ONTARIO PHARMACISTS ASSOCIATION

Advocating Excellence in Practice and Care

Methadone and Buprenorphine/Naloxone Toolkit for Pharmacists

Part A: Methadone

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

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Disclaimer

These tools have been developed by the Ontario Pharmacists Association for pharmacists in Ontario as a general guide to support those wishing to initiate a methadone program in their pharmacy setting. The resource materials provided in this toolkit are for general information purposes only and are NOT meant to be used "as is".

This toolkit is complementary and is not inclusive of all recommendations and considerations. The information provided is not a substitute for sound clinical judgement from the health care professional. Pharmacists are to exercise their professional judgment in accordance with the Ontario College of Pharmacists (OCP) Standards of Pharmacy Practice. This tool is not a substitute for established clinical practice guidelines or regulatory requirements. It is not intended to supersede or replace guidelines, practice standards, policies or procedures issued by OCP, the Ministry or corporate employers. It is also not intended, and should not be construed, as legal or professional advice or opinion.

While OPA strives to ensure the accuracy of the information provided in this document, information may be subject to change, and it is the responsibility of the user of this document to ensure they have the most up-to-date and complete information from available resources.

Note: During the COVID-19 pandemic, modifications to the standard guidelines have been made in order to reduce community transmission. Please refer to the CAMH document "COVID-19 Opioid Agonist Treatment Guidance" for further information on these modifications to treatment delivery.

Acknowledgement

Compilation of this toolkit required the dedicated effort of many individuals. The Ontario Pharmacists Association would like to thank the following for their tireless work in revising and reviewing the toolkit for the benefit of all Ontario pharmacists and the patients they serve: Rose Fitzgerald, B.Sc.Phm; Satinder Sanghera, BScPhm, RPh; Andrew Tolmie, RPh, BScPhm; Shamim Rajan; Dr. Alice Ordean, MD, CCFP, MHSc, FCFP; Mohammad-Usman Imran, B.Sc.Phm., RPh; and the Ontario College of Pharmacists.

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Opioid Agonist Maintenance Treatment (OAMT)

OAMT involves the prescribing of methadone or buprenorphine as part of a comprehensive program which includes counselling to help the person in treatment reduce or stop the harmful use of opioids. (Kleber, 2008).
Currently, methadone and buprenorphine are the most prescribed treatment options. Methadone is the most studied and longest used pharmacological treatment for opioid dependence. A third option, oral slow-release morphine (e.g., Kadian®) may be used as OAMT in individuals who have not benefited from treatment with first line and second line treatment options (i.e., buprenorphine/naloxone and methadone). In Canada, this use is considered **off-label**, and requires careful review of the risks and benefits, fully informed consent of the patient and rigorous clinical documentation.

OAMT as a Harm Reduction Approach

Any program or policy designed to reduce drug-related harm without requiring the cessation of drug use. Interventions may be targeted at the individual, the family, community or society (Erickson et al, 2002).

Harm reduction includes both strategies that focus on reducing drug use and those that focus on reducing the harm of drug use.

OAMT has been shown to reduce:

- Use of other opioids (Brand et al., 2003; Davioli et al., 2007; Gibson et al., 2008)
- Criminal activity (Lind et al, 2005) as OAMT is legal and may keep patients away from the harmful consequences of acquiring and possessing illicit opioids and prescription opioids
- Patient mortality rates (Degenhardt et al., 2011; Gibson et al., 2008; Soyka et al., 2011) compared to people who continue to use opioids
- Injection-related risk (including behaviours and transmission of HIV and sexually transmitted infections (Hart, 2007)
- Cost of law enforcement, health care and social services for patients who are unemployed, homeless or in other difficulties (Hart, 2007)

OAMT improves (Brands et al., 2002)**:**

- Physical and mental health
- Social functioning
- Quality of life
- Pregnancy outcomes

In contrast to many short-acting opioids (e.g., heroin), methadone and buprenorphine:

- Are well absorbed and effective orally (methadone) or sublingually (buprenorphine)
- Take longer (e.g., 30 minutes vs. instantaneously) to produce an effect than opioids that are injected, smoked or snorted
- Are longer acting than other opioids (24 to 36 hours or longer vs. three to six hours) and are administered less frequently (once daily vs. three or more times daily)
- Do not cause drowsiness o euphoria in patients on an appropriate dose
- Do not cause significant impairment in thinking, behaviour or functioning when taken at an appropriate dose
- Do not dull normal emotions and physical sensations
- Diminish opioid craving
- Decrease drug-seeking behaviour
- Reduce the likelihood of euphoria from other opioids in stable patients
- Continue to be effective with long-term use without dose increases

Limitations to the use of OAMT

- Methadone is a high-risk medication with a narrow therapeutic range that can result in opioid overdose, especially at the beginning of treatment. It may prolong QT interval, leading to an increased risk of fatal arrhythmias.
- Buprenorphine has a lower overdose mortality risk but can still have severe health consequences including death – especially, if misused or combined with other CNS depressants or alcohol.

