



# **Management of Benzodiazepines in Medication-Assisted Treatment**

**Final Report on the Development of Clinical Guidelines**

**November 2013**

**Prepared for the City of Philadelphia Department of Behavioral Health and  
Intellectual disAbility Services**

**By the Institute for Research, Evaluation and Training in Addictions with Support  
from Community Care Behavioral Health Organization**



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**Management of Benzodiazepines in Medication-Assisted Treatment**  
Report to Philadelphia Department of Behavioral Health and disAbility Services  
November 2013

**EXECUTIVE SUMMARY**

In 2012, under contract with the Philadelphia Department of Behavioral Health and Intellectual disAbility Services (DBHIDS), and with additional support from Community Care Behavioral Health Organization (Community Care), the Institute for Research, Education and Training in Addictions (IRETA) conducted a project to determine best practice guidelines for the management of benzodiazepines in medication-assisted treatment (MAT). The project was conceived in response to frequent benzodiazepine use among individuals in MAT and a relative absence of research-based guidance on clinically effective treatment strategies for managing their use. Designed to be a resource for clinicians, these guidelines aim to distinguish areas of scientific/clinical consensus and areas where that does not exist. They are not intended to dictate clinical practice.

This report details the development of the project, methods, results and the final list of practice guidelines. IRETA utilized the RAND/UCLA Appropriateness Method to determine appropriate guideline statements based on the research and clinical experience of a panel of experts in the field. The two-round rating process and half-day expert panel meeting yielded 225 guideline statements, which IRETA distilled into a shorter list of guidelines for practitioners to use in real-world clinical settings.

Recommendations from the expert panel members include:

- CNS depressant use is not an absolute contraindication for the use of either methadone or buprenorphine in MAT, but is a reason for caution because of potential respiratory depression. Serious overdose and death may occur if MAT is administered in conjunction with benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol.
- Individuals who use benzodiazepines, even if used as a part of long-term therapy, should be considered at risk for adverse drug reactions including overdose and death.
- Many people presenting to services have an extensive history of multiple substance dependence and all substance abuse, including benzodiazepines, should be actively addressed in treatment.
- MAT should not generally be discontinued for persistent benzodiazepine abuse, but requires the implementation of risk management strategies.
- Clinicians should ensure that every step of decision-making is clearly documented.

During the half-day meeting in September 2012, expert panelists added an additional guideline statement: “Clinicians would benefit from the development of a toolkit about the management of benzodiazepines in methadone treatment that includes videos and written materials for individuals in MAT.” This recommendation is consistent with the overarching theme of patient education, which was discussed lengthily at the project’s Kickoff Conference in February 2012 and emerged as a significant issue in the final practice guidelines.

## INTRODUCTION

This report describes the project “Management of Benzodiazepines in Medication-Assisted Treatment,” which was conducted by the Institute for Research, Education and Training in Addictions (IRETA) under contract with the Philadelphia Department of Behavioral Health and disAbility Services (DBHIDS). The intent of this project was to:

- Identify current practices and outstanding questions regarding the safe and effective use of benzodiazepines in combination with opioid medications, particularly methadone.
- Utilize a panel of experts to compile best practice guidelines, based on clinical and research-based evidence, intended for use among Philadelphia-area MAT providers.
- Present these best practice guidelines to payers and providers in order to optimize care and enhance the effectiveness of the clinical treatment system.

## BACKGROUND

**Summary of Issue:** Published literature, treatment protocols and guidelines demonstrate variation and inconsistency in clinical practice. It is clearly documented that many people in MAT illicitly and licitly use benzodiazepines (Chen et al., 2011; Lintzeris and Nielsen, 2009; Nielsen et al., 2007; TIP 40; TIP 43), that some types of benzodiazepine use is linked to poorer outcomes among people receiving MAT (Brands et al., 2008; Ghitza et al., 2008), and that the combination of benzodiazepines and opiate substitutes risks morbidity and mortality due to impairment and overdose (Lintzeris et al., 2006; Paulozzi et al., 2009; Reynaud et al., 1998).

Worldwide, benzodiazepines are widely used and abused in conjunction with MAT. Estimates of people receiving methadone maintenance who abuse or are dependent on benzodiazepines range from 18 to 50% (Gelkopf et al, 1999; San et al., 1993; Miller & Gold, 1991; Darke, Top & Ross, 2002) and lifetime users of benzodiazepines are estimated to be between 66 and 100% of the global methadone maintenance population, with similar proportions reported in buprenorphine patient populations (Lintzeris & Nielsen, 2010).

Two Pennsylvania counties, Allegheny and Philadelphia, show high rates of concurrent benzodiazepine and opioid use among enrollees in their managed Medicaid programs. Between 2009 and 2011, data from Community Care Behavioral Health (CCBH) shows an average of almost 36% of methadone patients were also receiving benzodiazepine prescription in Allegheny County (Schuster, 2012). This does not include individuals receiving methadone who are using benzodiazepines illicitly without a prescription. CCBH found a total of 45.9% of methadone clients during that period received concurrent prescriptions for benzodiazepines and/or opiates. In a similar study, in July

2010, data from Community Behavioral Health (CBH) in Philadelphia County indicated that 45.6% of methadone clients were receiving prescriptions for benzodiazepines or opiates (Hurford 2012).

