Baltimore Substance Abuse Systems, Inc.

CLINICAL GUIDELINES FOR THE USE OF BENZODIAZEPINES AMONG PATIENTS RECEIVING MEDICATION-ASSISTED TREATMENT FOR OPIOID DEPENDENCE

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Preface

In Baltimore City, illicit drugs, specifically heroin, remain primary drugs of abuse, but the increasing availability of benzodiazepines is cause for concern.

- Reports from treatment providers, law enforcement, and concerned citizens indicate that benzodiazepine use and misuse are becoming more apparent.
- Patients in addiction treatment describe that benzodiazepines are easy to purchase on the street.
- According to the Baltimore Substance Abuse Systems, Inc., the number of admissions to grant-funded addiction treatment in which a benzodiazepine was mentioned as a substance of abuse increased from 258 (1.2%) in fiscal year 2009 to 409 (1.7%) in fiscal year 2011. [1]
- Data from the Maryland Alcohol and Drug Abuse Administration indicate that alprazolam, clonazepam, and diazepam are the top three benzodiazepines reported as substances of abuse. [2]

The concern about benzodiazepines increases when patients combine them with other controlled substances, including medications used to treat opioid addiction.

- While physicians should not delay treating opioid addiction with medications, they should recognize and intervene when patients present with or begin to take other potential substances of abuse, such as benzodiazepines.
- The combination of benzodiazepines and methadone or Suboxone® can present significant individual and public health risks of morbidity and mortality.

The goal of this guideline is to assist physicians and other healthcare providers treating opioid addiction in Baltimore City improve the management of patients who also use or misuse benzodiazepines.

The hope is to provide practical, useful tools and information that reflect a local standard of care for the use of benzodiazepines among patients receiving either methadone or Suboxone®, recognizing that specific individual clinical situations with patients may differ.

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Section 1: Benzodiazepine Pharmacology

Benzodiazepines belong to the class of medications frequently known as sedative-hypnotics. Since their initial introduction in the 1950's, over 3,000 benzodiazepine molecules have been developed with about 50 of them in clinical use.[3]

1. What is the mechanism of action of benzodiazepines?

- Benzodiazepines primarily potentiate the activity of GABA, the main, endogenous, inhibitory neurotransmitter in the central nervous system.
- All benzodiazepines in clinical use increase the binding of GABA to $GABA_A$ receptors.
- The $GABA_A$ receptor consists of 5 subunits that join together to form a chloride channel through which the receptor mediates neuronal excitability, sleep, and rapid mood changes, including anxiety.
- Benzodiazepines bind specifically to $GABA_A$ receptors with certain types of alpha (α) subunits that mediate sedation, balance, memory, learning, anxiety, and muscle tension.

2. What are the key clinical differences between the benzodiazepines?

Substitutions on the basic benzodiazepine ring structure account for the different types of benzodiazepines and the variation in their pharmacological properties. Benzodiazepines can be categorized on the basis of differences in:

- rapidity of onset
- existence of active metabolites
- existence of inactive parent compounds
- half-life
- duration of effect

3. What are the most common types of oral benzodiazepines in use in the United States?

The most common types of oral benzodiazepines in use in the United States include:

Generic Name	Brand Name
Alprazolam	Xanax®
Clonazepam	Klonopin®
Chlordiazepoxide	Librium™
Diazepam	Valium®
Lorazepam	Ativan™
Oxazepam	Serax™
Temazepam	Restoril™

4. Are there other types of benzodiazepines in clinical use?

Physicians may encounter other types of benzodiazepines. These include:

Generic Name	Brand Name	Comment
Midazolam	Versed®	Liquid formulation only
Halazepam	Paxipam®	Derivative of nordazepam
Chlorazepate	Tranxene®	
Estazolam	ProSom™	
Flunitrazepam	Rohypnol™	Not available in U.S.
Flurazepam	Dalmane®	
Nitrazepam	Mogadon™	Not available in U.S.
Prazepam	Centrax™	Not available in U.S.
Quazepam	Doral®	
Triazolam	Halcion™	Banned in several countries, including England

5. How are benzodiazepines metabolized?

Several different mechanisms are involved in the metabolism of benzodiazepines. These differences help explain some of the pharmacological variation noted within this class of medications.

- Some benzodiazepines undergo metabolism by the P450 3A4 hepatic enzyme system which contributes to medication interactions and reduced clearance in liver dysfunction
  - alprazolam (Xanax®)
  - clonazepam (Klonopin®)
  - midazolam (Versed®)
  - diazepam (partial) (Valium®)

- Many benzodiazepines are weak inhibitors of CYP 3A4 enzymes which, at high doses, may lead to higher methadone and Suboxone® peak serum levels
  - alprazolam (Xanax®)
  - diazepam (Valium®)
  - midazolam (Versed®)
  - triazolam (Halcion®)

- Other benzodiazepines are directly metabolized by hepatic conjugation and renally excreted, so are less prone to medication interactions and liver dysfunction has less effect on clearance
  - lorazepam (Ativan™)
  - oxazepam (Serax™)
  - temazepam (Restoril™)

6. What are the clinically significant medication interactions with benzodiazepines?

Benzodiazepines significantly enhance the sedating effects of other medications with such properties. This includes:

- All full-agonist opioids, including methadone
- Partial agonist opioids such as Suboxone®
- Alcohol
- Barbiturates
- Sedating anti-histamines

Inhibitors of CYP3A4 will increase serum levels of benzodiazepines metabolized through that system. Examples of drugs that inhibit CYP3A4 and increase serum levels of benzodiazepines include:

- Ketoconazole
- Itraconazole
- Macrolides
- Fluoxetine (Prozac™)
- Nefazodone (Serzone®)
- Cimetidine (Tagamet™)

7. How quickly does tolerance develop to benzodiazepines?

Tolerance develops to benzodiazepine-induced euphoria and sedation within a couple of days after reaching steady state but reportedly not to anxiolytic effects.[3,4,5] Patients who take benzodiazepines for their anxiolytic effect should not have to increase their dose.

- Some patients report improvement in anxiety with decrease of benzodiazepine dose[3]
- Tolerance develops to the anti-seizure effect but the timing varies between different formulations
- Partial tolerance can develop to the psychomotor and cognitive impairments

8. What is the withdrawal syndrome from benzodiazepines?

Patients may ask for increases in doses of methadone or Suboxone® believing that they are experiencing withdrawal symptoms from these medications when in reality they are experiencing withdrawal from benzodiazepines. The common benzodiazepine withdrawal symptoms include a mild and a severe form:

- Mild withdrawal:
  - Rebound insomnia
  - Sweats
  - Anxiety
  - Headache
  - Tremor and muscle twitching
  - Dysphoric mood

- Severe withdrawal:
  - Nausea and vomiting

- Agitation
- Hemodynamic instability
- Delirium
- Hallucinations
- Tonic-clonic seizures

The timing of benzodiazepine withdrawal varies depending on the half-life of the particular preparation used.

