordaz, Calmday)</td>
<td>36-200</td>
<td>10</td>
</tr>
<tr>
<td>Oxazepam (Serax, Serenid, Serepax)</td>
<td>4-15</td>
<td>20</td>
</tr>
<tr>
<td>Prazepam (Centrax)</td>
<td>[36-200]</td>
<td>10-20</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>25-100</td>
<td>20</td>
</tr>
<tr>
<td>Temazepam (Restoril, Normison, Euhynos)</td>
<td>8-22</td>
<td>20</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>2</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Benzodiazepines

• Benzo Withdrawal
  • May occur after ≥4 weeks of benzo use
  • Occurs within 1-7 days of DC use
  • Can last 4-14 days (short vs. long half-life, respectively)

• Physical symptoms
  • Stiffness, weakness, GI disturbance, flu like symptoms, paresthesia, visual disturbances, seizures

• Psychological symptoms
  • Anxiety/irritability, Insomnia/nightmares, depersonalization, decrease memory and concentration, delusion and hallucinations, depression

THM: Slow the taper if needed
Benzodiazepines

• Tapering Strategy #1 for Xanax
  • Taper by lowest commonly prescribed dose
    • E.g. Xanax 0.25 mg
  • Taper every 1-2 weeks (longer preferred)
  • If withdrawal occurs
    • Hold dose then resume or switch to a longer-acting benzodiazepine and resume.
      • E.g. Clonazepam or Diazepam

• If switch to long-acting, taper by the lowest commonly prescribed dose.
  • E.g. Clonazepam taper by 0.5 mg
  • E.g. Diazepam taper by 5mg

• Key—> Clonazepam 0.5mg is equivalent to ~ 10 mg of Diazepam. If withdrawal occurs...
  • Transition to Diazepam 5mg bid.
    • Continue taper
      • E.g. Diazepam 2 mg qam + 5mg qhs.
Benzodiazepines

• Taper Strategy #2 (Ashton Manuel)

| Schedule 1. Withdrawal from high dose (6mg) alprazolam (Xanax daily with diazepam (Valium) substitution. (6mg alprazolam is approximately equivalent to 120mg diazepam) |
|---|---|---|---|---|
| **Morning** | **Midday/Afternoon** | **Evening/Night** | **Daily Diazepam Equivalent** |
| Starting dosage | alprazolam 2mg | alprazolam 2mg | alprazolam 2mg | 120mg |
| Stage 1 (one week) | alprazolam 2mg | alprazolam 2mg | alprazolam 1.5mg diazepam 10mg | 120mg |
| Stage 2 (one week) | alprazolam 2mg | alprazolam 2mg | alprazolam 1mg diazepam 20mg | 120mg |
| Stage 3 (one week) | alprazolam 1.5mg diazepam 10mg | alprazolam 2mg | alprazolam 1mg diazepam 20mg | 120mg |
| Stage 4 (one week) | alprazolam 1mg diazepam 20mg | alprazolam 2mg | alprazolam 1mg diazepam 20mg | 120mg |
| Stage 5 (1-2 weeks) | alprazolam 1mg diazepam 20mg | alprazolam 1mg diazepam 10mg | alprazolam 1mg diazepam 20mg | 110mg |
| Stage 6 (1-2 weeks) | alprazolam 1mg diazepam 20mg | alprazolam 1mg diazepam 10mg | alprazolam 0.5mg diazepam 20mg | 100mg |
| Stage 7 (1-2 weeks) | alprazolam 1mg diazepam 20mg | alprazolam 1mg diazepam 10mg | Stop alprazolam diazepam 20mg | 90mg |
| Stage 8 (1-2 weeks) | alprazolam 0.5mg diazepam 20mg | alprazolam 1mg diazepam 10mg | diazepam 20mg | 80mg |
| Stage 9 (1-2 weeks) | alprazolam 0.5mg diazepam 20mg | alprazolam 0.5mg diazepam 10mg | diazepam 20mg | 80mg |
| Stage 10 (1-2 weeks) | alprazolam 0.5mg diazepam 20mg | Stop alprazolam diazepam 10mg | diazepam 20mg | 60mg |
| Stage 11 (1-2 weeks) | Stop alprazolam diazepam 20mg | diazepam 10mg | diazepam 20mg | 50mg |
| Stage 12 (1-2 weeks) | diazepam 25mg | Stop midday dose; divert 5mg each to morning and night doses | diazepam 25mg | 50mg |
| Stage 13 (1-2 weeks) | diazepam 20mg | -- | diazepam 25mg | 45mg |
| Stage 14 (1-2 weeks) | diazepam 20mg | -- | diazepam 20mg | 40mg |
Benzodiazepines

- Tapering Strategy #3 (VA rec’s)