In 2012, DBHIDS characterized benzodiazepine abuse in MAT programs as a long term problem that seemed to be expanding in severity and scope, whose impact played out on three levels:

1. For the *person* receiving care, where treatment and recovery issues have often been in conflict;
2. For the *providers* treating opiate dependence, where there has been an ongoing struggle to address the disease of addiction and manage risk; and
3. For the *payer/regulator*, where there has been a lack of clarity about how to authorize services for those chronically engaging in illicit drug use in MAT

Given the prevalence of concurrent use, there is surprisingly little scientific research on clinical practices to manage the use of benzodiazepines and opioid substitutes concurrently (Linterzeris & Nielsen 2010). Available scholarly literature points to correlations between benzodiazepine use and poor treatment outcomes in MAT, but rarely examines:

1. Effective methods at a practitioner-level to reduce or manage benzodiazepine use in MAT; or
2. Effective interventions at a payer-level to reduce the frequency of concurrent use of benzodiazepines in MAT

Existing guidelines that address issues of benzodiazepine use in MAT include:

- AAAP Draft Guidelines (Unpublished, 2010)
- [Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol \(TIP\) Series 40. DHHS Publication No. \(SMA\) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration](#)
- [Center for Substance Abuse Treatment. Detoxification and Substance Abuse Treatment. Treatment Improvement Protocol \(TIP\) Series 45. DHHS Publication No. \(SMA\) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration \(2006\)](#)
- [Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol \(TIP\) Series 43. DHHS Publication No. \(SMA\) 05-4048. Rockville, MD: Substance Abuse and Mental Health Services Administration \(2005\)](#)
- [Ford, C., Roberts, K., & Barjolin, J. \(2005\). Guidance on prescribing benzodiazepines to drug users in primary care. Substance Misuse Management in General Practice](#)
- [Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence, World Health Organization \(2009\)](#)
- [Lintzeris N, Nielsen S. \(2010\) Benzodiazepines, methadone and buprenorphine: interactions and clinical management. \*Am J Addict.\* 19\(1\):59-72](#)

- [Operational guidelines for the treatment of opioid dependence: Management of opioid dependence in the South-East Asia Region](#) (2008)
- [PCSS-B Guidance, Topic: Management of psychiatric medications in patients receiving buprenorphine/naloxone](#)
- [Practice Guideline for the Treatment of Patients with Substance Use Disorders, Second Edition, American Psychiatric Association](#) (2006)
- [VA/DoD Clinical Guidelines for Management of Substance Use Disorders](#) (2009)

Most current guidelines comment on the dearth of research literature on the effectiveness of clinical practices to manage benzodiazepines in MAT.

***Development of Project:*** In March 2011, Roland Lamb, Director of the Office of Addiction Services at the Department of Behavioral Health and disAbility Services (DBHIDS) in Philadelphia County, contacted James Schuster, M.D., M.B.A., Chief Medical Officer of Community Care Behavioral Health (CCBH) and Michael Flaherty, PhD, formerly of the Institute for Research, Education and Training in Addictions (IRETA), about their interest in the development of best practice guidelines for the management of benzodiazepines in MAT programs, focusing on methadone treatment.

From 2010-11, Dr. Schuster had overseen a joint project with IRETA utilizing the RAND/UCLA Appropriateness Method to develop best practice guidelines for the use of buprenorphine by gleaning from the combined knowledge of a panel of content experts. The same methodology appeared useful for the current set of clinical questions, for which no guidelines are readily available for practitioners to reference.

Mr. Lamb wanted to generate a Pennsylvania-specific perspective on standards around the management of benzodiazepines, particularly for Opioid Treatment Programs (OTPs). He and Trusandra Taylor, MD, Medical Director for ACT2 of JEVS Human Services, had spoken extensively about “how to serve people and manage medication,” instead of “managing people and serving them medication” and their mutual concern about variation among area OTPs in the management of problems related to use of benzodiazepines. Mr. Lamb and Arthur Evans, PhD, Commissioner of DBHIDS, saw a need for practice guidelines that “fit into our vision and values so we can better serve a population that need to be better served” (Lamb, 2012, Kickoff Conference).

Dr. Evans, whose clinical background includes methadone treatment, recalled, “A problem that bedeviled us back fifteen years ago was people who continued to use other substances. Fifteen years later, I don’t think that that has changed a whole lot. It’s a really big challenge for us. Our evidence base for how to address this problem hasn’t advanced as well as we’d like” (Evans, 2012, Kickoff Conference). DBHIDS committed to bringing together a panel of experts in the field, along with a broad base of providers in the CBH system, to consider “how we can address this issue in the absence of strong empirical support for what to do” (Evans, 2012, Kickoff Conference).

### *Purpose of the Guidelines*

Recognizing a need for a more uniform approach to the treatment of people who use benzodiazepines in MAT, DBHIDS sought to develop a set of best practice guidelines which would serve as a resource for clinicians. They were designed to distinguish areas of scientific/clinical consensus and areas where that does not exist.

As the Philadelphia project was conceived and planned, simultaneous activities were taking place at a national level. A roundtable session at the American Association for the Treatment of Opioid Dependence (AATOD) conference in April 2011 addressed this issue and there was a CSAT consensus panel assembled to offer guidance on benzodiazepine use in OTPs, though the subject was subsequently broadened to include the use of all psychotropic drugs in methadone treatment.

## **METHODS**

***Kickoff Conference:*** A one-day kickoff conference for this project, entitled “Management of Benzodiazepines in Medication-Assisted Treatment” was held on February 9, 2012 at the College of Physicians in Philadelphia, PA. The conference was sponsored by IRETA, DBHIDS, CCBH, UPMC and SAMHSA.

Representatives from DBHIDS, directors of methadone programs across Pennsylvania, and stakeholders throughout the region were invited to attend. Presenters addressed the following topic areas: “Rates of Benzodiazepine Use in Medication-Assisted Treatment in Pennsylvania and Nationally,” “Settings and Coordination of Care,” “Drug Interactions,” “Risk Management and Patient Education,” and “Development of Clinical Guidelines.”

Presenters included individuals on the Expert Panel, as well as Matthew Hurford, M.D. Chief Medical Officer of CBH in Philadelphia and Dr. Schuster of CCBH in Pittsburgh. Presentations at the conference identified topics that would later be addressed by the experts through the course of the project. Conference attendees also raised relevant practice issues, such as the availability of inpatient facilities for detoxification and the importance of treatment with a recovery-orientation. The program from the kickoff conference is included in Appendix 1.

