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MANITOBA OPIOID AGONIST THERAPY RECOMMENDED PRACTICE MANUAL

1.6 Managing Polypharmacy, Benzodiazepines, Alcohol, & Polysubstance Use in the Context of Opioid Agonist Therapy

GENERAL CONSIDERATIONS

Polypharmacy* and/or polysubstance use is common in patients with opioid use disorder and patients on opioid agonist therapy (OAT). It is the responsibility of the treating clinician(s), along with all members of the treatment team, to monitor clinical stability and safety on an ongoing basis. This includes screening for substance use that can increase the risk of harm for the patient and/or the community.

Prior to initiating OAT, the prescriber must collect a detailed history of the patient's use of other substances, including alcohol, nicotine, cannabis, prescription medications, over-the-counter medications (OTC), and illicit drugs. The prescriber must also review the patient's prescribing record (DPIN) to verify available prescription history.

It is imperative that the patient's pharmacy, primary care provider, psychiatrist and/or any other specialists involved in their care are notified of the plan to initiate OAT. This ensures that all relevant information is considered when managing medications and other substance use in patients on OAT. It also establishes a clear, mutual understanding regarding the future medication management plan between the OAT treatment team, the patient, and others involved. Ultimately, good communication facilitates patient safety. This is especially important for medications with psychoactive and/or sedating properties.

*For the purpose of this manual, **polypharmacy is defined as the concurrent prescribing of five or more medications with sedating and/or psychoactive properties**. Notwithstanding this definition, it is important to note that the inherent risks of polypharmacy also apply in situations where licit (e.g., alcohol and cannabis), or illicit drugs/prescription medications and/or over-the-counter medications with sedating and/or psychoactive properties, are combined with prescribed medications with similar properties. When prescribing OAT, it is important for the prescriber to educate patients regarding these risks on a regular basis. In this chapter, the authors will outline the risks and provide practical guidance on how to manage these risks.

The Office of the Chief Medical Examiner – Manitoba Data[1]

CPSM staff attend the monthly Adult Inquest Review Committee Meetings at the Office of the Chief Medical Examiner (OCME). At this meeting all unnatural deaths of adults between the ages of 18 and 65 are reviewed by an expert panel. CPSM conducts a detailed review of all deaths involving prescription medications, including buprenorphine/naloxone, methadone, and slow-release oral morphine (i.e., Kadian®). The review aims to understand the role that prescribing practices play in accidental overdose deaths. The program is educational and intended to promote quality improvement in prescribing, to ultimately enhance patient safety.

Several important themes have been identified from the review of cases involving prescription medications, including OAT, highlighted in the sidebar.

Additionally, the OCME death reviews indicate that certain combinations of prescription drugs increase the risk of death. Of particular importance, most opioid-related deaths can be attributed to one or more opioids combined with other drugs, often benzodiazepines and/or Z-drugs. The two drug classes that were the top contributors to opioid overdoses between 2014-2017, were benzodiazepines and antidepressants.

The leading prescription sedative-hypnotics contributing to deaths in Manitoba between 2016 and 2018 were alprazolam and zopiclone. Alprazolam has significant street value and has become a significant drug of abuse in Manitoba, along with gabapentin and diphenhydramine.

Lessons learned from Manitoba's provincial death data should transform prescribing practices. **The overall risk of polypharmacy, especially in the context of ongoing illicit substance use, often outweighs the benefit of individual medications.**

OCME Death Review Themes

- The largest category of overdose deaths involving prescription medications are accidental polypharmacy overdose deaths.
- Deaths involving polypharmacy most often involve prescriptions written by a single physician, filled at a single pharmacy.
- A smaller number of deaths involve multiple sedating prescription medications prescribed to the same patient by different physicians, filled at multiple different pharmacies (often including an opioid and one or more benzodiazepines/Z-drugs).
- OTC medication with sedating properties, used in combination with prescribed medications (often in polypharmacy situations as defined earlier), increases the risk of accidental overdose death.
- Diphenhydramine, a common ingredient in OTC medications, is of particular concern. Diphenhydramine contributed to twenty-one deaths in the first three quarters of 2020 alone.

Polypharmacy Risks

In addition to the above, polypharmacy is known to be associated with:

- Multiple drug interactions.
- **Additive adverse effects**, including memory impairment, falls, confusion, sedation, and additive respiratory depression/death.
- High doses of individual medication, further increasing the risk of diabetes mellitus, metabolic syndrome, and cognitive impairment.

It is important to note that there is very little evidence that combining agents from the same class increases efficacy (e.g., benzodiazepines, hypnotics, SSRI's). However, evidence does suggest that simplifying therapy without clinical deterioration is possible with medical supervision.

Local OCME findings are in keeping with the literature that demonstrates mounting evidence for the risks associated with prescribed sedative use along with OAT. Prescribed sedatives or psychoactive medications, such as benzodiazepines, Z-drugs, and pregabalin, were significantly associated with overdose deaths in patients on OAT (both methadone and buprenorphine), in a nation-wide 7-year Swedish study.[2] For patients on methadone maintenance, receipt of any prescription of a psychotropic drug (benzodiazepine, antidepressant, or antipsychotic) in the past year was associated with a twofold increase in the risk of opioid-related death, in a population-based 16-year study in Ontario.[3]

OAT Providers Must Manage Risks

OAT prescribers must be diligent in managing the risks of polypharmacy and polysubstance use in a patient population that already carries an increased risk of adverse outcomes.

While buprenorphine has a superior safety profile when compared to methadone, it is still important to recognize that psychoactive medications and/or illicit substances increase the risk of accidental overdose death. Review of prescribed and OTC medications, and screening for other substance use, is essential on intake and routine follow up to ensure that all relevant information is taken into consideration when managing medication regimens.

SPECIFIC CONSIDERATIONS

Recommendations for the management of psychoactive/sedating medications and other substance use, will be discussed under the following headings:

- An Approach to Polypharmacy in the Context of OAT
- Managing Prescribed and Illicit Benzodiazepine & Z-drug Use
- Managing Alcohol Use
- Managing Nicotine Use

- Managing Cannabis Use
- Managing Illicit Stimulant Use
- Managing Other Psychoactive Medication Use, both Prescribed and Illicit
    - Gabapentinoids
    - Muscle Relaxants
    - Quetiapine & Trazodone
    - Prescribed Stimulants
    - Antidepressants
- Managing Over-the-Counter Medication Use
- Other Substances to Consider

While the above categories are not an exhaustive list of possible prescription or illicit substances, they have been included for discussion due to their prevalence of use and associated safety risks in the context of OAT.