- Onset can occur within 24 hours to a week of abrupt discontinuation
- Symptoms can last for several weeks to months
- Return of underlying anxiety sometimes is confused with ongoing withdrawal

9. How do I distinguish between withdrawal from benzodiazepines and withdrawal from opioids?

Because many of the symptoms of benzodiazepine withdrawal and opioid withdrawal are non-specific and may overlap, it can often be difficult to distinguish between these two syndromes.[6] Reviewing a few factors may help clarify the clinical situation:

- Timing of symptom onset and its relation to discontinuation or decrease of benzodiazepines particularly when no changes are made to methadone or Suboxone® dose
- Exacerbation of symptoms, particularly abdominal cramps, muscle spasms, and muscle tension may be more indicative of both withdrawal syndromes compared to opioid withdrawal alone[6]
- Any new medications or changes in medication doses which may be interacting with either the benzodiazepine, the opioid, or both
- Other co-existing physical and/or psychiatric conditions, such as worsening of underlying anxiety, as indicated by Review of Systems or past history

Sometimes it will be extremely difficult to distinguish which withdrawal syndrome is occurring. In these instances, particularly if patients are moderately symptomatic, consider a small one-time increase in methadone dose (5-10mg) or Suboxone® (2-4mg), and re-assess withdrawal symptoms after 3-5 days. No change at all in a patient's withdrawal symptoms on careful questioning then likely reflects the presence of predominant benzodiazepine withdrawal and not opioid withdrawal, and the patient should return to the prior opioid dose. This intervention should be thoroughly explained to patients, including emphasizing that increases in opioid doses is not an effective or safe treatment for benzodiazepine withdrawal. Reassurance that symptoms are time limited, and assurance of support and assistance through the benzodiazepine withdrawal is critical to provide to the patient.

Section 2: Benzodiazepine Clinical Uses and Alternatives

Benzodiazepines are categorized as DEA Schedule IV medications, indicating that there are legitimate medical indications for their use with moderate to low abuse liability potential. The rapid-onset effect of benzodiazepines is what has made them appealing as treatment for anxiety or insomnia. Most other interventions, such as SSRIs or behavioral therapies, are effective long-term but with slower onsets of action.

By themselves, benzodiazepines have fairly broad safety profiles since they do not alone suppress respiration. In combination with opioids, particularly full-agonist opioids, however, the risks of sedation and respiratory depression increase significantly. Individuals with histories of any addiction are at much higher risk for benzodiazepine abuse and dependence compared to individuals without such a history.[4,7] Despite the known increased risks of overdose and abuse, opioid-dependent individuals often receive prescriptions for benzodiazepines as treatment for insomnia or anxiety.

1. What are appropriate uses of benzodiazepines in patients taking methadone or Suboxone®?

There are a few acute clinical situations where a benzodiazepine may be appropriate for short-term use in patients receiving methadone or Suboxone®. In these situations, patients should primarily receive longer acting preparations at low doses and for periods limited to the acute situation.

- Acute alcohol withdrawal, especially when complicated by Delirium Tremens and alcohol withdrawal seizures[8]
- Conscious sedation for a procedure
- Acute trauma or severe stress[9]

2. Are there specific benzodiazepines that should be favored or others that should be avoided?

Several factors determine the abuse liability of specific benzodiazepines, including accessibility to different formulations, and particular pharmacokinetic properties. Differences in rate of absorption, metabolism, intrinsic activity, and elimination half-life should be considered when making decisions about which, if any, benzodiazepine to prescribe for a patient on methadone or Suboxone®.

- Avoid formulations with rapid absorption and greater lipid solubility
    - alprazolam (Xanax®)
    - diazepam (Valium®)
    - lorazepam (Ativan™)
- Avoid preparations that interact with the CYP3A4 hepatic enzyme system
    - alprazolam (Xanax®)
    - diazepam (Valium®)
- Avoid formulations that are epidemiologically associated with abuse
    - alprazolam (Xanax®)
    - clonazepam (Klonopin®)
- Favor formulations that require hepatic metabolism from inactive pro-drug to active metabolite because these have less abuse potential than active parent compounds
    - chlorazepate (Tranxene®)

- Favor longer-acting preparations that have slower onset of action
    - Chlordiazepoxide (Librium™)
    - Oxazepam (Serax™)
- In liver disease, consider formulations metabolized through conjugation with more renal clearance
    - oxazepam (Serax™)
    - temazepam (Restoril™)

3. What is the effect of benzodiazepines on sleep?

Benzodiazepines are indicated for short term use in the treatment of insomnia.

- All benzodiazepines suppress stage 4, deep sleep but not REM sleep
- While not clearly understood, this may occur through non-GABA mediated mechanisms.

4. Can the newer non-benzodiazepine hypnotics be considered?

Four non-benzodiazepine hypnotics, commonly known as the "Z" drugs, are currently available and are increasingly prescribed for sleep.

- zopiclone (Imovane®) – available in Canada but not the U.S.
- eszopiclone (Lunesta®)
- zaleplon (Sonata®)
- zolpidem (Ambien®)

These medications positively act at the $GABA_A$ receptors in much the same way as benzodiazepines, but have more specific affinities for different subtypes of the receptor.

- Laboratory studies and post-marketing surveillance of these medications demonstrate a mixed picture for their abuse liability.[10]
- Based on their similar pharmacological properties compared with benzodiazepines, it is recommended that they be avoided in patients taking methadone or Suboxone®.

5. What are effective alternatives to benzodiazepines for treatment of insomnia?

Rebound insomnia is a significant challenge for patients withdrawing from benzodiazepines and is often a trigger for relapse. Poor quality sleep may also indicate the presence of sleep apnea. Treatment alternatives include both pharmacological and behavioral options. Pharmacological alternatives are recommended primarily for short-term use at low doses. Helping patients incorporate behavioral interventions should be the focus.

- Behavioral interventions
    - Appropriate sleep hygiene
        - Go to bed and wake up at the same time each day
        - Make the sleep environment dark and quiet (e.g. use earplugs)
        - Avoid using bed for anything other than sleep or sexual activity (e.g. no reading, watching TV, or eating in bed)
        - Avoid watching TV or using any electronic screen at least 30 minutes before bed time
    - Exercise, except near bedtime
    - Avoid caffeine after 12 noon
- Medications with minimal abuse liability and effective for insomnia
    - trazodone (Oleptro™) – 25mg to 200mg are typical doses
    - doxepin (Silenor®) – 3mg to 6mg of brand name or 25mg to 100mg of generic

- ramelteon (Rozerem™) – 8mg is usual dose
- Treat underlying anxiety or depression through pharmacologic or non-pharmacologic therapy
- Consider referral for a sleep study to evaluate for sleep apnea

6. What are effective alternatives to benzodiazepines for the treatment of anxiety?

Patients receiving methadone or Suboxone® often present with symptoms of anxiety and often believe that benzodiazepines are the only medication that can alleviate those symptoms. There are both pharmacological and non-pharmacological alternatives that can be used alone or in combination. Evidence is sparse in opioid-dependent individuals to support one pharmacological agent over another, so clinical judgment predominates.