***RAND/UCLA Appropriateness Method:*** The RAM was developed in the 1980s to assist in identifying the overuse or underuse of medical procedures. The unique methodology combines the best available scientific evidence with the collective judgment of experts to yield statements regarding the appropriateness of a given clinical practice (RAND, 2001). It is ideal for examining procedures that are



associated with substantial morbidity and/or mortality and procedures whose use is controversial, and therefore highly appropriate for addressing the management of benzodiazepines in MAT.

**Expert Panel:** Potential expert panel members were compiled collaboratively by DBHIDS, IRETA and other stakeholders. Expert panel members were invited via phone call and/or email to give a presentation at the kickoff conference and to participate as experts in the RAM process. Expert panel members were offered an honorarium for their participation in the project. The individuals who participated in the expert panel are listed in Appendix 3 with their biographical descriptions.

**Literature Review, Medical Advisors, and Development of Proposed Guidelines:** The initial review of the literature was conducted with the assistance of Community Care Behavioral Health and Dr. James Schuster. PubMed (MEDLINE) was the primary source for searching the published literature. The following MeSH term searches were conducted, with a filter for references within the past 10 years only.

- “benzodiazepines” AND “methadone”
- “benzodiazepines” AND “buprenorphine”
- “benzodiazepines” AND “naltrexone”

This initial search yielded approximately 370 references. The titles were scanned by two project team members for relevance to the project. About 100 abstracts were then reviewed, and 20 articles were selected to be included on a CD with other background materials and distributed to conference attendees.

Notably, only a few of these published articles offered significant clinical guidance with respect to the management of benzodiazepines in medication-assisted treatment. One example was Lintzeris and Nielsen, 2010, which did include a lengthy section on “Implications for Clinical Practice” that influenced the development of the proposed guidelines. Other than these exceptions, the literature review revealed a gap in the published literature with respect to findings that would inform clinical decisions on this topic.

In addition to the published literature, as noted above, an internet search was performed for any existing clinical guidelines addressing the management of benzodiazepines in MAT. Several documents were discovered and are discussed in the Background Paper (see Appendix 4). Prior to the conference, expert panel member Peter Cohen, MD, compiled a document summarizing several sets of existing guidelines addressing the management of benzodiazepines in MAT, including two sets of WHO Guidelines, SMMGP, Practice Guidelines from APA, PCSS, and relevant titles from the TIP series. While the original sources were comprehensively reviewed during the drafting of the proposed

guidelines, the summary compiled by Dr. Cohen served as an additional guiding document for the project.

With over 25 years experience as a medical director in OTPs, Dr. Taylor initially assumed the role of the medical advisor for the project. She was joined by Carl R. Sullivan, MD, professor, vice-chair, and director of training at the West Virginia University School of Medicine, director of a buprenorphine program at Chestnut Ridge Center in Morgantown, WV, and who served as an expert panelist in the CCBH buprenorphine practice guideline project. Dr. Sullivan's experience as a buprenorphine prescriber complemented Dr. Taylor's experience as medical director for ACT2 JEVS Human Services. Dr. Sullivan shared the "Draft AAAP Guidelines" from 2010 with the project team, another key document source.

During the planning process, DBHIDS expressed a desire that the guidelines be consistent with their practice guidelines. Thus, the organizing principle of "a recovery-oriented approach to treatment recognizing risk management considerations" was adopted and woven throughout the statements.

The proposed guidelines were initially developed around two hypothetical scenarios: a) a person using benzodiazepines seeking MAT and b) a person in MAT seeking benzodiazepines.

**Round 1 Ratings:** Round 1 Rating forms were distributed to members of the expert panel on August 24, 2012, accompanied by a Background Paper (See Appendix 4) with supporting documentation for the statements and Instructions for the Rating Process, which included language about numerical ratings and appropriateness. The rating instructions read:

"Just because we propose a guideline does not mean it is valid. We define a guideline statement to be valid if:

- Adequate scientific evidence or professional consensus exists to support a link between the performance of care specified by the guideline, and the accrual of health benefits to patients with opioid dependence (e.g. physical, mental, social);
- A physician or payer with significantly higher rates of adherence to a guideline would be considered a higher quality provider;
- A majority of factors that determine adherence to the guideline are under the influence of the physician or health plan (or are subject to influence, such as smoking cessation).

We ask you to rate the validity of the draft guidelines on a 1-9 point scale.

Validity:

- 1 = Definitely not valid
- 5 = Uncertain or equivocal validity
- 9 = Definitely valid

In this type of study, we have generally defined guidelines that the group rates 7 or higher as valid.”

The image shows a rectangular form with a title bar at the top containing the word "Validity". Below the title bar, the text "Response (1-9):" is centered. Underneath this, there are nine radio buttons labeled "1" through "9" in a horizontal row. At the bottom of the form, there is a line of text that reads: "Instructions: Please rate each guideline statement on a scale of 1 (least valid) to 9 (most valid) and provide comments if desired."

**Figure 1. Example of rating scale seen in the Round 1 Rating Form.**

By September 18, eight expert panelists had returned Round 1 rating forms. IRETA analyzed the round 1 data and classified each statement according to the RAND/UCLA Appropriateness methodology.

**Expert Panel Meeting:** The expert panel meeting was held on September 27, 2012 from 26 pm via webinar.

In advance of the meeting, IRETA worked with DBHIDS to organize a slideshow presentation of the round 1 rating results and ensure that it addressed the Department’s priorities. The presentation was organized as follows:

- I. Benzodiazepines in MAT Context: “Who and When?”
- II. Benzodiazepines in MAT Methods and Strategies: “How?”
- III. Alternatives to Benzodiazepines
- IV. Additional Comments
- IV. Next Steps

Matthew O. Hurford, MD, Chief Medical Officer of CBH and Special Advisor to the Commissioner of DBHIDS, served as the expert panel meeting chair. IRETA staff, Mr. Lamb and DBHIDS staff, Dr. Schuster and Marge Hanna from CCBH, and medical advisor Dr. Taylor attended the meeting but did not participate.