AN APPROACH TO POLYPHARMACY IN THE CONTEXT OF OAT

Create a List of Active Clinical Issues

To facilitate appropriate discussion and clinical decision making around medication management, the OAT clinician needs to determine the patient's current clinical needs, in order of priority. The comprehensive history and physical completed during the OAT intake process will assist in generating an **updated list of active clinical issues** that require management. Some issues may need to be addressed right away, some may need attention in the coming months, and some may be deferred for ongoing management by the patient's primary care provider or medical specialist.

Conduct a Detailed Review of DPIN Profile

A critical aspect of intake and assessment is a detailed review of the patient's medication record (DPIN). Ideally, a DPIN record including all medication entries over the preceding six months should be reviewed. A longer interval may be required if medications are dispensed infrequently. This review supplements the detailed substance use history collected during the interview process and is ideally conducted together with the patient. **The DPIN review must occur in conjunction with the updated list of active clinical issues** and is therefore often the final step in the treatment planning process. This allows the treating clinician an opportunity to clarify how medication is being used and where a particular medication ranks in terms of clinical importance in managing the list of active clinical concerns.

A detailed DPIN review also gives the prescriber and patient an opportunity to discuss which medications have been stopped (even though they may still be dispensed regularly), which ones

the patient may be selling or sharing, and how the patient feels about stopping or tapering undesirable medications that are no longer clinically relevant or useful. A non-judgemental interview style, along with evidence-informed and patient-centred explanations of why certain medications are undesirable with OAT, can go a long way to promote patient engagement in the plan to simplify a complex medication regimen.

It is crucial to emphasize which medication changes are required to ensure patient safety during OAT induction and ongoing care. Reassure the patient that the treatment team will support them through frequent reassessment and medication adjustments as needed. Combining this strategy with emotional support increases the likelihood of success. Highlighting gains over time, such as improved mental alertness, memory, and cognitive function, can also support the medication management strategy. These benefits are often achieved without any measurable increases in symptoms such as anxiety or insomnia. Some patients may even report a decrease in their baseline anxiety and other forms of mental health distress. The patient's pharmacy should be notified of any medication changes. This ensures consistent messaging from all members of the treatment team and enables pharmacy staff to support the patient with changes.

As below, KEY QUESTIONS can be used to explore each medication on the DPIN. It is important to also note that the absence of prescribed medications on DPIN does not rule out polypharmacy; the patient may be using psychoactive medications from a non-prescribed source.

MEDICATION REVIEW – KEY QUESTIONS TO EXPLORE WITH THE PATIENT

Are there psychoactive/sedating medications on the list that they are not taking, selling, or sharing? Medications that have been stopped by the patient, or that are rarely taken, should be discontinued and the pharmacy notified. The patient should also be encouraged to return any unused medication at home to their pharmacy for safe destruction.

What medications are they taking regularly? What was the initial indication for each medication (why did they start them)? How long have they been taking the medication overall (days, months, years)? How many days of the week do they take them? How many times a day and how many tablets at a time? How do they take them (swallowed, chewed, snorted, injected)? If this is their regular pattern of use, are there ever days when they use a lot more (binge use)?

Do they ever run out of certain medications? What symptoms do they experience when this happens? Do they buy/borrow more from family or friends? What is this costing them? Have they ever found themselves in unsafe situations because of needing these medications?

Do they believe these medications are a problem? Do they feel "addicted"? Are they used as a "rescue" during opioid withdrawal? Do they think they can stop using the medication if opioid withdrawal is eliminated in the context of OAT?

Are they taking any other medications not prescribed to them? Shared, traded, or illicitly acquired? Are they using any OTC medications?

Scope of Practice

The typical scope of practice of an OAT prescriber requires them to be actively involved in the management of the OAT medications, medications prescribed for other substance use disorders, medications prescribed for mental health concerns and insomnia, as well as any medication prescribed for acute, chronic, and/or peri-operative pain.

It is NOT acceptable for OAT prescribers to initiate or continue OAT without a thoroughly documented plan regarding the management of all psychoactive medications during induction and the subsequent stages of treatment. This plan should be regularly updated as part of the cumulative summary of care. This is a requirement of CPSM's Standard of Practice for Documentation in Patient Records.

STRONG RECOMMENDATION: ONE PRESCRIBER - ONE PHARMACY

It is best practice for ALL medications prescribed for the above-mentioned conditions to be prescribed by a single prescriber (or group of prescribers) and dispensed from a single community pharmacy. This is particularly important for all psychoactive/sedating medications. This prescriber (or group of prescribers) should generally be the OAT prescriber(s).

If for any reason, some medications must be prescribed by another provider involved in the patient's care, frequent communication must occur between the OAT prescriber, the additional prescriber of psychoactive medications, and the pharmacy. This is essential for patient safety and to ensure that all prescribers participate in the agreed upon plan to manage polypharmacy.

Polypharmacy Management Plan

By updating the list of active clinical issues and completing a DPIN review with the patient, the OAT prescriber can now formulate the polypharmacy medication management plan. This plan must be discussed/negotiated with the patient and other prescribers involved in their care.

In creating the final plan, the prescriber must consider the following:

- After stopping medications that have been discontinued or that are taken infrequently, how many psychoactive/sedating agents remain?
- Can any of these medications be consolidated (e.g., replace 2 or more different benzodiazepines/Z-drugs with a single agent)?
- Can a one-time dose reduction of undesirable medications be considered, especially when prescribed in high doses? Benzodiazepines are a good example; an initial dose reduction can enhance patient safety immediately, followed by a slow taper over time. See *Dosing Recommendations* under the subsequent section "Managing Prescribed and Illicit Benzodiazepines & Z-Drug Use" for details.

- Which medications remaining on the list are most beneficial in terms of the list of active clinical concerns? Which medications are no longer clinically relevant or useful? *Ask the patient this question*. Can any of them be discontinued without the need for a taper?
- In the context of significant polypharmacy, were any medications started recently enough that they can be stopped without clinical deterioration?

The above considerations may help simplify a complex medication regimen, especially if the current regimen carries significant risk for accidental polypharmacy overdose death. This risk should also be considered in the context of adding OAT. In some cases, medication changes can be made over time, but in the context of extreme polypharmacy, substantial medication changes may be indicated on day one of the OAT induction.

Communication with the patient's primary care provider or specialist(s) is strongly recommended to review the plan and rationale for the OAT prescriber to take over psychoactive/sedating medications. It is important to emphasize that their ongoing care is essential to the patient's other medical needs, while highlighting that some changes to the medication regimen may be required for safe OAT induction and care. A letter that confirms these arrangements is excellent practice and informs all providers about the plan moving forward.

STRONG RECOMMENDATION: DISPENSE WITH OAT

Typically, all psychoactive/sedating medications should be dispensed with OAT, i.e., on the same schedule as OAT. Communicating with the patient's pharmacy about the plan for managing these medications is essential. Controlled dispensing instructions, such as "dispense as per OAT schedule", must be written on all relevant prescriptions.