- Medications effective for anxiety[7]
  - Selective serotonin reuptake inhibitors (SSRIs)
    - Several have good evidence across different anxiety disorders[5,11,12]
      - escitalopram (Lexapro®)
      - paroxetine (Paxil™)
      - sertraline (Zoloft®)
      - citalopram (Celexa™)
      - fluoxetine (Prozac®)
      - fluvoxamine (Luvox®)
    - Consider starting at low doses to avoid initial increase in anxiety and restlessness[13]
    - QT prolongation may be a class effect for SSRIs but is most pronounced with citalopram[14]
  - venlafaxine XR (Effexor XR®)[12]
  - hydroxyzine (Vistaril®)
    - Weaker efficacy but more effective than placebo and with fewer side effects and safety concerns compared with other medications[5,11]
    - Consider evening dosing to avoid daytime drowsiness
  - buspirone (Buspar®)
    - Weaker efficacy but relatively well tolerated[5,15,16]
  - pregabalin (Lyrica®)[5]
    - Studies demonstrate better efficacy than placebo and as effective as benzodiazepines and venlafaxine[5,12]
    - Onset of action may be quicker than with venlafaxine[5]
    - May enhance sedative effect of other medications and may lead to weight gain
    - Less clinical experience with this medication for anxiety
    - gabapentin (Neurontin®) may be a cheaper alternative but with few, mixed-result studies
  - Tricyclic antidepressants (TCAs)
    - Several have evidence in different anxiety disorders[5]
      - desipramine (Norpramin®)
      - imipramine (Tofranil™)
      - doxepin (no trade name for anxiety and depression dose formulations)

        - Methadone slows TCA metabolism potentially exacerbating significant anticholinergic side effects[15]
        - QT prolongation is a recognized class effect and concern[11]
- Non-pharmacological interventions
    - Cognitive-behavioral therapy[5,12]
    - Exercise
    - Mindfulness meditation
    - Yoga

7. Could a physician who manages a patient's methadone or Suboxone® prescribe benzodiazepines?

Physicians who are managing a patient's methadone or Suboxone® and who feel comfortable managing benzodiazepines could consider taking over prescribing of the latter medication.

- In situations where patients are tapering off benzodiazepines with a benzodiazepine, it allows for more control.
- Physicians should ensure that specific agreements are in place with patients.
- Physicians should have clear plans for how they will address other patients' requests for benzodiazepines.

8. When might a physician wait to start Suboxone®/methadone due to the use of benzodiazepines?

When patients present to either start or continue Suboxone® or methadone treatment, it is critical to engage them and not turn them away, as they may not return. Part of the initial visit should include an assessment of other medications and substances the patient may be taking, and a brief mental status examination. Only a few circumstances warrant delaying the start of Suboxone® or methadone:

- Confusion
- Delirium
- Respiratory distress
- Recent head trauma
- An inability to understand the risks and benefits associated with either Suboxone® or methadone, as applicable

If any of the above is present, further evaluation and potentially emergency care is needed prior to initiating any CNS-active medications.

Section 3: Benzodiazepine Use Risk Assessment and Related Issues

When dealing with any prescription medication, physicians must weigh risks and benefits in individual patients. This same principle applies to patients taking benzodiazepines, even if a physician is not the prescriber.

1. What are key risks of benzodiazepines in patients taking methadone or Subxone®?

Opioid dependent patients receiving methadone or Subxoxone® experience a higher risk of adverse outcomes from concomitant benzodiazepine use, as compared to patients who are not taking methadone or Subxone®. This applies to both prescribed and illicitly obtained benzodiazepines.

- Memory loss/amnesia leading to unintentional increased dosing of methadone or Suboxone®
- General cognitive difficulties
- Mood instability including disinhibition and lability
- Possible long-term worsening of depression and anxiety disorders
- Sedation, respiratory depression, coma, and death
- High risk of benzodiazepine abuse or dependence
- Physical dependence with withdrawal syndrome, which may consist of sweating, insomnia, tremor, and anxiety triggering relapse to opioid addiction and continued benzodiazepine use
- Withdrawal seizures and status epilepticus can occur with abrupt withdrawal
- Lower retention in opioid addiction treatment

2. How do I determine if a new patient is taking benzodiazepines?

The most common method for determining if a new patient is taking benzodiazepines is through the medical history, either directly through asking about substance use history and current medications or indirectly by probing on past medical and psychiatric history. Point-of-care urine toxicology testing can also be performed to document the presence or absence of a benzodiazepine but is not necessary in most cases.

3. What history should I obtain in patients using benzodiazepines?

In triaging and negotiating interventions and a treatment plan with patients taking methadone or Suboxone® and benzodiazepines, it is critical to understand the severity and history of use.

A few key clinical questions can establish patterns of use:

- Which benzodiazepines has the patient been prescribed, when, and at what dose?
- Which benzodiazepines bought off the street has the patient taken, when, and how much?
- What was the predominant feeling with the first benzodiazepine?[1]
- When did the patient start to escalate the dose, if that occurred?
- Was there a dose at which the patient stopped escalating the dose?
- How long has the patient been able to go without taking any benzodiazepine?
- Has the patient ever tried to decrease or taper off the benzodiazepines?
  - When?
  - How?

[1] This question may help distinguish between the euphoric vs anxiolytic effects of benzodiazepines

    - What happened?
- What other substances, including alcohol, does the patient use?
- When was the last time the patient took any benzodiazepines and how much?

In addition to getting a use history for benzodiazepines, there are additional important questions to ask in the medical and psychiatric history.

- What treatment has the patient had or is getting now for anxiety, including panic disorder and PTSD, or depression?
- Is insomnia or a diagnosed sleep disorder present?
- Is there a history of a seizure disorder?
- Is there presence of a personality disorder?
- What is the perceived or real benefit to the patient of taking benzodiazepines?

Other psychosocial history is also important.

- Current sources of income
- Current use of alcohol and other drugs by family or others in the same living environment
- Are there small children in the household?

4. How does this history fit with DSM-IV diagnostic criteria?

The DSM-IV does not contain separate diagnostic categories for benzodiazepine abuse or dependence but includes them in "Sedative, Hypnotic, or Anxiolytic" abuse or dependence, respectively. Criteria for these diagnoses reflect the compulsive, destructive, continued use of benzodiazepines despite impaired functioning in the multiple domains that characterize other diagnoses of substance abuse or dependence.

5. What are the physical examination findings of benzodiazepine abuse or dependence?

Certain non-specific physical examination findings may indicate either benzodiazepine intoxication or withdrawal. This can confirm a diagnosis of benzodiazepine abuse or dependence, but these signs alone do not make either of these diagnoses.