<table>
<thead>
<tr>
<th>Milestone Suggestions</th>
<th>Example: Lorazepam 4 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Convert to 40 mg diazepam daily</td>
</tr>
<tr>
<td>Week 1</td>
<td>35 mg/day</td>
</tr>
<tr>
<td>Week 2</td>
<td>Decrease dose by 25%</td>
</tr>
<tr>
<td></td>
<td>30 mg/day (25%)</td>
</tr>
<tr>
<td>Week 3</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Week 4</td>
<td>Decrease dose by 25%</td>
</tr>
<tr>
<td></td>
<td>20 mg/day (50%)</td>
</tr>
<tr>
<td>Week 5-8</td>
<td>Hold dose 1-2 months</td>
</tr>
<tr>
<td></td>
<td>Continue at 20 mg/day for 1 month</td>
</tr>
<tr>
<td>Week 9-10</td>
<td>15 mg/day</td>
</tr>
<tr>
<td>Week 11-12</td>
<td>Decrease dose by 25% at week 11</td>
</tr>
<tr>
<td></td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Week 13-14</td>
<td>Decrease dose by 25% at week 13</td>
</tr>
<tr>
<td></td>
<td>5 mg/day</td>
</tr>
<tr>
<td>Week 15</td>
<td>discontinue</td>
</tr>
</tbody>
</table>

Benzodiazepines

1. Augmentation
   • Valproate
   • Gabapentin
   • Pregabalin
   • Topiramate
     • Carbamazepine
     • Oxcarbazepine

2. Support Medications—No evidence supporting one over the other... trial and error.
   • Antihistamines
     • Hydroxyzine
   • Adrenergic Antagonist
     • Clonodine, Propranolol
   • Muscle relaxants
     • Baclofen, Tizanidine
   • Sedating Antidepressants
     • Trazodone, Mirtazapine
Methamphetamines
Methamphetamines
Methamphetamines
Methamphetamines

- Immunoassay Drug Screen
  - Detection window ~2-3 days
  - False positives: Pseudoephedrine, labetolol, ranitidine, trazodone, TCA’s... etc.
  - 2 methamphetamine isomers: D (CNS) and L (Peripheral)
Methamphetamines

• Basic Assumptions
  • Substance use can be reduced using operant conditioning
  • Useful in promoting treatment retention and adherence
  • Incentives for negative urine test useful in decreasing drug use
Methamphetamines

• Key Concepts
  • Behavior to be modified (e.g. stimulant use) must be objectively measured
  • Behavior to be modified (e.g. UDS) must be monitored frequently
  • Reinforcement must be immediate
  • Penalties for unsuccessful behavior (e.g. +UDS) include reduced voucher amount

Nancy Petry’s Fishbowl
Fishbowl Method

Incentive = draws from a bowl
- Draws earned for each negative urine
- Number of draws can escalate
- Bonus draws can be given for consecutive weeks of abstinence

Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt
Half the slips are winners
Win frequency inversely related to cost

- largest chance of winning a small $1 prize
- moderate chance of winning a large $20 prize
- small chance of winning a jumbo $100 prize

Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University
SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt
Voucher Incentives in Outpatient Treatment


Cocaine negative urines

Weeks of Treatment

Percent of Subjects

Slide Credit: Maxine Stitzer, Ph.D., Johns Hopkins University SOM, ctndisseminationlibrary.org/PPT/485Stitzer.ppt
Methamphetamine

1. MATRIX model
   - Research-based framework for engaging stimulant abusers in treatment and helping achieve abstinence

2. Composed of
   - Group psychotherapy
   - Individual counseling
   - Family therapy
   - Contingency management
   - Crystal meth anonymous (self-help groups)
   - Treatment of co-occurring disorders
Methamphetamines—Fentanyl

Figure. Nonprescribed Fentanyl Positivity Among Urine Drug Test Results Positive for Cocaine or Methamphetamine

Dots represent monthly fentanyl positivity values; shaded areas, binomial 95% CIs.
Methamphetamines—Mirtazapine 30mg qhs

Figure 2.
Observed and fitted weekly urinalysis results, according to treatment arm. Fitted trend lines are based on the primary outcome model.
Methamphetamines—Bupropion

Randomized trial of bupropion SR 150 mg bid vs placebo for 12 weeks in methamphetamine users with less than daily meth use

<table>
<thead>
<tr>
<th>Total sample</th>
<th>Bupropion (N=41)</th>
<th>Placebo (N=43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment abstinence</td>
<td>29% (12)</td>
<td>14% (6)</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Only 32% (13/41) of bupropion participants were deemed medication adherent via week 6 plasma bupropion level. Adherence was strongly associated with end of treatment meth abstinence.