There may be occasional circumstances when the prescriber's risk assessment, considering all medication use and psychosocial factors, would safely allow for less controlled dispensing of psychoactive/sedating medications. Clinical judgment can be applied in such circumstances (e.g., when a patient is paying out of pocket for all medications and there are no high-risk behaviours identified, and the additional cost of daily dispensing may not be justifiable). The prescriber must document their risk assessment and rationale for dispensing intervals that diverge from the OAT schedule.

Verbal or written pharmacy communication may also include any dose or medication changes, tapering plans, and specific concerns to highlight, such as monitoring for sedation or withdrawal, notifying the OAT prescriber of new prescriptions for psychoactive agents from other providers, and/or missed or declined doses of medication.

Polypharmacy is typically not a reason to delay induction of OAT, but it must be factored into the documented management plan. Thorough assessment of polypharmacy will inform decisions about the induction approach (starting dose and rate of dose increases) and follow-up intervals.

In the context of extreme polypharmacy and/or novice prescribers, it may be a necessary to delay community induction and seek additional support from an experienced prescriber. Extreme polypharmacy may even warrant admission to hospital for induction and medication adjustment under close medical supervision.

A well-documented polypharmacy management plan should outline, where relevant, the following issues discussed with the patient:

- Patient education regarding the risk of polypharmacy in the context of OAT.
- A summary of the DPIN review findings.
- The plan to take over prescribing of psychoactive/sedating medications.
- Communication and/or correspondence with other prescribers and the pharmacy.
- The dispensing interval that will apply to all psychoactive medications, and how this will be adjusted if the patient is awarded gradual take-home doses. Typically, the take-home supply of psychoactive medications will mirror the OAT dispensing schedule. If the prescriber's clinical judgment varies from this approach, they should document the risk assessment and rationale for the dispensing interval applied to each medication.
- Evidence of a treatment agreement, including a single prescriber (or group of prescribers) and single pharmacy agreement.
- Collaborative, prioritized care goals, medication changes, and relevant (eventual) taper plans, noting the benefits of a slow and stepwise approach to deprescribing.

Important Note for Emergent or Brief Care Providers

It may not be feasible or ideal for OAT prescribers treating patients in an emergent or brief care setting to take over prescribing of all psychoactive medications. For example, in Rapid Access to Addiction Medicine (RAAM) clinics, Emergency Departments, or following brief Addictions Medicine Consultation in hospital. An interim prescription for OAT may be provided by the consultant, while other medications are managed by the attending physician or regular community provider(s).

However, even under such circumstances, the consultant remains responsible for appropriate screening, assessment, and documentation around polypharmacy. It is recommended that the consultant connect with the other prescribers and/or pharmacy to discuss relevant expert recommendations around the OAT and other medication plans.

If misuse of prescribed medications or a concurrent substance use disorder is identified (e.g., overuse of gabapentinoids or benzodiazepines), medication changes and/or dispensing interval changes **may warrant immediate intervention in the interest of patient safety**, and further collaboration with other prescribers/pharmacies. The OAT prescriber can offer guidance and support to the other prescribers to implement safer prescribing practices, especially when care is shared or transferred back to primary care.

Urine Drug Screens

Relevant to the assessment of polysubstance use and prescribed polypharmacy, it is worthwhile to note that not all benzodiazepines or other psychoactive agents are detected on a street drug screen or point-of-care urine drug screen (UDS). These tests typically identify drug categories and are subject to false positives and negatives. See the Use of UDT in the Management of OUD for a general approach to testing, including the recommended frequency and important issues to consider when interpreting results.

When conducting an initial assessment or monitoring for ongoing polysubstance and prescription medication use, a comprehensive UDS (laboratory GC-MS) offers more detailed and clinically useful information about the specific substances/medications detected. Likewise, a comprehensive UDS can also provide useful information about prescribed medications the patient is *not taking* when evaluating medication compliance.

KNOW YOUR TOOL: INTERPRETING COMPREHENSIVE UDS RESULTS

When interpreting comprehensive UDS results, knowledge of which drugs are captured is essential to safe and effective patient care. Previously, Diagnostic Services, under Shared Health, identified most prescription and illicit drugs in samples submitted for comprehensive urine drug screening. This "forensic approach" was very expensive. The lengthy list of substances previously tested for was reduced as of June 17, 2021.

A specific list of the now 80 substances tested for on a comprehensive screen is available here. This specific panel of drugs is intended to balance clinical utility with a cost-effective approach to testing. This is essential information for prescribers when interpreting comprehensive UDS results to inform clinical judgement, particularly in the context of prescribing medications with psychoactive properties.

NOTE: If prescribers need a specific medication identified that is not included on the list of 80 substances (often to monitor compliance with a prescribed medication), they may request Diagnostic Services test for that medication, by adding a written request on the comprehensive UDS requisition. Date and time of sample collection and the clinical rationale for needing this information should also be documented on the requisition.

Ongoing Monitoring

Like OAT take-home doses, dispensing intervals for psychoactive/sedating medications must be re-evaluated during periods of instability. If circumstances warrant removal of OAT carries, then take-home doses of other psychoactive medications should mirror this approach. Earned take-home doses may need to be removed if concerns arise, such as relapse or a lack of adherence to prescribing agreements. See take-home (carry) recommendations for Buprenorphine and Methadone for details. Again, regular comprehensive UDS can help monitor adherence to the polypharmacy management plan. Regular conversations between the patient and treatment team, and **routine evaluation of the DPIN,** are essential components of ongoing monitoring.

MANAGING PRESCRIBED AND ILLICIT BENZODIAZEPINES & Z-DRUG USE

General Considerations

The CPSM Standard of Practice for Prescribing Benzodiazepines & Z-Drugs came into effect November 1, 2020. In the context of the evolving medical evidence of the risk-benefit ratio of these medications, the Standard establishes the standard of practice and ethical requirements of all members in relation to prescribing benzodiazepines and/or Z-Drugs.

While keeping the Standard in mind, there are some special considerations for the management of benzodiazepines and Z-drugs in patients on OAT. It is not uncommon for patients diagnosed with an opioid use disorder to have a history of benzodiazepine and/or Z-drug use. This can vary from intermittent use to alleviate the discomfort of opioid withdrawal symptoms, to a concurrent sedative-hypnotic use disorder.

Additionally, benzodiazepines and Z-drugs were historically and commonly prescribed for anxiety and insomnia, and many patients with opioid use disorder experience these symptoms. However, the evidence for the long-term use of these medications to treat anxiety disorders and insomnia is poor, and the long-term risks are well known. Notably, the number needed to treat with a benzodiazepine and/or Z-Drug for improved sleep is 13, whereas the number needed to harm is only 6[4].