Signs of benzodiazepine intoxication:

- Sedation is a common sign of benzodiazepine abuse, particularly when combined with methadone or Suboxone®
- Ataxia can be appreciated through gait and cerebellar testing
- Short- and long-term memory problems can be identified through performance of a mini-mental status examination

Signs of benzodiazepine withdrawal:

- Elevated BP or tachycardia are potential signs of benzodiazepine withdrawal
- Tremulousness may be an early sign of benzodiazepine withdrawal

6. Do I need to wait to start methadone or Suboxone® in a patient taking benzodiazepines?

Because of the morbidity and mortality related to opioid addiction, it is not recommended to wait to start methadone or Suboxone® until a patient is completely off benzodiazepines.[17]

- Start at a low dose and increase slowly

- Monitor closely for sedation and intervene as indicated based on severity of sedation
- Obtain information from other sources regarding patient's functioning
  - Family members
  - Other healthcare providers, particularly physicians prescribing benzodiazepines
  - Other treatment team members

7. How are maintenance doses of methadone/Suboxone® managed in patients starting benzodiazepines?
Methadone and Suboxone® doses may need to be decreased in patients who take benzodiazepines. This is particularly the case in patients who are tapering off the benzodiazepines or who present with excessive sedation due to the combination of medications.

- Amount of methadone/Suboxone® decrease depends on the amount of sedation present
- Re-assess frequently for sedation and intervene as indicated based on severity of sedation
- Obtain information from other sources regarding patient's functioning
  - Family members
  - Other healthcare providers, particularly physicians prescribing benzodiazepines
  - Other treatment team members

8. How do I manage sedation among patients taking methadone or Suboxone® and benzodiazepines?
The approach to patients who develop sedation while taking methadone or Suboxone® with benzodiazepines depends on an assessment of the clinical situation and the severity of the sedation.

- Obtain additional history and information from the patient, family members, and other providers
- Assess state of alertness and vital signs, including O2 saturation
- Consider using a sedation assessment scale[18]

If a patient is observed experiencing significant respiratory depression and mental status change, call 911 and provide appropriate first aid. Once the emergency situation has resolved, the patient should resume methadone or Suboxone®, in most cases at a lower dose, especially initially. The specific dose and titration schedule need to be individualized with the goals of minimizing the risk of recurrent respiratory depression while retaining the patient in treatment.

If patients are observed mildly to moderately sedated or complain of sedation, small decreases of methadone (5-10mg) or Suboxone® (2-4mg) may be warranted, depending on the severity of the sedation. Closely monitor and frequently re-assess patients for improvement in symptoms, and decrease doses further as needed.

In all instances, the provider managing the methadone or Suboxone® should review the patient's complete medication list, including over-the-counter or herbal medications, to identify sedating medications or supplements. Patients should be educated about the safety risks of combining any sedating medications and supplements, and to avoid these combinations if possible.

Providers should also work with patients and benzodiazepine prescribers on a plan for how to maximize patient safety and minimize sedation from combinations of medications.

9. How can I effectively coordinate care with outside prescribers of benzodiazepines?

Physicians treating opioid dependent patients with methadone or Suboxone® often express frustration with attempts to coordinate care with outside prescribers of benzodiazepines. Several approaches may help:

- Direct communication from physician to physician works best.
- Consider scheduling a time to discuss the situation when all parties are free.
- Written communication takes time and is sometimes ineffective in achieving change in physician prescribing behavior but can be a useful tool as follow-up to a telephone conversation.
- Ask about clinical rationale for prescribing the original prescription.
- Emphasize safety concerns with the combination of benzodiazepines and methadone or Suboxone®, as appropriate.
- Consider communicating that discontinuation of the benzodiazepine is a requirement for the patient to continue opioid dependence treatment with medication, if that is your practice.
- Offer to work with the prescriber in identifying and implementing alternatives to benzodiazepines.
- Offer to assist the prescriber in managing discontinuation of the benzodiazepine, including communicating with patients and identifying appropriate detoxification resources**.**

Section 4: Monitoring in Patients Taking Benzodiazepines

Whether a physician is going to prescribe benzodiazepines or not, monitoring their use is an essential component of good clinical care. The goals are to ensure patient safety and strengthen recovery. Physicians have several tools at their disposal.

4.1 Assessment of aberrant drug-taking behaviors

One of the key indicators of recovery is positive behavior change and improvement in health and wellness. From time to time, patients may exhibit behaviors that are of concern to physicians and other healthcare providers. Many of these behaviors used to be known as "drug-seeking" behaviors and are often applied to patients taking benzodiazepines.

- The preferred term now is aberrant drug-taking behaviors.
- Aberrant drug-taking behaviors do not necessarily equal prescription drug abuse or active addiction.
- Aberrant drug-taking behaviors represent risk factors that warrant addressing and increased monitoring.
- There is a spectrum of aberrant drug-taking behaviors from less concerning (and less predictive of a substance use problem) to extremely serious (see Appendix A).[19]

1. What do I do if a patient exhibits aberrant drug-taking behaviors?

If aberrant drug-taking behaviors occur, particularly a pattern of them or any of the more serious ones, respond as follows:

- Increase the frequency of visits
- Monitor closely for sedation and adjust methadone or Suboxone® dose as needed
- Evaluate for and help the patient manage any relapse
- Increase the frequency of urine toxicology testing for benzodiazepines.
- Consider temporarily increasing amount of counseling

4.2 Urine toxicology testing

Urine toxicology testing is a core component of monitoring. It is strongly recommended that physicians become familiar with their laboratories and which parent compound(s) and/or metabolites are used in particular assays, as these vary by laboratory and testing method.

2. What method should I use to test for benzodiazepines?

Testing methods for benzodiazepines depend on the rationale for testing and the clinical situation.

- Patients abstaining from benzodiazepine use
    - Rationale for testing is to identify relapse early
    - Rely on commonly available immunoassays
    - This will be positive across several different benzodiazepines
    - Any positive test result needs addressing quickly
- Patients receiving benzodiazepines from outside prescribers
    - Rationale for testing is to assess patient safety

    - Rely on commonly available immunoassays that are positive across different benzodiazepines
    - Coordinate with outside prescribers to obtain copies of more specific urine toxicology test results
    - If there is concern regarding misuse, abuse or dependence, strongly consider requesting a specific immunoassay or testing with gas or liquid chromatography and mass spectrometry (GC/MS or LC-MS/MS) as these can distinguish specific benzodiazepines.
- Physicians prescribing benzodiazepines and managing methadone or Suboxone®
    - Rationale for testing is to monitor appropriate use of the medication
    - Consider requesting a specific immunoassay for that particular benzodiazepine
    - Alternatively, could request gas or liquid chromatography and mass spectrometry (GC/MS or LC-MS/MS) as these can distinguish specific benzodiazepines and quantify levels.

3. How frequently should I order urine toxicology testing for benzodiazepines?

The frequency of testing depends on the patient, his/her progress in recovery, and his/her overall health status.

- No less than monthly urine toxicology test is recommended for most patients.
- If there is concern for misuse or during detoxification, temporarily increase the frequency of testing.
- Testing more than once a week is unlikely to provide significantly more information, adds to cost, and may be difficult for patients and clinic staff to achieve.
- Random testing is best.