During the meeting, experts identified and jointly modified guideline statements that, as phrased, did not pass muster. These modified guideline statements were included in the Round 2 Rating Forms.

**Round 2 Ratings:** Round 2 Rating forms were distributed on October 1, 2012 along with the following instructions:

“Expert Instructions: Please re-rate the guidelines in the "rating" column, where 1=highly inappropriate and 9=highly appropriate. Feel free to include comments. Note: The original version of the guideline statements are bolded. Potential modifications to statements (based on the panel meeting 9/27/12) follow some of the original statements (e.g. 1.04a, 1.04b, etc).”

By October 26, the eight expert panelists had returned Round 2 ratings. IRETA analyzed the Round 2 data and classified each statement according to the RAND/UCLA Appropriateness methodology.

**Development of Final Guidelines:** To compile final guidelines, IRETA drew from the wide range of information generated throughout the course of the project, including:

- Quantitative data from round 1 and round 2 of the RAND/UCLA rating process
- Qualitative data from round 1 and round 2 of the RAND/UCLA rating process
- Qualitative data from the expert panel meeting
- Input from medical advisors
- Statements and values from Philadelphia DBHIDS’ practice guidelines

Because DBHIDS expressed a desire throughout the process to solicit feedback from CBH providers (in accordance with their Practice Guidelines’ Core Values #2: Community Inclusion, Partnership & Collaboration and #7: Partnership & Transparency), IRETA packaged a final set of best practice guidelines with an eye toward coherence and utility at the practitioner-level.

The original statements were broken out into two hypothetical scenarios: a) a person using benzodiazepines seeking MAT and b) a person in MAT seeking benzodiazepines. The process revealed that these distinctions didn’t prove useful in real world settings, so IRETA simplified the structure of the guidelines.

The RAND/UCLA Appropriateness Method also generated a significant number of appropriate guideline statements: 225 in total. This was an expected product of the process, where individual elements of treatment had been pulled out one-by-one for experts to rate. To package a product for DBHIDS staff and CBH providers, IRETA collapsed many statements deemed appropriate into general categories (e.g. MAT Assessment, Addressing Benzodiazepines, Risk Management, and Special

Circumstances).

## RESULTS

***Kickoff Conference Outcomes:*** Over 150 individuals attended the one-day kickoff conference in February. Although the majority of the attendees were from the Philadelphia area, a number of states were represented among the stakeholders, including Pennsylvania, Maryland, New York and West Virginia.

All the attendees were asked to complete a Training Satisfaction Survey. 131 respondents returned these surveys, resulting in an approximately 87% response rate. Respondents were 55% female and 73% were white (23% black, 4% other). Respondents were relatively well educated; 67% held Master's or Doctoral degrees, and 21% held Bachelor's degrees. A wide range of job areas were represented, including physicians (24%), addiction professionals (24%), public administrators (11%), and counselors (10%). Nurses, social workers, and recovery specialists also were represented, resulting in a truly multidisciplinary exchange.

With respect to the overall session, virtually all of the respondents were "very satisfied" or "satisfied" with the overall quality of the training, information provided, and the training materials (97% each). Additionally, the majority of respondents "strongly agreed" or "agreed" that they expected to use the information gained (97%), that the instructor was knowledgeable about the subject matter (98%) and that they would recommend the training to a colleague (97%). When asked an open-ended question about which aspect of the training was most useful, responses included "the diversity of opinions regarding the process of best practice," "risks and benefits (of benzodiazepines in MAT)," and "outstanding ethics of the treatment providers/presenters."

The training satisfaction data demonstrate that the conference was extremely well received. The information from the presentations was continually reviewed during the drafting of the proposed clinical guidelines. In addition, as a result of the open discussion at the end of the conference, the decision was made to provide more information about the next steps of the clinical guideline development, which was accomplished via webinar in April 2012 (See Appendix 5). This discussion also contributed to the decision to solicit as much feedback as possible from the CBH community of practitioners throughout the process.

### ***RAND/UCLA Appropriateness Method Outcomes***

***Round 1 Ratings:*** A total of 266 proposed guideline statements, divided into 13 guidelines covering aspects of assessment, initiation, treatment, and withdrawal, were included in Round 1. Of these, 220 guideline statements were deemed "appropriate" by the panel. This means that the median rating was

in the 7-9 range, and no more than two experts rated the statement outside that range. The remaining 46 statements fell into the “uncertain” category. This means either the median was in the 7-9 range, but three or more experts rated the statement outside this range (34 statements), OR that the median was in the 4-6 range, the middle of the scale (12 statements). Notably, none of the initial proposed guideline statements were rated as clearly “inappropriate” by the panel. This would be indicated by a median in the 1-3 range, and no more than two experts rating the statement outside that range.

The statements in the “uncertain” category were not evenly distributed among the subgroups of proposed guidelines. That is, certain subgroups of statements exhibited greater levels of disagreement or uncertainty among the experts. For example, two of the 13 guidelines dealing with maintenance dosing of benzodiazepines had the highest proportion of “uncertain” statements. Specifically, 57% of the statements about whether to provide a maintenance dose were in the uncertain category, and 71% of the statements about how to provide that maintenance dose were in the uncertain category.

General areas of dispute from Round 1 Ratings included the following:

- Alternatives to benzodiazepines, especially for insomnia
- Individuals with long term controlled benzodiazepine use as MAT candidates
- Whether an individual should detoxify or taper from benzodiazepines before MAT
- Whether a physician should tell an individual to self-taper from benzodiazepines
- Whether a person in long term recovery on MAT should receive a short term benzodiazepine prescription
- The best types of benzodiazepine to use concurrently with MAT
- Whether a person should ever receive a maintenance dose of benzodiazepines
- What is an advisable benzodiazepine taper regimen/plan

These 46 statements were incorporated into the PowerPoint presentation for discussion during the expert panel meeting (See Appendix 6).