Furthermore, individuals seeking treatment for substance use disorders are particularly vulnerable to the addictive potential (and many other known harms) of benzodiazepines and Z-drugs. These harms are exacerbated when these medications are combined with opioids, including OAT. Risks increase even further when this combination is prescribed in the context of sedating polypharmacy or to the elderly.

The known harms of benzodiazepines and Z-drugs include:

- Sedation, confusion, drowsiness, and postural instability contributing to the risk of falls and subsequent fractures.
- Impairment of psychomotor skills, judgment, and coordination increasing the risk of motor vehicle accidents.
- Negative effects on cognition and memory, delirium, drug-related pseudo-dementia and a possible link to cognitive decline and Alzheimer's disease.
- Sleep automatism (in the case of Z-drugs), including food binging, and even driving while asleep or in a sleep-like state.
- Abuse and the potential to develop a sedative-hypnotic use disorder.
- Risky interactions with other psychoactive/sedating medications, increasing the risk of respiratory depression and ultimately, accidental polypharmacy overdose death.

Of note, alprazolam (Xanax®) has been identified as a benzodiazepine with significant risks of abuse and diversion in Manitoba. The rapid onset of action provides a sought-after "high" for some patients, while the relatively short half-life means the effects wear off rapidly, feeding the compulsion to take more for lasting effect. Cycling through this pattern of use regularly can reinforce the patient's belief that they *need* the drug when they experience rebound symptoms, including anxiety. **Given the risk of abuse, and the role this benzodiazepine continues to play in overdose deaths, prescribing of alprazolam is *not* recommended**. For the purposes of managing sedative-hypnotic use disorders and/or benzodiazepine tapers, longer-acting formulations (diazepam or clonazepam) are preferred for greater clinical stability.

Managing Benzodiazepines & Z-Drugs in the Context of OAT

Not unlike the general approach to polypharmacy, thorough assessment and collaborative decision-making are required to address benzodiazepine and Z-drug use when prescribing OAT. A detailed history of benzodiazepine and Z-drug use will ensure a clinically appropriate plan is made that minimizes the inherent risks of these medications. The KEY QUESTIONS below should be reviewed with the patient, as part of a comprehensive intake history.

BENZODIAZEPINE & Z-DRUG REVIEW – KEY QUESTIONS TO EXPLORE WITH THE PATIENT

Do they use any benzodiazepines or Z-drugs? Ask about them by name. If yes, what is the source? Are they prescribed or illicitly acquired, or both?

If prescribed, what was the initial indication? How are they used? How many days of the week do they use these medications? How many pills per day? Are there ever days when they use more (binge use)? What is the effect (what would the patient say it "helps with")?

Review the DPIN and dispensing frequency; does it align with the patient's reported pattern of use? Are there any early refills? If the patient runs out early, do they buy or borrow more? Are there multiple prescribers and pharmacies involved? Are multiple benzodiazepines and/or Z-drugs being prescribed concurrently?

If illicitly acquired, can the patient name the benzodiazepines/Z-drugs they are using, or can they describe the pill, and the approximate milligrams? How many do they buy and how long does that supply typically last?

How do they feel between doses or periods of use? What happens if they run out?

Do they think benzodiazepines or Z-drugs are a problem? Do they feel "addicted"? Does the patient meet criteria for a sedative-hypnotic use disorder?

Physical examination can identify signs of opioid withdrawal in the context of the OAT intake or subsequent appointments. Opioid withdrawal symptoms can overlap with benzodiazepine withdrawal signs, and it can be hard to distinguish between these two conditions early on.

As the OAT induction progresses, opioid withdrawal settles and is often eliminated once the patient reaches a stable dose. At this point, residual benzodiazepine withdrawal signs and symptoms may become more apparent. Assessment of these symptoms is then part of the monitoring process if benzodiazepines are prescribed to patients on OAT to promote overall stability.

When NOT to Prescribe Benzodiazepines or Z-drugs

Benzodiazepines and Z-drugs are **highly undesirable** medications in patients on OAT and should be avoided whenever possible. The risks of sedative-hypnotics to the vulnerable OAT population have already been discussed. Hence, if the patient's history and UDS results indicate **no benzodiazepine and/or Z-drug use, the patient should be educated regarding the risks of these medications and advised to continue avoiding them**. There are almost NO reasonable indications to start a *new* prescription for a benzodiazepine or Z-drug for a patient on OAT. Even for acute anxiety, there are almost always better options, both non-pharmacological and pharmacological.

When the patient's history and UDS results indicate **infrequent use of benzodiazepines or Z-drugs, the patient should be educated and supported in discontinuing benzodiazepine and/or Z-drug use**. Even when prescribed, patients do not always take a benzodiazepine or Z-drug prescription regularly enough to become physiologically dependent. They may admit to selling or sharing the prescription to facilitate access to other drugs or resources. If the patient uses a current prescription infrequently or not at all, this prescription MUST be discontinued. This will sometimes require communication with the current pharmacy and prescriber of the benzodiazepine or Z-drug to explain why this prescription can be discontinued without the need for a taper over time.

Intermittent *illicit* benzodiazepine use, in patients who are not prescribed benzodiazepines by the OAT provider, is treated the same as other forms of intermittent substance use in the context of OAT. This involves non-judgemental education and treatment planning.

When a Trial of Benzodiazepines or Z-drugs May Be Appropriate

A trial of benzodiazepine prescribing is indicated when the patient identifies regular benzodiazepine use for a prolonged period. Regular use is defined as taking a benzodiazepine or Z-drug at least 5 days per week. Prolonged use being more than 6 weeks, but in many cases for months or years. Regular use that occurred over 6 weeks or less can typically be managed with a relatively short-term benzodiazepine taper to zero.

Regular, long-term use is an indication to take over existing prescriptions or prescribe benzodiazepines/Z-drugs as a trial. In the context of illicit use only, interim prescribing for stability may also be considered if the patient describes regular use and physical/UDS findings are consistent with the reported history.

A *stability prescription* can facilitate the patient working a recovery plan if they adhere to expectations and agree to an eventual taper. While benzodiazepines and Z-drugs are overall undesirable medications, a stable prescription has the following potential benefits:

- Reliable, often covered medication access, eliminating the cost and risks associated with illicit access.
- Stable blood levels, facilitating emotional regulation and engagement in psychotherapy.
- It can facilitate a slow taper once more stable on OAT.