4. How do I manage a patient with a positive urine toxicology result who denies taking benzodiazepines?

- Review all medications, including over the counter and dietary supplements, with the patient to identify those that may cause false-positive test results.
- Contact the lab's toxicologist for assistance with test interpretation.
- Consider ordering a GC/MS or LC-MS/MS for more specific substance identification.
- Consider the positive urine toxicology test result in the context of how the patient is doing otherwise.
- Strongly consider temporarily increasing frequency of toxicology testing.

5. What medications are known to cause a false positive urine toxicology test result for benzodiazepines?

Several medications have been shown to potentially cause false-positive test results for benzodiazepines. A confirmatory test may be needed for clarification.

- Diphenhydramine (Benadryl®)
- Oxaprozin (Daypro®)
- Sertraline (Zoloft®)
- Zolpidem (Ambien®)

6. Does heroin contain benzodiazepines and might this appear as a positive test result?

Instances of heroin mixed with benzodiazepines have been reported in Baltimore City from time to time. In this instance, urine toxicology tests should be positive for both opiates and benzodiazepines. Physicians should use such test results to open, in a non-judgmental way, a conversation with patients about potential use.

7. Should I do point of care urine toxicology testing or send patients/urine specimens to the lab?

Assays for point-of-care testing are commercially available, but requires a Maryland State Lab Permit in addition to a CLIA waiver. All point-of-care test kits employ immunoassay methods so will only provide

information regarding the presence or absence of benzodiazepines as a class. If further identification is required, patients or samples must be sent to the lab.

4.3 Patient-physician/practice Controlled Medication Agreements

For physicians who may prescribe benzodiazepines to patients taking methadone or Suboxone®, a written agreement with the patient can help (see Appendix B for example):

4.3.1.1.1 Minimize diversion
4.3.1.1.2 Set clear expectations for patients and practice staff
4.3.1.1.3 Prevent conflict when aberrant drug-taking behaviors occur

Physicians who manage methadone or Suboxone® but do not serve as the benzodiazepine prescriber may also want to consider a written patient agreement (see Appendix C for an example). Such an agreement would:

- Set clear expectations for patients and their methadone or Suboxone® provider
- Serve as informed consent for the patient on the risks of combining these medications
- Prevent conflict when aberrant drug-taking behaviors occur

Key Points on implementing a Controlled Substance Agreement:

- Have a practice staff member (physician or nurse typically), review the agreement with each new patient, have the patient and reviewer sign, and provide a copy to the patient. This ensures that patients and staff know what is being agreed upon.
- Periodically review the salient items in the agreement. This ensures that patients clearly understand what is expected of them (e.g. not to increase the dose on their own, importance of adhering with visit appointments, safekeeping their medication, etc), and can help prevent misunderstandings or miscommunications.
- An annual review of the signed agreement with the patient may help reinforce appropriate medication management.
- If it is clear that the patient fully understands the expectations, then failure to adhere to them can be interpreted as an aberrant behavior.

Key components of an agreement include:

1. Expectations of patients:
   a. Appropriate follow-through with and behavior at appointments
   b. Storing of controlled medications at home in locked cabinets, particularly for patients residing in homes with adolescents or other adults
   c. Open communication and collaboration with the prescribing physician and the clinic
   d. Having one prescriber and one pharmacy
2. Expectations of the prescriber and the practice:
   a. Provision of adequate doses and lengths of prescriptions to ensure continuity of medication
   b. Access to assistance in case of problems at the pharmacy with prescriptions
   c. Respectful interactions with patients

d. Collaborative care with the patient
e. Provision of effective care

3. Actions the physician and/or clinic may take if[2]:
   a. Patients are unable to follow expectations or
   b. The side effects of the medication outweigh the benefit the patient may be achieving or
   c. The controlled medication is no longer effective for the condition it is meant to treat.
4. Identification of the prescriber responsible for the controlled medication
5. Identification of the pharmacy chosen by the patient as the only place where he/she will fill controlled medications
6. Identification of the patient's preferred hospital and emergency department
7. A release of information to the patient's chosen pharmacy

4.4 Pill counts

Consider having patients bring in their benzodiazepine bottles at every visit to the clinic even if the visit has nothing to do with their benzodiazepine use. Count the pills only on randomly selected visits. Be aware that pill counts during all regularly scheduled appointments are not random and often uninformative as patients can save just enough pills for the count.

4.5 Documentation of benzodiazepine prescriptions

If nothing else, patients taking benzodiazepines in conjunction with methadone or Suboxone® should provide regular documentation of current prescriptions and on-going indication for the benzodiazepines. If patients do not provide such documentation, then it is incumbent on the physician managing the methadone or Suboxone® to obtain it.

- Patients are sometimes unwilling to provide consent for a physician to speak with the benzodiazepine prescriber
- Explore with the patient the reason for this unwillingness
- Explain that it is important for physicians to communicate so that patient safety is ensured and assistance with recovery is maximized
- If the patient fears that the benzodiazepine will be taken away, empathically discuss the patient's current clinical situation, the desire to help the patient strengthen his/her recovery, and physician intention of initially gathering information which will be discussed with the patient

[2] It is often helpful to include a menu of different options here that can be applied in a step-wise, progressive fashion and aligned with the seriousness of the aberrant behavior or clinical situation.

Section 5: Benzodiazepine Detoxification and Taper

For the vast majority of patients treated with methadone or Suboxone®, the risks of taking benzodiazepines will likely outweigh the benefits.[20] Physicians in OTPs and those prescribing Suboxone® will then need to engage their patients in often difficult conversations to set the stage for further interventions. Benzodiazepine detoxification or taper, either in an outpatient or inpatient setting, are the four ways of helping patients achieve abstinence from benzodiazepines, although none is 100% effective.

1. How do I effectively address benzodiazepine detoxification or taper with my patients?

The first step is to empathically communicate with patients regarding coming off benzodiazepines. This often takes more than one visit.

- Assess the stage of change of the patient
  - Pre-contemplation
  - Contemplation
  - Preparation
  - Action
- Explain the risks of benzodiazepines and concern for the patient's safety and health
- Discuss the reasons for taking them
- Explain and offer alternatives for treatment of the current problem
- Express desire to help with the original, underlying condition (anxiety, insomnia)
- Empathically present his/her choice of either adequate opioid dependence treatment or continued benzodiazepine use
- Acknowledge the distress patients feel about coming off benzodiazepines but maintain firm stance on weaning
- Discuss how the patient will manage the loss of the perceived or real benefits derived from the benzodiazepines
- Reassure patients that symptoms are expected to improve with recovery and with effective treatment

2. What determines the need for inpatient or outpatient benzodiazepine detoxification or taper?

The goal both of benzodiazepine detoxification and taper is sustained abstinence from benzodiazepines after complete discontinuation. Either method can be applied in the outpatient or inpatient setting, but local resources for inpatient benzodiazepine taper are minimal. Little evidence exists to suggest one method versus another but a few factors can help guide discussion and decision-making with patients:

- A history of seizure, psychosis, or delirium during benzodiazepine withdrawal is usually an indication for inpatient detoxification or taper.[7]
- Patients with benzodiazepine addiction likely will not do well with outpatient benzodiazepine detoxification or taper and should be offered inpatient services as the preferred intervention.
- If patients with benzodiazepine addiction only agree to outpatient treatment, then outpatient detoxification is preferable, using a phenobarbital-based protocol.
- Patients with long-term, high-dose benzodiazepine use, even if not addicted, may have difficulty sustaining abstinence with an outpatient taper of a benzodiazepine, particularly if motivation is low.