***Expert Panel Meeting:*** Discussion during the expert panel meeting yielded important insights into the proposed clinical guidelines that were in the “uncertain” category, and also into the management of benzodiazepines in MAT overall. Two important issues came to light that required modification of the final guidelines:

*The panel meeting revealed that the ability to coordinate care depended heavily on the treatment setting.* The panel was hesitant to evaluate statements regarding clinical practices which are limited by regulation or to specific clinical settings. For example, some statements addressed recommendations for onsite concurrent dosing of methadone and benzodiazepines. However, concurrent dosing is not permitted in many Pennsylvania OTPs because of state regulatory

requirements regarding the dispensing of controlled substance medications. Other statements regarding best clinical practices assumed clinical settings that were ideal rather than typical. For example, some statements evaluated the appropriate length of time to observe an individual after MAT dosing. However, most clinical settings would be logistically unable to adhere to a guideline recommending observation at all, much less for a recommended length of time.

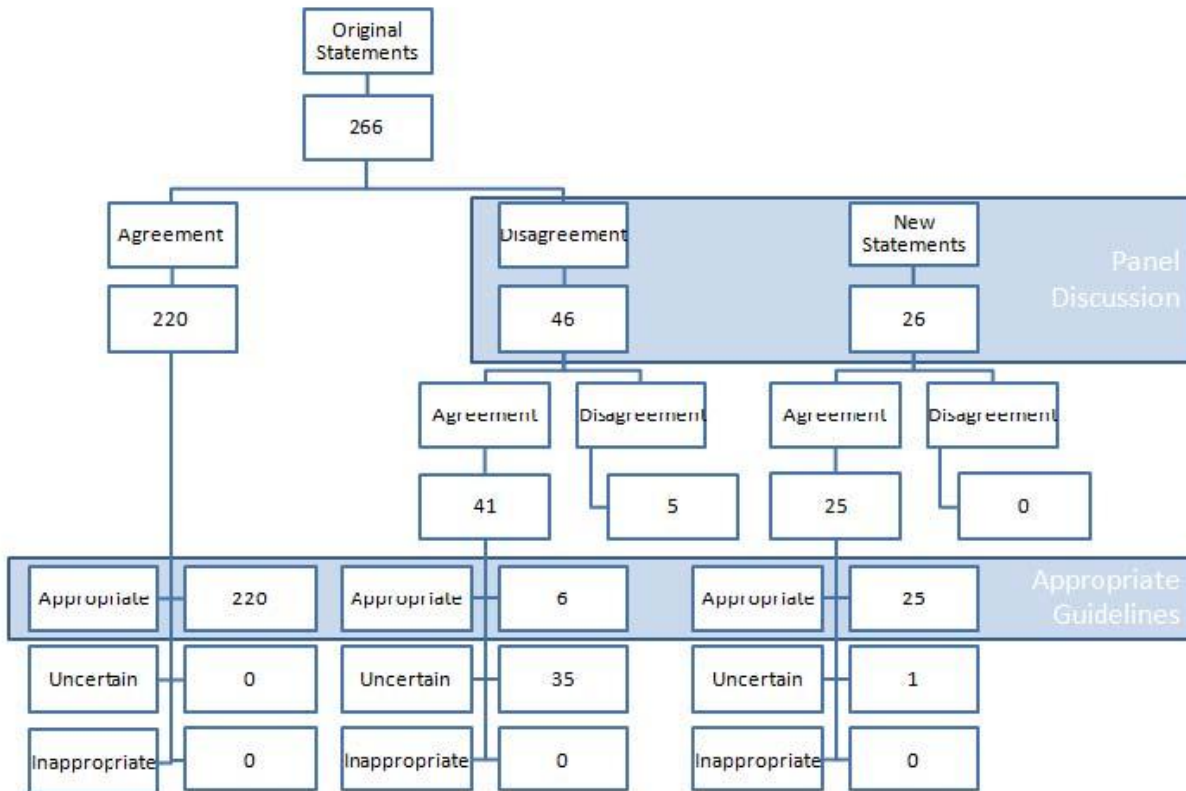
*The expert panelists discussed guidelines containing specific pharmacological treatment for mental health disorders and suggested that they exceed the original scope of the project.* For tapering or concurrent use of benzodiazepines in MAT, diazepam and clonazepam were suggested in existing guidelines and therefore in the initial proposed guideline statements. Experts agreed that neither is appropriate in certain scenarios. Although the expert panel as a whole was hesitant to propose specific benzodiazepines to be included in the guidelines, they generally concluded that alprazolam should be avoided. Likewise, the expert panel preferred to avoid designating specific non-benzodiazepine alternatives for depression, anxiety, and insomnia.

During the course of the expert panel meeting, several guideline statements were modified, or alternatives were generated for rating during Round 2. In total, 26 guideline statements were added to the 46 “uncertain” statements from Round 1. On the other hand, 5 guidelines having to do with maintenance dosing were dropped by a unanimous vote of the expert panel.

**Round 2 Ratings:** As a result of the Expert Panel meeting, a total of 67 guideline statements were rated during Round 2. Similar criteria were utilized to categorize statements as “appropriate,” “uncertain” or “inappropriate,” with one exception. Several of the ratings were missing from the Round 2 data, so that many of the statements had only 6 or 7 raters rather than 8. Thus a more conservative approach was taken, where a statement was rated “uncertain” if the median was in the 7-9 range and more than one expert (rather than two) rated it outside of this range.

Of the 67 statements rated during Round 2, 36 were in the “uncertain” category and 31 were in the “appropriate” category. However, the distribution of ratings between statements from Round 1 and those generated during the expert panel meeting were quite different. Of the 41 statements that were in the “uncertain” category after Round 1 (not including the 5 that were dropped from further consideration), 35 statements (85%) remained in the uncertain category, and 6 statements (15%) were newly categorized as “appropriate”. In contrast, 25 of the 26 statements (96%) that were generated during the expert panel meeting were rated as “appropriate” and only one (3.10a) was in the “uncertain” category. This is unsurprising due to the fact that the experts collaborated on the creation of the 26 additional statements during the meeting.