When a prescribing trial is indicated, all benzodiazepines and Z-drugs must be consolidated into one long-acting agent, in the lowest-effective dosage. Long-acting agents, such as diazepam, are preferred in clients with substance use disorder(s) and diazepam tablet sizes are helpful for small dose reductions in eventual tapering attempts. Clonazepam is an acceptable alternative if preferred by the patient. The prescriber must account for variable cross-tolerance and note that diazepam can be more sedating than some short-acting formulations.

Dosing Recommendations

Patients can present for OAT intake using variable doses of benzodiazepines and/or Z-drugs. A useful strategy is to start by calculating the overall diazepam dose equivalency the patient is taking; see **Appendix G** for a table of benzodiazepine equivalency.[5] Typically, 40 mg of diazepam equivalents and higher is considered high-dose benzodiazepine use. This is very risky in the context of OAT. Understanding the range in which a patient's current benzodiazepine use falls is useful context when initiating and monitoring a trial of prescribing.

Despite the variable and high-dose benzodiazepine use patients may describe, moderate doses of diazepam are often enough to stabilize benzodiazepine withdrawal symptoms and maintain alertness, once on a stable dose of OAT. This occurs for several reasons. Firstly, when patients with opioid use disorder are actively using opioids, they may also use benzodiazepines and Z-drugs to manage opioid withdrawal symptoms to some degree. Clinical experience has demonstrated that as patients stabilize on agonist therapy, the overall physiological need for benzodiazepines, or other sedatives, will decrease. Furthermore, the consistent daily dosing of a prescribed long-acting benzodiazepine can provide serum level stability to patients with concurrent sedative-hypnotic use disorder (compared to illicit use), thereby further decreasing the overall need. Lastly, given incomplete cross-tolerance and because diazepam can be more sedating than other (particularly shorter acting) benzodiazepines, a lower dose than the calculated equivalency can be very effective.

Primary care evidence also indicates that it is safe to reduce high-dose benzodiazepines by 25-50% at once, without risking serious complications of withdrawal. Again, the more sedating medications a patient is taking, the more aggressive you can be with initial dose reductions.

For patients with lower dose use, a starting dose of 5-10 mg po OD is often sufficient to prevent benzodiazepine withdrawal. Once-daily dosing is preferred as it can enhance safety with daily dispensing and possibly witnessed ingestion, if warranted, due to diversion concerns.

However, patients with significant benzodiazepine and/or Z-drug use may, initially, require split dosing to achieve stability. For patients with significant use, a practical strategy is to start diazepam 5 mg po BID, along with the OAT induction. If this is not sufficient to prevent benzodiazepine withdrawal, the dose can be adjusted every 1-3 days until the patient is clinically stable. Even for patients with high-dose daily benzodiazepine use, the maximum diazepam dose required for stability should be in the range of 10-15 mg po BID. Very rarely, a patient may require slightly more. Typically, after the first 1-2 weeks on split dosing and once patients are tolerant to the sedating effects of diazepam, consolidating to once-daily dosing is preferred, as outlined above.

In summary, the starting dose for stability and tapering is often much lower than what the patient may report using regularly. Reassuring the patient that regular reassessment will occur can decrease patient anxiety around medication changes and foster therapeutic rapport.

Dispensing Intervals

The dispensing interval of any prescribed benzodiazepines/Z-drugs should mirror the OAT dispensing schedule. As the patient earns OAT take-home doses (carries), they may also receive the same number of take-home doses of benzodiazepines/Z-drugs.

IMPORTANT NOTE: BENZODIAZEPINES/Z-DRUGS & CARRIES

In patients prescribed benzodiazepines/Z-drugs in the context of agonist therapy with methadone, the **maximum number of carries permitted per week is five**. If not medially essential, the patient should be encouraged to slowly taper off benzodiazepines over time. Once a taper to zero is complete, they may be awarded a sixth and final carry dose per week.

In the context of agonist therapy with buprenorphine and prescribed benzodiazepines/Z-drugs, the approach to carries is identical to the recommendations outlined in the Buprenorphine/naloxone Take-home (Carry) Dosing Recommendations section of this manual.

Monitoring & Non-Prescribed Supplementation

In patients who are physiologically dependent on benzodiazepines/Z-drugs, a structured trial of prescribed benzodiazepines is considered beneficial for the reasons already outlined. However, if patients are supplementing their use with non-prescribed sources of benzodiazepines and Z-drugs in addition to their prescribed medication, these benefits are likely offset by greater potential harms, including:

- A larger overall dose, increasing side-effects like cognitive impairment.
- Erratic use of extra medication, leading to exacerbated overdose risk, greater emotional dysregulation, and potentially poorer mental health overall.
- The risk of binge use, which is associated with a higher risk of accidental overdose death.
- The harms of accessing medication from illicit sources are no longer avoided by prescribing an undesirable medication.

Therefore, monitoring patient compliance is important when prescribing benzodiazepines. **Monitoring occurs by**:

- **Routine follow up**. Ask patients regularly about additional non-prescribed medication use and observe for sedation or impairment during clinical visits.
- **Reviewing DPIN regularly**. Identify additional medication from other prescribers. Communication with the pharmacy about prescribing agreements and requesting a call if other benzodiazepines/Z-drugs are prescribed can be very helpful.
- **Pay attention to collateral**. Information from family and other care providers/pharmacists about concerning use, sedation, or impairment adds to the clinical assessment.
- **Periodic comprehensive UDS**. Objective monitoring with periodic comprehensive UDS can evaluate use of prescribed medications and rule out illicit supplementation.
- **Pill counts**. This can occur during clinical or pharmacy visits to evaluate take-home dose compliance.

If non-prescribed supplementation or diversion of prescribed benzodiazepines/Z-drugs is suspected or confirmed, the patient should receive education regarding the risks again. Regular discussions with the patient are essential to reinforce the expectation that the patient only use their prescribed medication. **If the patient has ongoing access to illicit benzodiazepines/Z-drugs and they do not adhere to the established treatment agreement, the benzodiazepine prescription should be stopped**.

In the context of ongoing illicit use, stability prescribing of a benzodiazepine is more likely to contribute to a polypharmacy overdose, rather than minimize the harm of illicit substance use. Additionally, the OAT dose and carry schedule may need to be re-evaluated. Patients may require intensification of treatment to address illicit use and build further coping skills.

Benzodiazepines & Z-drug Tapers

During OAT inductions and early recovery, it is reasonable to allow patients time on a stable dose of a long-acting benzodiazepine to adjust to treatment and the many changes recovery can bring (e.g., 3-6 months). Slow tapers of benzodiazepines are recommended in all patients on OAT after 3-6 months.

Tapers may be more urgent in the context of high doses, polypharmacy, reported or observed patient sedation, falls, motor vehicle collisions, other significant side-effects, or for the elderly.