- Housing stability, especially homelessness or lack of drug-free living space, may indicate a need for inpatient services.
- Highly motivated patients especially may benefit from a trial of outpatient taper with a benzodiazepine.

3. How do I manage an outpatient benzodiazepine taper?

In motivated patients, especially those with less severe benzodiazepine use, outpatient benzodiazepine taper may a reasonable approach, and several methods have been suggested in the literature.[4,21,22] The resources required to manage an outpatient benzodiazepine taper are not as intense as those needed for benzodiazepine detoxification, but planning and thought is still necessary prior to embarking on this. Across all cited methods, a positive, supportive approach is reassuring and therapeutic, and common threads emerge.

Checklist for Outpatient Benzodiazepine Taper

1. Assess motivation for benzodiazepine abstinence and readiness to change using readiness ruler.
2. Consider switching the patient to a longer acting benzodiazepine such as chlordiazepoxide.
3. Develop a plan with the patient for a slow, gradual taper, usually over 6-12 weeks, with weekly visits.
4. Consider starting an SSRI, such as escitalopram, paroxetine, or sertraline, early in patients with anxiety, at a low dose to avoid an activating effect. Escitalopram is the least activating of these examples.
5. Address insomnia aggressively with behavioral interventions, and a pharmacological agent such as trazodone if needed. Avoid benzodiazepines and the "Z" sedatives such as Ambien.
6. Individual dose decrements of benzodiazepine towards the end of the taper may need to be very small.
7. To help ameliorate withdrawal symptoms, consider starting carbamazepine 2 weeks prior to reaching zero milligrams of benzodiazepine. Less evidence exists for other anticonvulsants.
    a. Start carbamazepine at 200mg BID then increase gradually to 800mg daily or as much as tolerated.
    b. Continue for 1-2 weeks after reaching zero milligrams of benzodiazepine.
    c. Monitor for opioid withdrawal symptoms, as carbamazepine may potentially decrease serum levels of methadone in particular. This effect has not been clinically observed with Suboxone®.
8. Offer a future of greater freedom once the patient is off benzodiazepines altogether, including longer duration of Suboxone® prescriptions or more take-home doses of medication.
9. Take a firm stance on tapering, but a flexible stance on the rate of tapering as long as the taper progresses.

4. How do I switch from a short-acting to a longer-acting benzodiazepine?

There is not one standard method for switching from a short-acting to a longer-acting benzodiazepine, but physicians should identify one approach initially with which to become familiar.[10,23] In choosing a replacement benzodiazepine, consideration should be given to longer-acting formulations that have less local street value. In Baltimore City, chlordiazepoxide (Librium™) may be a reasonable choice and is used in the examples below.

Note that both 1 mg of alprazolam and 1 mg of clonazepam are each approximately equal to 50mg of chlordiazepoxide.

Example Approach #1 (gradual overlapping):

- Add 25 mg of chlordiazepoxide at bedtime to the current dose of the original benzodiazepine.
- After about 1 week, serum levels of chlordiazepoxide should have reached steady state.
- Successive portions of the short-acting agent can be partially replaced by chlordiazepoxide with the speed of transition to only chlordiazepoxide individualized.
- Goal of dosing for chlordiazepoxide is twice daily (BID) with no short-acting agent.
- Once the patient is taking only chlordiazepoxide, a gradual taper in 5-10mg increments every 2-3 weeks can begin with the goal of minimizing or avoiding benzodiazepine withdrawal symptoms.
- Longer time between decreases in chlordiazepoxide doses may be needed towards the end of the taper.
- Address underlying mental health symptoms.

Example Approach #2 (abrupt switch):

- Add 25 mg of chlordiazepoxide at bedtime to the current dose of the original benzodiazepine.
- For one week, the patient can continue to take the original benzodiazepine but only as needed and only up to doses he/she was taking before starting the switch.
- After about 1 week, serum levels of chlordiazepoxide should have reached steady state.
- Stop the original benzodiazepine and increase chloridazepoxide slightly if anxiety or other benzodiazepine withdrawal symptoms are unbearable.
- Begin a gradual taper of chlordiazepoxide in 5-10mg increments every 2-3 weeks with the goal of minimizing or avoiding benzodiazepine withdrawal symptoms.
- Longer time between decreases in chlordiazepoxide doses may be needed towards the end of the taper.
- Address underlying mental health symptoms.

5. What resources do I need to incorporate outpatient benzodiazepine detoxification into my practice?

Before deciding to incorporate outpatient benzodiazepine detoxification into a practice, it is helpful to assess readiness of the practice to manage this. Benzodiazepine detoxification typically requires significant and frequent communication with patients, more regular visits with the physician and other clinical staff than some settings are accustomed to, and management of often highly anxious patients. Physicians should feel comfortable prescribing phenobarbital and adjunct anti-seizure medications, have systems in place that can accommodate frequent, sometimes daily visits, and have effective on-call mechanisms.

6. How do I manage outpatient benzodiazepine detoxification?

After a practice completes an organizational readiness assessment and decides to incorporate outpatient benzodiazepine detoxification, protocols are needed. Outpatient benzodiazepine detoxification is currently primarily done using phenobarbital, with different protocols calling for different lengths of tapering doses of the medication.[4,24,25,26] Little evidence exists to suggest one method over another so consultation with experienced clinicians and good clinical judgment is recommended.

There are some commonalities between different protocols:

- Most protocols call for 30mg doses of phenobarbital taken three to four times a day, with subsequent tapering in increments of 30mg.
- Tapering is variable but often done over 7-21 days, with either daily or weekly clinic visits for assessment of symptoms, medication adjustment, and counseling services.
- Some protocols allow patients to continue a small dose of benzodiazepine for part of the protocol while other protocols have patients stop the benzodiazepine on the day that phenobarbital starts.
- Most protocols add one or more adjuvant medications to the phenobarbital for the duration of the taper.
    - Doxepin or trazodone for sleep.
    - A second anticonvulsant, often carbamazepine.[27] Less solid evidence exists for other anticonvulsants.[28,29,30]
    - Propranolol or clonidine as tolerated to suppress withdrawal symptoms.
- All protocols advise assessing for and treating opioid withdrawal symptoms as phenobarbital may decrease serum levels of methadone (much less so with Suboxone®).