In summary then, a total of 251 statements were in the “appropriate” category at the end of the RAND/UCLA Appropriateness Method process. These statements were considered in the development of the Final Guidelines as described below.



**Figure 2. Summary of results from the RAND/UCLA Appropriateness Method ratings for Round 1 and Round 2.**

See Appendix 7 for the complete chart of all guideline statements discussed above.



**Final Guidelines:** The guideline statements that follow emerged from the RAND/UCLA Appropriateness ratings, as well as feedback from the experts throughout the process. They are organized into categories:

- General guidelines
- Assessment for MAT
- Addressing benzodiazepine use
- MAT for patients with concurrent benzodiazepine use
- Noncompliance with treatment agreement
- Risk management/Impairment assessment
- Special circumstances

Guideline statements from Round 1 and Round 2 that address alternative treatments for insomnia, anxiety and depression were omitted, as they exceeded the scope of the project.

Guideline statements from Round 1 and Round 2 that address concurrent dosing and prescription from the same physician were removed, as the experience of practitioners in OTPs in Pennsylvania is that patients in OTPs commonly receive prescription for benzodiazepines from physicians outside of the OTP. Thus, guidelines suggesting concurrent dosing did not address the majority of clinical scenarios faced by practitioners in Pennsylvania OTPs.

Duplicative statements have been removed and the guidelines have been edited for brevity and readability.

### **General Guidelines**

- CNS depressant use is not an absolute contraindication for either methadone or buprenorphine, but is a reason for caution because of potential respiratory depression. Serious overdose and death may occur if MAT is administered in conjunction with benzodiazepines, sedatives, tranquilizers, anti-depressants, or alcohol.
- People who use benzodiazepines, even if used as a part of long-term therapy, should be considered at risk for adverse drug reactions including overdose and death.
- Many people presenting to services have an extensive history of multiple substance dependence and all substance abuse, including benzodiazepines, should be actively addressed in treatment. MAT should not generally be discontinued for persistent benzodiazepine abuse, but requires the implementation of risk management strategies.
- Clinicians should ensure that every step of decision-making is clearly documented.
- Clinicians would benefit from the development of a toolkit about the management of benzodiazepines in methadone treatment that includes videos and written materials for

individuals in MAT.

## **Assessment for MAT**

*Given the prevalence of benzodiazepine use among the MAT population, MAT assessment should include careful examination of benzodiazepine use and education about benzodiazepine use.*

Generally:

- Conduct a full assessment according to best practices outlined in the TIP 40 (for office-based MAT), TIP 43 (for OTPs), VA/DoD (for individuals in the VA/DoD medical system), and other practice guidelines as applicable.
- As outlined in the TIP 43, VA/DoD guidelines and elsewhere, screening and assessment should include a person's prescription drug and over-the-counter medication use, history of co-occurring disorders, a mental status assessment, and an initial drug screen that identifies benzodiazepines.

Patient education:

- One of the goals of the initial MAT assessment is education. The clinician should use the screening and assessment process as an opportunity to communicate essential information about MAT, including treatment requirements, addiction as a brain disease, and a discussion of the benefits and drawbacks of MAT, to help applicants make an informed decision about treatment. The risks of benzodiazepine use may be folded into this educational component of assessment for MAT.
- Provide education regarding the potential adverse consequences of benzodiazepine use that includes:
  - "Immediate" effects of benzodiazepine co-intoxication including motor vehicle accidents and risk of overdose death.
  - Risk of depression and suicide.
  - The potential for a protracted, uncomfortable withdrawal syndrome that can last for months to years. Long-term disturbances in sleep and mood, increased risk of hip fracture, emotional blunting, and substantial and growing literature that suggests long-term use of benzodiazepines (especially large doses) leads to cognitive decline.
  - Research on benzodiazepines' negative effects on MAT treatment outcomes.

## Addressing Benzodiazepine Use

*If assessment for MAT shows benzodiazepine use, determine its context and create a plan to address it.*

Generally:

- Individuals must be agreeable to engage in a plan to address their benzodiazepine use before beginning MAT.
- Uncontrolled use of benzodiazepines in a person presenting for MAT with methadone or buprenorphine is contraindicated. It presents an extremely high risk for adverse drug reaction involving overdose and/or death during the induction process.
- CNS depressant use is not an absolute contraindication for either methadone or buprenorphine, but is a reason for caution because of potential respiratory depression. Serious overdose and death may occur if MAT is administered in conjunction with benzodiazepines, sedatives, tranquilizers, anti-depressants, or alcohol.
- Individuals who use benzodiazepines, even if used as a part of long-term therapy, should be considered at risk for adverse drug reactions including overdose and death.
- Many people presenting to services have an extensive history of multiple substance dependence and all substance abuse, including benzodiazepines, should be actively addressed in treatment. People who have a history of benzodiazepine abuse should not be disallowed from receiving previously prescribed benzodiazepines, provided they are monitored carefully and have stopped the earlier abuse.
- If a person presenting for MAT will not allow a clinician to coordinate care, he or she may not be appropriate for methadone and/or buprenorphine.

Coordination of Care:

- Obtain information from the prescribing physicians regarding diagnosis, reason for prescribing benzodiazepines, documentation of prescription, physician-observed aberrant behavior, adverse reactions to benzodiazepines, the individual's prior experience (failure, success, inadequate therapeutic trial) with non-benzodiazepine medications or non-pharmacological therapy to address symptoms.
- Clinicians who take on the care of individuals who state that they have been maintained on benzodiazepines should be sure to confirm this history by communicating with the previously prescribing physician.

Determine level of care to address benzodiazepine use in the context of MAT:

- Clinicians should follow PCPC criteria to guide the appropriate level of care for benzodiazepine taper/detoxification.
- Consider:
  - The policy of the treatment setting on concurrent benzodiazepine use with MAT.