Tapers can be approached very slowly to support the patient, but **must be attempted**, in accordance with the Standard of Practice for Prescribing Benzodiazepines & Z-Drugs. The patient disagreeing with the taper attempt *is not an acceptable reason to indefinitely postpone the attempt*. The goal remains decreasing harms and the overall medication burden, while ideally maintaining or improving function and quality of life. Patients often do not recognize the benefits of the taper themselves until it is well underway.

Recommendations for tapering are outlined in the Standard. In general, gradual dose reductions in small increments can minimize withdrawal symptoms to make tapers more manageable for patients (e.g., 10-25% every 2-3 weeks). Overall, tapers may be highly individualized. Patient circumstances may influence the rate and continuation of a taper.

Even small dose reductions can be beneficial and celebrated with the patient.

Pharmacy collaboration and the direct guidance/supervision the pharmacy team can provide are essential components of a successful taper. Their expertise in dosage forms, equivalencies, and compounding can be useful to individualize tapers. Again, you can ask the pharmacist to alert you to any new prescriptions for benzodiazepines or other psychoactive agents. Ongoing discussion with the patient throughout treatment is essential, as well as documenting changes in the plan and expectations.

If the patient experiences frequent hospital admissions for a comorbid condition, where benzodiazepines may be adjusted or restarted, a care plan can be created in collaboration with hospital clinicians to limit unplanned dose escalations.

Tapering, although difficult for many, is possible. When tapering is attempted and ultimately is not feasible, and there is a documented benefit to the patient outweighing the potential harms, treatment with a long-acting benzodiazepine at the lowest-effective dose can continue.

Collaboration & Documentation Are Key

Overall, when managing benzodiazepines and/or polypharmacy, regular conversations and realistic expectations must be set upon initial assessment and throughout treatment. The patient must know what prescribers can reasonably support for the interim and long-term.

Collaboration and education are crucial, but there may be a degree of unilateral decision making when managing benzodiazepines, especially in the context of OAT and complex polypharmacy. In the end, patient safety must come first.

When prescribing benzodiazepines/Z-drugs to OAT patients, prescribers should ensure quality documentation, as outlined below.

IF PRESCRIBING BENZODIAZEPINES/Z-DRUGS & OAT, PROVIDER SHOULD DOCUMENT:

Patient education regarding the ongoing risks of these medications, interpreted in the context of the entire medication regimen, the patient's age, and other comorbid conditions. Education should highlight the benefits of deprescribing.

Discussion regarding a discontinuation strategy with approximate timeframe to begin tapering.

If available, non-pharmacological treatment modalities (e.g., cognitive behavioural therapy or sleep hygiene strategies) recommended or arranged, and non-benzodiazepine/non-Z-drug medications trialed to support recovery.

Clearly outlined expectations, including dispensing intervals (mirroring the OAT schedule), and a one-prescriber (or group of prescribers) and one-pharmacy agreement.

Discussion regarding the consequences of illicit supplementation and behaviours that will jeopardize ongoing prescriptions.

Communication and correspondence regarding the plan with other care providers, other prescribers, and the pharmacy.

MANAGING ALCOHOL USE

As with other sedatives, it is important to evaluate alcohol use at intake and throughout treatment. A detailed alcohol history will inform decisions about the induction approach and treatment planning. Alcohol use is not a reason to delay OAT induction but must be factored into the treatment plan. When regular and/or heavy alcohol use is suspected or confirmed it may be a reason to seek additional support, particularly for novice prescribers. It may even warrant admission to hospital for induction under closer supervision and for concurrent management of alcohol withdrawal.

Of note, given the improved safety profile, buprenorphine is recommended over methadone for patients with concurrent alcohol use. Furthermore, alcohol use is not an indication for benzodiazepine prescribing, but rather a contraindication if benzodiazepines are being considered for management of other clinical issues. If benzodiazepines are required for the management of alcohol withdrawal, this should be short-term and should occur under close medical supervision, preferably in an inpatient environment.

Alcohol Use & Overdose Risk

Problematic alcohol use, or alcohol use disorder, is a significant safety risk for patients on OAT, including buprenorphine. This risk is compounded by any prescribed or OTC medications with sedating properties and/or polypharmacy. The OAT dose and carry schedule may need to be re-evaluated in the context of persistent alcohol use.

Similarly, the prescribing and dispensing of all psychoactive medications warrants review, as alcohol combined with benzodiazepines or other sedatives substantially increases overdose risk. Tapering of prescribed sedatives may need to occur to offset this risk.

Collaboration with pharmacy is crucial if concerns persist around alcohol. Prescribers should discuss expectations with the patient about holding doses if sedation or intoxication is observed. Making pharmacists aware of alcohol use concerns can increase their vigilance when assessing the patient during pharmacy visits.

It is important to keep in mind that alcohol use can be normalized within patient social circles, and they may not identify their consumption as problematic. Patients may need reminding about the compounding risk of combining alcohol with OAT and other medications. Discuss and document safety considerations, consumption parameters, and treatment options.

Of note, alcohol use is not detected on comprehensive urine drug screens.

Medication-Assisted Treatment

Patients meeting criteria for alcohol use disorder may benefit from relapse-prevention medications to promote abstinence. Patients who are not on opioids/OAT may be appropriate for treatment with naltrexone. Patients on OAT cannot take naltrexone as it is an opioid-receptor antagonist, but they may be suitable for a trial of acamprosate.

Acamprosate can also be considered over naltrexone in the case of severe liver impairment.

Acamprosate is a structural analogue of γ-aminobutyric acid (GABA). The exact mechanism of action of acamprosate is unknown. While the evidence for acamprosate to assist with maintaining sobriety is not as robust as for naltrexone, it may be valuable as an adjunctive treatment in patients who are engaging in psychosocial treatment for alcohol use disorder. One of the advantages of acamprosate is that it does not need to be discontinued if the patient has a brief relapse to alcohol consumption.

Acamprosate is typically well tolerated, with the most common side effect being diarrhea. This is dose-related and usually transient. Starting acamprosate at 333 mg po TID for a few days, before escalating the dose to 666 mg po TID, may be helpful to ameliorate this side effect. In moderate renal impairment the maintenance dose is 333 mg po TID.

Acamprosate is rather costly if a patient does not have public or private medication coverage. This issue needs to be explored with patients as part of the discussion around this treatment option.

Patients with problematic alcohol use may also benefit from more intensive addiction treatment to reduce their drinking or to achieve their goal of abstinence.

MANAGING NICOTINE USE

Cigarette smoking and other forms of tobacco/nicotine use remains common in patients with opioid use disorder. **This continues to be a major cause of morbidity and mortality**. All patients must be asked about smoking and the use of other nicotine products, including vaping.