7. How should I prepare a patient for inpatient benzodiazepine detoxification?

- Acknowledge and support the patient's decision to seek inpatient detoxification
- Time is of the essence
    - Work with inpatient facilities to get patients admitted when their motivation is at its peak
- Communicate and coordinate with the inpatient facility regarding:
    - Patient's medication list
    - Diagnoses
    - Past attempts at benzodiazepine detoxification
    - Specific alternatives and their duration of use in the past for anxiety
    - Recovery supports and relevant treatment that may be in place post-detoxification

8. What local resources are available for patients, families, and providers?

- Baltimore Substance Abuse Systems, Inc. (BSAS) - General substance abuse treatment referrals; Benzodiazepine detoxification referrals; www.bsasinc.org or 410-637-1900
- Baltimore Mental Health System, Inc. (BMHS) - Mental health treatment information; www.bmhsi.org or 410-837-2647
- Residential treatment facilities that offer benzodiazepine detoxification
    - Gaudenzia - www.gaudenzia.org or 443-423-1500
    - Baltimore Crisis Response, Inc. (BCRI): Short term only - www.bcresponse.org or 410-433-5255
    - Johns Hopkins Bayview Chemical Dependence Unit: Short term only - www.hopkinsbayview.org/chemicaldependence/cdu or 410-550-1910
- Outpatient benzodiazepine detoxification
    - Center for Addiction Medicine (insured patients only) - www.camtreatment.com or 410-225-8240
    - Johns Hopkins Bayview Addiction Treatment Services (uninsured only) - www.hopkinsmedicine.org/psychiatry/bayview/substance_abuse/addiction_treatment_service or 410-550-0051

Appendix A: Spectrum of Aberrant Drug-Taking Behaviors

Less Serious → **Most serious**

Aggressively complaining about need for medication Asking for specific medications by name Asking for non-generic medication Request to have medication dose increased Taking a few extra, unauthorized doses on occasion	Claiming multiple pain medicine allergies Visiting multiple doctors for controlled substances Hoarding medication Frequent calls to clinic Using a controlled substance for non-pain relief purposes (e.g. to enhance mood, sleep aid)	Frequent unscheduled clinic visits for early refills Consistent disruptive behavior when arrives in clinic Obtaining controlled substances medications from family members Pattern of lost or stolen prescriptions Anger or irritability when questioned closely about pain Unwilling to consider other medications or non-pharmacologic treatments Frequent unauthorized dose escalations after being told that is inappropriate	Injecting an oral formulation Forging prescriptions Unwilling to sign controlled substances agreement Selling medications Use of aliases Refuse diagnostic workup or consultation More concern about the drug than their medical problem that persists beyond the third clinic visit Obtaining controlled substance analgesics from illicit sources Consistently calling outside of clinic hours or when a particular physician is on call who prescribes controlled substances Deterioration at home or work or reduction of social activities because of medication side effects

Appendix B: Example of a Patient-Physician Benzodiazepine Prescription Agreement

Patient Name: _____ MR#: _____ DOB: _____

My doctor, _____, who provides methadone or Suboxone® to me as a treatment for opioid addiction, has agreed to now also prescribe _____, a benzodiazepine. This benzodiazepine is to treat _____. I freely and voluntarily agree to accept this benzodiazepine prescription agreement and I understand what is being expected of me and what I can expect of my doctor and my clinic as outlined below:

a. I agree to keep, and be on time for, all my scheduled appointments with the doctor and any of his/her assistants.
b. I agree to call the clinic ahead of time if I cannot make an appointment or am running late.
c. I agree to conduct myself in a courteous manner in the doctor's or clinic's office and, in return, I understand that my doctor and other clinic staff will treat me with respect and courtesy.
d. I agree to not seek out other doctors other places for additional benzodiazepine prescriptions.
e. I agree to fill my prescriptions at one pharmacy, and I will give my doctor and clinic the name and phone number to this pharmacy. I agree to conduct myself in a courteous manner at the pharmacy, and, in return, I understand that my doctor and/or clinic will assist me if I have trouble there with my prescription.
f. If I have to change pharmacies, I will let my doctor know and provide him/her with the new pharmacy's information.
g. I agree that the medication I receive is my responsibility and I will store it in a safe, secure place, away from children and teenagers. I agree that lost medication will not be replaced, unless I have a police report to document that it has been stolen.
h. I agree not to sell, share, or give any of my medication to another person. I understand that such mishandling of my medication is very serious and likely will result in my being unable to receive any further medication from my doctor. Instead, I may be referred for other services.
i. I agree that my doctor will only give me prescriptions at my regular office visits. If I miss a visit, I likely will not be able to get a prescription until the next scheduled visit. If my doctor has to cancel my appointment, he/she will make sure I receive my prescription in time to not disrupt my treatment.
j. I understand that mixing benzodiazepines with other medications, including methadone or Suboxone®, and/or alcohol and other drugs of abuse can be dangerous and even lead to death.
k. I agree to communicate openly and honestly with my doctor and report any use of drugs or alcohol that may negatively affect my recovery. In return, I understand that my doctor will work with me to the utmost of his/her ability to help me maintain and strengthen my recovery.
l. I agree to take my medication as my doctor has instructed, and not to change the way I take my medication without first consulting my doctor.
m. I understand that my doctor will prescribe me medication at an effective dose that helps me with the least amount of side effects. If my doctor determines that the benzodiazepine is no longer effective, I understand that my doctor may recommend tapering me off it in a safe manner.
n. I understand that my doctor or clinic may call me at any time to bring in my medication or provide a urine sample for testing. I understand that not adhering with this may be considered a risk factor for mishandling of my medication and likely will result in changes to my treatment.
o. I understand that medication alone is not sufficient treatment and I agree to participate in counseling and/or recovery-related activities that my doctor either recommends or that he/she and I agree on together.

Patient Signature:_____ **Date**:_____

Appendix C: Example of an Opioid Addiction Treatment and Benzodiazepine Use Agreement

Patient Name: _____ MR#: _____ DOB: _____

I am requesting that my doctor treat me for opioid addiction with methadone or Suboxone®. I also acknowledge that I take _____, a benzodiazepine. I freely and voluntarily agree to accept this opioid addiction treatment and benzodiazepine agreement and I understand what is being expected of me and what I can expect of my doctor and my clinic as outlined below:

a. I understand that mixing benzodiazepines with other medications, including methadone or Suboxone®, and/or alcohol and other drugs of abuse can be dangerous and even lead to death.
b. I understand that my taking benzodiazepines may limit the amount of methadone or Suboxone® my doctor may be able to safely give me.
c. I also understand that my doctor is concerned for my safety so may advise that I safely stop taking the benzodiazepines.
d. I understand that it is important for my doctor to be able to communicate and coordinate care with my doctors who prescribe the benzodiazepines. If I do not permit my doctors to communicate, I may jeopardize some of the privileges I could get as part of treatment.
e. I agree that the benzodiazepines are my responsibility and I will store them in a safe, secure place, away from children and teenagers.
f. I agree not to sell, share, or give any of my benzodiazepines to another person. I understand that such mishandling of my medication is very serious and may result in my being referred for treatment elsewhere.
g. I understand that my doctor or clinic may call me at any time to bring in my medication or provide a urine sample for testing. I understand that not adhering with this may be considered a risk factor for mishandling of my medication and likely will result in changes to my treatment.
h. I agree to conduct myself in a courteous manner in the doctor's or clinic's office and, in return, I understand that my doctor and other clinic staff will treat me with respect and courtesy.
i. I agree to communicate openly and honestly with my doctor and report any use of drugs or alcohol that may negatively affect my recovery. In return, I understand that my doctor will work with me to the utmost of his/her ability to help me maintain and strengthen my recovery.
j. I understand that benzodiazepines alone may not be sufficient treatment and I agree to participate in counseling that my doctor either recommends or that he/she and I agree on together.