- The individual's transportation to the treatment setting and whether he or she will be driving alone.
- The individual's recovery environment, including his or her social network, those living in the residence, stability of housing.
- The individual's experience with tapering/withdrawal in the past, including managing cravings and adverse medical events, such as seizures.
- Physicians should not abruptly cease high-dose benzodiazepines due to the risk of seizures.
- Tapering of benzodiazepines in outpatient settings may be attempted in patients without complications of overdose, seizures, or co-morbid medical or psychiatric disorders.
- Some people may be able to accomplish a self-taper from benzodiazepine, and this should be offered as an option. Frequent monitoring and contingency management models may be considered in this case.
- If applicable, the MAT clinician should contact the prescribing physician requesting that the individual be weaned with instructions and information about the mutually-decided upon goals and timeline of the taper. The prescribing physician should be willing to taper the patient.
- Detoxification in inpatient settings is indicated for pregnant patients.
- Detoxification in the inpatient setting is preferable in patients with overdose, seizures, comorbid medical or psychiatric disorders, as well as patients on high doses of benzodiazepines over a long period of time.
- Detoxification in inpatient settings may be necessary for patients who have had unsuccessful attempts to taper in outpatient settings.
- Depending on capacity, it may be more appropriate for clinical settings to choose not to induct a person in MAT until benzodiazepine use has ceased and not manage a patient's taper from benzodiazepines during MAT induction. This person may be more appropriate for inpatient detoxification.
- It may be appropriate for a clinician to taper benzodiazepines in an outpatient setting if there are no available inpatient facilities.

#### Patient Education:

- Education should emphasize that symptoms of benzodiazepine withdrawal may persist for weeks after tapering is complete.
- Education should emphasize that symptoms of benzodiazepine withdrawal may persist for weeks after detoxification is complete.

#### **MAT Induction**

*For anyone in MAT, the induction period carries with it the most risk of harm. Extra care is required when inducting a person who uses benzodiazepines.*

Generally:

- Physicians should follow best practice (TIP 43 and/or TIP 40) dosing and timing protocols for induction of MAT.
- Clinicians should be aware when inducing a person onto methadone that the long half-life of methadone, possible synergistic effects and drug-drug interactions may alter methadone metabolism.
- Clinicians should note that highest risk of overdose or death is in first two weeks; therefore people should be monitored extremely closely during the first two weeks of induction.
- High variation among individuals in MAT and unverifiable information warrants highly individualized care in dosing and enhanced monitoring for first five days or until stabilization.
- People who receive/use CNS depressants may need to be inducted on methadone at a lower dose than those who do not receive/use CNS depressants.
- People should receive a daily directly-observed administration of methadone dose during the induction period until stabilization.

Patient Education:

- Clinicians should request that individuals sign an informed consent form before initiating MAT agreeing that if he or she appears impaired, the treatment center has permission to notify a family member and refuse medication.
- Inform individuals receiving MAT of the treatment setting's policy on impairment. Provide education about impairment, especially about drug-to-drug interactions. Give them sources of information and encourage them to ask questions.
- Individuals should be prohibited from driving themselves to the treatment setting during MAT induction until they are stabilized.

### **MAT for people with concurrent benzodiazepine use**

*A person's use of benzodiazepines may change over time, or even from visit to visit. Effective, individualized treatment includes ongoing communication, appropriate dosing, and careful monitoring.*

Generally:

- For a person with concurrent benzodiazepine use, following best practices outlined in TIP 43, MAT clinician should provide treatment appropriate for a patient in the stabilization phase of MAT.
- A contingency management framework can be incorporated into treatment conditions.
- Avoid prescribing alprazolam to individuals receiving methadone.

### Dosing:

- Ensure adequate, appropriate MAT dose. ☑ Methadone dosing decisions should be individualized; dose should not be changed for punitive reasons but rather on clinical grounds.
- Take-home doses should be guided by the CSAT 2008 “Dear Colleague” letter, which states that “8-point criteria must be considered and documented for patients even for clinic closures” but “the assessment does allow for a physician to use clinical judgment in determining whether a patient is responsible in handling a take home dose(s) and whether the rehabilitative benefit the patient would gain from reduced attendance for directly observed dosing outweighs the potential risk of diversion.”

### Tapered withdrawal protocol:

- Clinicians and individuals in MAT need to mutually agree on a period of time they envision tapering the patient from benzodiazepines. A longer and slower detoxification is more successful for most, but not longer than six months.
- Benzodiazepines should be tapered no faster than 10-15% at a time.
- It is advisable that people using or abusing multiple benzodiazepines should have their prescriptions converted to a single benzodiazepine for the purpose of simplifying the taper. Very rarely, if the person in MAT is very anxious, converting to one benzodiazepine can be done over 1-2 weeks.
- If possible, a person who is tapering from benzodiazepines should be seen daily. A higher level of care may be necessary for a patient who is tapering than one who has been detoxified from benzodiazepines.
- Close monitoring of adherence to benzodiazepine tapering protocol with observed urine drug screens is indicated.
- Practice continuous monitoring of symptoms during the taper, and alternative treatments to address these symptoms.
- If the physician is prescribing benzodiazepines while the individual in MAT is tapering and there is a recurrence of lost prescriptions or the individual runs out early too often, discontinue benzodiazepine prescription.
- People should be discouraged from stopping MAT before tapering from benzodiazepine is complete.

### Patient Education:

- Frequently re-evaluate the treatment agreement with the individual receiving treatment.
- Clinicians should offer referrals and information regarding twelve-step and other mutual aid groups available within the region.
- Provide education to address the use of benzodiazepines that incorporates a stages of change

model, motivational enhancement, and a recovery-orientation.

- For all people in MAT, reductions and withdrawal from benzodiazepines should regularly be proposed.

Monitoring:

- If applicable, work closely with the physician who prescribes benzodiazepines.
- Undertake regular monitoring, including clinical review and urine testing.
- Regularly utilize information from prescription drug monitoring programs.