There are no contraindications to the use of nicotine-containing smoking cessation aids with OAT, including combined nicotine replacement therapy. Other options to consider and review with patients are varenicline and bupropion. Combined therapy may be more effective for some patients, e.g., combined nicotine replacement in combination with varenicline or bupropion.

The treatment plan, potential side-effects of prescribed agents, and discussion regarding complementary non-pharmacological treatment options should be documented.

MANAGING CANNABIS USE

Screening and discussion around the use of cannabis products should be part of an OAT intake assessment and regular follow up. Like other drug use, ask about duration of use, patterns of use, amount, route, source, and the effects. Patients may use cannabis by smoking, vaping, and/or ingestion and may acquire it from a licensed dealer, commercial store front, or illicitly. They may use to offset symptoms or side-effects of the intoxication and withdrawal cycle, or to cope with other mental health symptoms.

Although cannabis use does not typically affect a patient's ability to earn or maintain carries – unless associated with other forms of problematic substance use – it can still negatively impact patients who smoke regularly and/or heavily. Amotivation, psychosis, and heightened anxiety can arise from regular use and exacerbate overall mental health issues.

Additional information can be found in the CPSM Standard of Practice for Authorizing Cannabis for Medical Purposes, which came into effect November 1, 2020.

MANAGING ILLICIT STIMULANT USE

Stimulant use is also common in patients with opioid use disorder. Use may be intermittent or chronic. Stimulants may be used recreationally, to cope with opioid withdrawal symptoms, or patients may meet criteria for a concurrent stimulant use disorder. Stimulant use requires evaluation upon intake and routine screening throughout care. Cocaine and/or methamphetamine use is of particular concern, as it may cause instability and involves risky behaviours that can lead to increased harm or overdose. Presently, methamphetamines play a significant and concerning role in the Manitoba overdose crisis.

Routine monitoring for stimulant use should be factored into take-home dose decisions and the overall polypharmacy management plan. Again, patient safety is paramount.

Patients continuing to use stimulants may also benefit from education regarding harm-reduction strategies. Regular testing for sexually transmitted and blood-borne infections (STBBIs) is recommended for most patients with substance use disorders but can be particularly relevant for people who use stimulants.

More intensive addiction treatment may be warranted to promote abstinence if that is the patient's goal. Patients can also be educated about crisis and emergency services for urgent intervention around substance-related mental health issues or psychosis.

MANAGING OTHER PSYCHOACTIVE MEDICATION USE, BOTH PRESCRIBED AND ILLICIT

The medications included here are commonly prescribed and often part of the polypharmacy picture. The OAT provider may inherit prescribed gabapentinoids, cyclobenzaprine, quetiapine, trazodone, or antidepressants. These medications may also be diverted, and some patients will use them to manage opioid withdrawal symptoms, or they may develop concurrent use disorders. Upon intake, evaluation of these medications is crucial.

Key questions to consider for other psychoactive medications include:

- What is the source; is it prescribed or illicitly acquired, or both?
- What was the initial indication for prescribing?
- Review the DPIN and dispensing frequency; is the medication filled more often than intended? Are there multiple prescribers and pharmacies involved?
- Do they take them as prescribed? Do they skip doses or overuse these medications?
- If illicitly acquired, can they name or describe the pills and the approximate milligrams?
- What symptoms does the medication help with? Do they find them effective?
- Do they think these medications are a problem?

If taking over a prescription, discuss and document the plan with the patient, other care providers, and the pharmacy as described in the APPROACH TO POLYPHARMACY section. Dispensing intervals should mirror the OAT schedule in most cases.

Gabapentinoids

Gabapentinoids are commonly prescribed, often without a clear indication, and can be part of the polypharmacy picture. Given their sedating and psychoactive properties they can also substantially increase the overall risk of overdose when combined with OAT and/or other sedatives. Patients may use these from prescribed and/or diverted sources, often in high doses, to alleviate opioid or benzodiazepine withdrawal symptoms, or to treat physical and/or emotional pain. If a prescription is inherited, review the DPIN, clarify the indication, ask how they are taking the medication, and if it is effective.

If there is no clear neuropathic pain or other appropriate medical indication, a taper to zero is indicated. Gradual tapers are recommended to prevent unpleasant withdrawal symptoms. Non-urgent tapers are typically well tolerated when the overall dose is reduced by 100 mg daily, per week. In more urgent cases, the dose can be reduced by 300 mg daily, per week. If the initial dose exceeds 3600 mg, an initial larger dose reduction of up to 25% may be considered, especially in the context of polypharmacy.

It is not recommended to prescribe gabapentin when the patient reports exclusively illicit use. Education and support to reduce illicit use is indicated, along with careful management and tight dispensing of OAT and other sedating medications.

If gabapentinoids are indicated for the treatment of neuropathic pain and demonstrated as effective to improve the patient's function and quality of life, ongoing prescribing may be appropriate. Document the benefit to the patient, the discussion regarding the potential harms, and ensure polypharmacy management strategies are in place. Prescribe the lowest-effective dose and do not exceed the maximum recommended daily dose of 3600 mg.

There is some evidence for use of gabapentin to support early abstinence in patients with alcohol use disorder. In the context of OAT, gabapentin is not routinely recommended for this purpose, given the abuse and diversion potential identified in Manitoba. However, in a patient with severe and treatment-resistant alcohol use disorder, a controlled trial of gabapentin for this indication may be reasonable if other options have failed and there is ongoing significant use with harms. Prescribers should discuss such treatment in consultation with an addiction medicine specialist.

Muscle Relaxants

Like gabapentinoids, the use of muscle relaxants (e.g., cyclobenzaprine and baclofen) can be common and warrants review. If inheriting prescriptions, review the DPIN, clarify the indication, ask how patients are taking them, and if they are effective. With all muscle relaxants, document a clear indication for continued prescribing, as well as a discussion of the intended use and risks, and implement safe dispensing practices. **In general, in the OAT population, these medications should be discontinued and avoided whenever possible.**

Quetiapine & Trazodone

These medications are commonly prescribed in lower doses to manage insomnia and/or acute anxiety, in early treatment. This strategy is often used while waiting for a SSRI, SNRI and/or CBT interventions to take effect. Also, sleep often improves naturally once patients stabilize on OAT and establish a healthier diurnal sleep-awake cycle, but this may take several weeks.

It is important to note that given their sedating and psychoactive properties, quetiapine and trazodone can also increase the overall risk of overdose when combined with other sedatives. These medications can also be diverted and may be used illicitly by some patients for the

sedative effects or to cope with opioid-withdrawal symptoms. Ask patients if they have used either quetiapine or trazodone from non-prescribed sources. If inheriting prescriptions, review the DPIN, clarify the indication, ask how patients are taking them, and if they are effective. Again, if prescribing is indicated and effective, dispensing intervals should mirror the OAT schedule in most cases.