Patient Signature:_____ **Date**:_____

References

1. **Baltimore Substance Abuse Systems, Inc.** *Outlook and Outcomes Baltimore City. Fiscal Year 2011.* Baltimore, MD: BSAS, Inc., 2012.

2. **Maryland Alcohol and Drug Abuse Administration.** *County Program Statistics Report: Baltimore City.* Catonsville, MD: ADAA, 2010.

3. **Ciraulo, DA, Knapp CM.** The Pharmacology of Nonalcohol Sedative Hypnotics. In Principles of Addiction Medicine Fourth Edition. Ries RK, Fiellin DA, Miller SC, Saitz R, eds. Philadelphia, PA: Lippincott Williams & Wilkins, 2009; pp. 99-112.

4. **DuPont, RL**. A Physician's Guide to Discontinuing Benzodiazepine Therapy. West J Med 1990; 152:600-603.

5. **Bandelow B, Zohar J, Hollander E, Kasper S, Moller H, & WFSBP Task Force on Treatment Guidelines for Anxiety Obsessive-Compulsive Post-Traumatic Stress Disorder.** World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders - First Revision. World J Biol Psychiatry 2008; 9:248-312.

6. **de Wet C, Reed L, Glasper A, Moran P, Bearn J, Gossop M.** Benzodiazepine co-dependence exacerbates the opiate withdrawal syndrome. Drug Alcohol Depend 2004; 76:31-35.

7. **Center for Substance Abuse Treatment.** *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs.* Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 08-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005, reprinted 2006 and 2008.

8. **Mayo-Smith, MF.** Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA 1997; 278(2):144-151.

9. **Ashton, H.** Guidelines for the rational use of benzodiazepines. When and what to use. Drugs 1994; 48(1):25-40.

10. **Ford C, Roberts K, Barjolin JC.** *Guidance on Prescribing Benzodiazepines to Drug Users in Primary Care.* Manchester, UK: SMMGP Production, c/o Bolton, Salford and Trafford Mental Health NHS Trust, 2005. Available at: www.smmgp.org.uk. Last accessed 3/8/13.

11. **Davidson, J.** *Clinician's Manual on Generalized Anxiety Disorder.* Philadelphia, PA: Current Medicine, LLC, 2004:25-37.

12. **Clinical Practice Guidelines: Management of Anxiety Disorders.** Generalized Anxiety Disorder. Can J Psychiatry 2006; 51(S2):51S-56S.

13. **Katon, WJ.** Panic Disorder. NEJM 2006; 354:2360-2367.

14. **Food and Drug Administration.** *FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses.* March 27, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm. Last accessed 3/8/13.

15. **Scott J, Gilvarry E, Farrell M.** Managing Anxiety and Depression in Alcohol and Drug Dependence. Addict Behav 1998; 23(6):919-931.

16. **Renner, JA.** Management of psychiatric medications in patients receiving buprenorphine/naloxone. PCSS-B Training. April 17, 2006. Available at: http://pcssb.org/wp-content/uploads/2010/09/PCSS-B-Management-of-psychiatric-medications-in-patients-receiving-buprenorphine-naloxone.pdf. Last accessed 3/9/13.

17. **Kleber H, Weiss RD, Anton RF, et al.** *Practice Guideline for the Treatment of Patients with Substance Use Disorders Second Edition.* American Psychiatric Association 2006:122.

18. **Nisbet AT, Mooney-Cotter F**. Comparison of Selected Sedation Scales for Reporting Opioid-Induced Sedation Assessment. Pain Manag Nurs 2009: 10(3):154-164.

19. **Olsen Y, Alford DP.** Chronic Pain Management in Patients with Substance Use Disorders. Adv Studies in Med 2006; 6(3):537-549.

20. **Meiler A, Mino A, Chatton A, Broers B.** Benzodiazepine use in a methadone maintenance programme: patient characteristics and the physician's dilemma. Schweizer Archiv für Neurologie und Psychiatrie 2005; 156(6):310-317.

21. **McDuff DR, Schwartz RP, Tommasello A, Donovan T, Johnson JL.** Outpatient benzodiazepine detoxification procedure for methadone patients. J Subst Abuse Treat 1993; 10(3):297-302.

22. **Weizman T, Gelkopf M, Melamed Y, Adelson M, Bleich A.** Treatment of benzodiazepine dependence in methadone maintenance treatment patients: a comparison of two therapeutic modalities and the role of psychiatric comorbidity. Aust N Z J Psychiatry 2003; 37:458-463.

23. **World Health Organization, Regional Office for South-East Asia.** *Operational Guidelines for the management of opioid dependence in the South-East Asia Region.* World Health Organization 2008:47-50. Available at: www.searo.who.int/LinkFiles/Publications_guidelines_management_opioid_in_SEAR.pdf. Last accessed 3/12/13.

24. **Smith DE, Wesson DR, Sabnani SA.** Benzodiazepine and Other Sedative-Hypnotic Dependence. In *Gabbard's Treatments of Psychiatric Disorders Fourth Edition.* Gabbard G. ed. Arlington, VA: American Psychiatric Publishing, 2007:211-215.

25. **Randall, L.** Benzodiazepine Taper Protocol. Glass Substance Abuse Programs, Inc. Baltimore, MD: 2010.

26. **Currens M, Hayes M.** Outpatient benzodiazepine detoxification protocol. Personal Communication. Sept 24, 2012.

27. **Denis F, Fatseas M, Lavie E, Auriacombe M.** Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings.. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005194. DOI: 10.1002/14651858.CD005194.pub2

28. **Crockford D, White WD, Campbell B.** Gabapentin use in benzodiazepine detoxification. Can J Psychiatry 2001; 46(3):287.

29. **Croissant B, Grosshans M, Klein O, Mann K.** Scheme-Based Benzodiazepine Detoxification with Oxcarbazepine: A Case Report. Pharmacopsychiatry 2005; 38:222-223.

30. **Rickels K, Schweizer E, Garcia Espana F.** Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. Psychopharmacology 1999; 141:1-5.