### **Noncompliance with treatment agreement**

*Individuals in MAT may deviate from the treatment agreement. Clinical judgment is required to address noncompliance.*

Generally:

- MAT should not generally be discontinued for persistent benzodiazepine abuse, but requires the implementation of risk management strategies.
- Retain people in a system of care when possible.
- Physicians have some responsibility to reduce diversion.

In case of noncompliance:

- If an individual uses benzodiazepines illicitly while in MAT, change to daily dose of MAT until the benzodiazepines clears.
- Limit or cease all take-home MAT doses if a person uses benzodiazepines illicitly while in MAT.
- Consider providing increased intensity of psychosocial treatment.
- Consider a higher level of care with the goal of eliminating aberrant behavior so that the individual may safely and successfully continue MAT with methadone or buprenorphine.
- If efforts are unsuccessful in elimination of the aberrant behavior that presents serious risks for patient safety, non-MAT alternative therapy may be indicated and advised.

### **Risk Management/Impairment Assessment**

*Clinicians should use caution with people in MAT who use benzodiazepines because they have increased risk for adverse drug reactions including overdose and death.*

Generally:

- The treatment setting should create an environment where all staff are involved in awareness of impairment. Receptionists and security personnel have opportunities to observe and

identify impairment. Dosing nurses and counselors are on the front lines of identifying impairment. Individuals in MAT themselves are underutilized resources in helping to identify others who are impaired or at risk.

- Assess everyone for impairment every time they appear for treatment.
- Routinely explore a person's transportation to receive MAT, where from and whether the patient drives alone. For people who drive long distances to the OTP, risk of loss is higher.
- Particular caution should be used when a benzodiazepine-dependent person on opioid substitution therapy has missed doses as such people may be at high risk for overdose.
- Clinicians should ensure that every step of decision-making is clearly documented.

#### Impairment Assessment Tools:

- Assessment tools include the Clinical Sobriety Checklist, Standardized Field Sobriety Testing, and DSM-IV diagnostic criteria for sedative, hypnotic or anxiolytic intoxication.
- If an individual appears clinically impaired, a validated instrument may be helpful for assessment, but should not replace clinical judgment.

#### In case of impairment:

- Always apply a no-tolerance policy for impairment.
- Identifying impairment is typically grounds to support refusing to medicate.
- If the individual has signed an informed consent form before initiating MAT, notify a family member and refuse medication if he or she appears impaired.
- If an individual presents for MAT and appears impaired, examine the MAT dose. A state of withdrawal can bring on impairment. He or she may not be receiving an adequate dose and may therefore be self-medicating.

### ***Special Circumstances***

#### **People in MAT seeking benzodiazepines**

*Giving benzodiazepine prescriptions to people in MAT is controversial. Guidelines specific to the practice of benzodiazepine prescribing in the context of MAT are listed below. Clinicians are advised to use recovery-oriented approaches to education and risk management approaches as detailed in the rest of the guidelines.*

#### Generally:

- People who are maintained on sedative medications, especially opioids, should only receive benzodiazepine prescriptions with extreme caution because of the potential for a fatal drug interaction.
- If a person is stable in long term recovery on MAT and experiences a major stressful event, a clinician may consider a short-term (i.e. 7-10 days) prescription for benzodiazepines to help



stabilize the patient but this treatment should not be considered first line.

- Individuals who claim that “nothing else helps” should have a careful evaluation for addiction. Physicians should be aware that the subjective nature of anxiety allows for dishonest presentations of symptoms. The claim that “nothing else helps” is often a direct demand for benzodiazepines from the physician. A reasonable response is a trial of psychotherapy and medications without addictive potential.
- Benzodiazepines should not be the first-line drug for any disorder.

Psychiatric disorders:

- Clinicians are advised not to use benzodiazepines to treat co-occurring psychiatric disorders.
- Clinicians are advised not to use benzodiazepines to treat co-morbid physical/medical disorder that may mask a person’s mental status symptoms for anxiety, depression, and/or insomnia.

Considerations:

- Consider individual’s past/current relationship with benzodiazepines.
- Think carefully about the goals the individual in MAT and the clinician hope to achieve before starting a prescription of benzodiazepine, even a short-term reduction.

Guidelines for benzodiazepine prescriptions:

- For people receiving methadone, physicians are advised to prescribe a benzodiazepine with a slow onset and long duration of action, at the lowest dose, and for the shortest duration possible.
- Document education and treatment decisions during the initiation of benzodiazepines.
- Avoid prescribing alprazolam to individuals receiving methadone.
- Benzodiazepines with substantially lower abuse potential (e.g. oxazepam, clorazepate) are strongly preferred over benzodiazepines with a rapid onset, such as diazepam and alprazolam, which should be avoided because of their abuse potential.
- Initiate short-term benzodiazepines with a prescription for no longer than one week.
- For a short-course of treatment, the benzodiazepine prescription should be for less than one month.

## **Benzodiazepine Maintenance**

*Benzodiazepine maintenance treatment is controversial. Current best practice guidelines are listed below.*

Considerations:

- Long-term maintenance of benzodiazepines is rarely indicated and should be avoided.
- Providing a maintenance benzodiazepine dose in the context of MAT is to be considered a last-resort option after other alternatives have been exhausted.
- One of the few who may benefit from a maintenance dose of benzodiazepine is a person who has long-term opioid and benzodiazepine abuse and is not able to stabilize on opioid substitution medication alone.

#### Non-MAT alternatives:

- It may be more appropriate for individuals maintained on benzodiazepines to consider non-methadone alternatives than those who are not maintained on benzodiazepines.
- Individuals should be willing to consider non-MAT alternative therapy for opioid dependence if maintained on benzodiazepines.

#### Guidelines for maintenance treatment:

- Physicians are advised to consider a consultation with a specialist in addiction medicine/psychiatry or utilize a mentor from the Physicians Clinical Support System (PCSS) before commencing a maintenance dose.
- People maintained on benzodiazepines should be monitored more closely than others in MAT.
- If maintained on benzodiazepines, it is strongly recommended that a single, long-acting benzodiazepine is used for people in MAT.

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