Prescribed Stimulants

Patients may be inherited on prescribed stimulants and the same diligence described above must be applied to evaluate appropriate or inappropriate use, addictive potential, and safe prescribing of such medications, if indicated. If concerns exist around attention-deficit symptomology, a referral for psychiatric evaluation and treatment recommendations is strongly recommended prior to initiating prescription stimulants. If a trial is warranted, long-acting tamper-proof formulations are preferred whenever possible. Restricted dispensing of prescription stimulants is also strongly recommended, mirroring the OAT carry schedule.

Antidepressants (Bupropion, Tricyclics, SSRI/SNRIs)

Management of mood and anxiety symptoms or concurrent disorders can be critical to improve the overall well-being for patients on OAT. Treatment with antidepressants is worthwhile, with safe prescribing practices in place as antidepressants can also contribute to overdose deaths. Limited dispensing and routine screening for compliance is warranted. Comprehensive UDS can be a useful tool to supplement clinical monitoring, however, knowledge of what medications are detected is essential – see KNOW YOUR TOOL on page 9.

IMPORTANT NOTE: LESS IS OFTEN MORE

There is little evidence that prescribing more than one agent from the same class of drug improves clinical outcomes, but it can contribute to polypharmacy and all the associated risks. If available, non-pharmacological treatment modalities for depression, anxiety, trauma, and pain should be explored to support recovery. Consider referral to additional services or an addiction-aware psychiatrist for recommendations, especially for patients with complex needs.

A clear indication should exist when prescribing an antidepressant. Select the medication best suited to the symptoms; is depression, anxiety, insomnia, wakefulness and/or chronic pain the target for intervention? Discuss the intended effect, trial duration, expectations, and safety concerns with the patient, and document the plan.

Note that some antidepressants may carry an increased risk of abuse or diversion; there have been reports of illicit bupropion use for the stimulant properties. Tricyclic antidepressants are commonly used as adjunctive therapy in the management of chronic pain and certain types of headaches. However, **tricyclics remain lethal in overdose and the amount of medication required for a lethal overdose is relatively small. Therefore, in the OAT population, tricyclics should only be prescribed when other options have been exhausted, and dispensing must be tightly controlled.**

MANAGING OVER-THE-COUNTER MEDICATION USE

As noted, the OCME death reviews demonstrate that OTC medication use, combined with illicit and/or prescription drugs, significantly increases overdose risk. The use of OTC medications by patients with opioid use disorder is common to manage a variety of symptoms. Prescribers must screen patients for OTC use upon initial assessment and routinely throughout care.

Diphenhydramine, Dimenhydrinate & Dextromethorphan

In 2018, the OTC medicinal ingredients contributing to the largest number of overdoses included diphenhydramine, dimenhydrinate, and dextromethorphan. Diphenhydramine, an antihistamine and anticholinergic, is widely used in non-prescription sleep aids for insomnia, namely for its sedative and anxiolytic properties. Diphenhydramine is also the primary constituent of dimenhydrinate, an antiemetic, and dictates the primary effect. The main difference relative to pure diphenhydramine is a lower potency in comparison, due to the combination with 8-chlorotheophylline that has stimulant properties.

Dextromethorphan, a cough suppressant commonly found in cold medications, can act as a dissociative anesthetic in doses exceeding the recommended range. Dextromethorphan at high doses and its major metabolite, dextrorphan, can produce similar effects to the dissociative states created by other anesthetics such as ketamine and phencyclidine (or phenyl cyclohexyl piperidine, PCP).

Codeine is also a major contributor to polypharmacy overdose and some codeine-containing products are still available over the counter in many provinces.

Patients with opioid use disorder may use these OTC medications to alleviate opioid-withdrawal symptoms. Symptoms such as anxiety, irritability, restlessness, agitation, or insomnia may be muted by OTC overuse, and this may develop into a concurrent use disorder. Patients may also use dimenhydrinate or loperamide products for nausea or gastrointestinal issues associated with opioid use or withdrawal.

Screen & Manage Like Other Sedatives

Like other sedatives and psychoactive agents, screening for OTC medication use is an important part of comprehensive care. Ask patients if they use any OTC medications to manage the effects of withdrawal or intoxication, perhaps listing common trade name examples such as, but not limited to, Gravol™, Benadryl®, Nyquil™, Benylin®, or Tylenol® PM.

As patients stabilize on OAT, the frequency of OTC use may naturally diminish as the cycle of intoxication and withdrawal normalizes. Conversely, other patients may continue or increase the use of OTC medications while on OAT to escape unpleasant feelings. Some patients may wrongly perceive OTC medications as safe compared to illicit substances, particularly if they continue to struggle with symptoms such as anxiety or insomnia.

As part of regular screening, prescribers should consult with the treatment team, including pharmacists, regarding concerning presentations or behaviours that may suggest OTC medication use. Collateral from family can also be helpful to determine frequency of purchase and the impact on the patient. Routine comprehensive UDS's can also provide useful information.

As noted, OTC medication use can develop into a separate substance use disorder and some patients may require intensification of treatment. Management strategies to increase safety may include removal of carry doses or tapering of other prescribed sedatives to offset the overdose risk. Patients may benefit from referral for more support to develop non-chemical coping skills through counselling and/or residential treatment to break the pattern of use.

OTHER SUBSTANCES TO CONSIDER

As noted, the substances outlined above are not an exhaustive list of possible medications or drugs of abuse. Other medications that may warrant review for safety considerations include, but are not limited to, nabilone, nabiximols (Sativex®), ketamine, and sodium oxybate (Xyrem®), which is the sodium salt of *gamma*-hydroxybutyric acid or GHB.

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Appendix G

BENZODIAZEPINE EQUIVALENT TABLE

from The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain PRACTICE TOOL KIT [5]

Benzodiazepine Equivalent Table Source: Adapted from Kalvik 1995; Canadian Pharmacists Association 1999.

Benzodiazepine	Equivalent to 5 mg diazepam (mg) *
Alprazolam (Xanax®)**	0.5
Bromazepam (Lectopam®)	3–6
Chlordiazepoxide (Librium®)	10–25
Clonazepam (Rivotril®)	0.5–1
Clorazepate (Tranxene®)	7.5
Flurazepam (Dalmane®)	15
Lorazepam (Ativan®)	0.5–1
Nitrazepam (Mogadon®)	5–10
Oxazepam (Serax®)	15
Temazepam (Restoril®)	10–15
Triazolam (Halcion®)**	0.25

* Equivalences are approximate. Careful monitoring is required to avoid over-sedation, particularly in older adults and those with impaired hepatic metabolism.
**Equivalency uncertain.