<table>
<thead>
<tr>
<th>Bupropion only</th>
<th>Adherent (N=13)</th>
<th>Non-adherent (N=28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of treatment abstinence</td>
<td>54% (7)</td>
<td>18% (5)</td>
<td>0.018</td>
</tr>
</tbody>
</table>
Methamphetamines—Naltrexone LAI + Bupropion XL

- Naltrexone 380 mg monthly + Bupropion XL 300 mg – 450 mg daily.
- Warrants further study
Topiramate

- May be more effective if UDS negative at baseline
- Target maintenance dose 200mg/day

THM: Does not appear to promote abstinence in MA users but can reduce the amount taken and reduce relapse in those who are already abstinent
Challenging comorbidities and conditions
Pain Conditions
Pain Conditions—Buprenorphine
Pain Conditions—Buprenorphine

[Diagram showing dose-response curves for three opioid painkillers: Fentanyl, Buprenorphine, and Heroin.]

Drugs:
- Fentanyl
- Buprenorphine
- Heroin

Effects:
- Total apnea (fatal overdose)
- Powerful hospital pain relief
- One normal Vicodin tablet

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Fig. 4. The time course of plasma levels of buprenorphine, norbuprenorphine and naloxone for a subject receiving a sublingual dose of the combination tablet of buprenorphine (16 mg) and naloxone (4 mg) (data from Jones et al., 1997).
Pain Conditions—Buprenorphine & Surgery

A Surgeon’s knot should Never give away.
Pain Conditions—The Old Recommendations

“While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. Note that until buprenorphine clears the body, it may be difficult to achieve analgesia with short-acting opioids.”
## Pain Conditions

<table>
<thead>
<tr>
<th></th>
<th>All Buprenorphine</th>
<th>Buprenorphine Given</th>
<th>Buprenorphine NOT given</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st 24 hour MSE</strong></td>
<td>200 (+/- 128.6)</td>
<td>155.2 (+/- 135.5)</td>
<td>245.5 (+/- 109.3)</td>
</tr>
<tr>
<td><strong>NSAID</strong></td>
<td>31.8</td>
<td>18.2</td>
<td>45.5</td>
</tr>
<tr>
<td><strong>Ketamine</strong></td>
<td>63.6</td>
<td>27.3</td>
<td>100</td>
</tr>
<tr>
<td><strong>Days APS</strong></td>
<td>4.5 (+/- 3.3)</td>
<td>3.0 (+/- 1.7)</td>
<td>5.9 (+/- 3.9)</td>
</tr>
</tbody>
</table>

Chart adopted from Andrea Rubinstein, MD - CSAM Webinar 6: managing Acute and Perioperative Pain in Patients on Medication-Assisted Treatment (MAT).
Pain Conditions

1. Buprenorphine Sublingual
   - Analgesia duration ranges from 6-8 hours
     - Analgesia will likely require multiple daily dosing—TID or QID
   - OUD cravings controlled on Once Daily or BID dosing
   - Peak plasma concentration SL ~90 mins
   - Brain levels exceed plasma levels as Bup is very lipophilic

2. Transdermal Buprenorphine patch
   - Duration ~7 days
   - 5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr

3. Buprenorphine Buccal Film
   - Greater bioavailable dose than SL tablets or film
   - BID dosing
   - 300 mcg bup buccal film dose is equivalent to 20 mcg transdermal bup patch
## Pain Conditions

<table>
<thead>
<tr>
<th>Oral morphine (mg/day)</th>
<th>Transdermal buprenorphine (µg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>84</td>
<td>35</td>
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<tr>
<td>126</td>
<td>52.5</td>
</tr>
<tr>
<td>168</td>
<td>70</td>
</tr>
</tbody>
</table>

*From the palliativedrugs.com newsletter, November/December 2006*
Methadone
Methadone
Methadone

1. Switching to Suboxone...
   - Elimination ½ life at steady state ~28 hrs
     - LONG-ACTING
   - Outpatient induction
     - Recommend patient taper to 30-40 mg per day for one week.
     - After 1 week DC Methadone for 48-72 hrs.
     - Key→ until develop mild-moderate withdrawal sx’s.
   - Consider beginning induction with Buprenorphine mono-product for 1-2 days.
     - Dose 2 mg at a time
     - Transition to Buprenorphine/Naloxone combination product

THM: Recommend office-based induction when you first begin doing this.

THM: Recommend prescribing comfort medication for the induction
Methadone

1. Comfort Medication
   - Withdrawal support
     - Clonidine 0.1 mg q6 hr prn
     - Phenergan 25mg q4-6 hr prn
     - Zofran 8 mg q8-12 hr prn
     - Loperamide 2 mg prn

   • Pain Support
     - Acetaminophen 325 mg q4-6 hr prn muscle/joint pain
     - Ibuprofen 600 mg q6-8 hr prn muscle/joint pain
     - Cyclobenzaprine 10 mg q8 hr prn muscle cramps

   • Insomnia Support
     - Hydroxyzine 25 mg, 1-2, qhs prn
7. CBHSQ 2018 NSDUH 2017
Any Questions?