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- People (including health professionals) may inadvertently or inappropriately label patients as ‘still addicted’, thus stigmatizing them further.
- Program practices may be experienced by patients as demeaning (e.g., observed urine collection, waiting in line at the pharmacy for their dose).
- OAMT requires regular visits to the pharmacy, physician and counsellor.
- Cost may be a barrier for some patients.
- Both buprenorphine and methadone can produce adverse side-effects and may interact with other medications.
- OAMT practices may limit patient’s ‘flexibility’ for work or travel.
- There may be limited availability of physicians and pharmacies that offer OAMT.
- Pharmacists can aid their patient’s recovery by supervising drug administration, monitoring their dosage, communicating with the treatment team, dispensing take-home doses in accordance with established guidelines and providing encouragement and support.

CAMH Opioid Agonist Maintenance Treatment: A pharmacist’s guide to methadone and buprenorphine for opioid use disorder. Third edition 2015

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Methadone Dispensing at a Glance

For Methadone Maintenance Therapy (MMT)

Prescription must include:

- Registration number of the certificate of registration for the prescriber (specific to each province's college)
- Name of the person for whom the methadone is prescribed
- Name and dose of methadone
- Directions for use of methadone
- Name and address of the prescriber
- Date the methadone is prescribed
- ID number of the patient and the type of ID used

As per CAMH Guidelines:

- Start and stop dates (use the word 'inclusive' to minimize ambiguity)
  Total quantity is not required as this can be clearly and exactly calculated based on start and stop dates
- Best practice for Prescribers – specific days methadone doses are to be ingested/observed; and days that dose(s) can be given as take-home/carry doses
- Dose spelled out in words, as well as in numbers
- Instructions to 'dispense in drink/juice'
- Name of the dispensing pharmacy (the patient has a choice, but the physician needs to know to ensure physician-patient communication)
- Best practice – information about changes in dose (i.e., cancel previous prescription, dose change, carry change etc.)
- Other instructions as needed

Confirm Narcotic Monitoring System (NMS) requirements and evaluate NMS alerts
https://www.ocpinfo.com/library/practice-related/download/Narcotics%20Monitoring%20System.pdf

Process and prepare the prescription using the DIN for commercially available methadone solution (e.g., Methadose™ 10mg/ml) indicated for opioid agonist treatment.

Prescription label should make the following clear:

- The drug product (name, manufacturer) and amount in the bottle
- The total dose of methadone in milligrams contained in the bottle
- A notation that the drug product has been diluted (i.e., 'in orange drink')
- The date for ingestion (for take-home/carry doses)

For take-home/carry doses, include:

- Child resistant safety cap
- Tamper-proof tape/cap (best practice)
- 'Keep in Refrigerator' label
- Methadone auxiliary label which reads-
  'Methadone may cause serious harm to someone other than the intended patient. Not to be used by anyone other than the patient for whom it was intended. MAY BE FATAL TO CHILD OR ADULTS'
  OR
  'Methadone may cause serious harm to someone other than the intended patient. MAY BE FATAL TO CHILD OR ADULTS'

Compounded methadone is only permitted in the following:

- Therapeutic need* – patient is unable to tolerate the commercially manufactured product
- NB: ODB requires the physician to submit a request to the Exceptional Access Program along with a completed Adverse Drug Reaction form
- Lack of product availability
- A concentration less than the commercially manufactured 10mg/ml solution is required

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- It is not a patient choice based on preference.
- https://www.ocpinfo.com/wp-content/uploads/documents/archived-methadone-maintenance-treatment-mmt-policy.pdf

Where a compounded product is prescribed and dispensed, the pharmacist shall label with the expiry date and concentration in accordance with NAPRA Model Standards for Pharmacy Compounding of Non-sterile preparations.
https://napra.ca/general-practice-resources/model-standards-pharmacy-compounding-non-sterile-preparation

Take-home/carry doses

- Do not dispense methadone take home doses unless authorized by prescriber
- May only be given to the patient.
  NB: During this time of COVID-19, the pharmacist may consider delivering a small number of carries/take-home doses at one time to enhance patient safety.
  https://www.camh.ca/-/media/files/camh-covid-19-oat-guidance-for-pharmacists-pdf.pdf?la=en&hash=ECEB406CEB7E973EE4A3B637520AAAA974D642B7
- Lock box and return of take-home bottle(s) can be considered best practices - this process should be established with the prescriber and explained to the patient.
  NB: During this time of Covid-19, pharmacists should advise patients that the return of used carry bottles is not recommended at this time. Pharmacists must provide direction to these patients to ensure the used carry bottles are rinsed prior to disposal.
  https://www.camh.ca/-/media/files/camh-covid-19-oat-guidance-for-pharmacists-pdf.pdf?la=en&hash=ECEB406CEB7E973EE4A3B637520AAAA974D642B7
- Use of tamper evident tape, caps or seals is best practice to enhance safety and monitoring
- Once patient qualifies, the take home dose schedule is determined by the prescriber. The usual number of take-home doses can range from one to a maximum of six (with a few minor exceptions).
  NB: During this time of COVID-19, exceptional carries can be considered as a way to provide ongoing care that balances the facilitation of physical distancing by reducing pharmacy and clinic visit with considerations of patient and community safety.
  Some patients who might not have been considered eligible for methadone carries under the Guidelines may be given carries in light of the COVID-19 pandemic.
  https://www.camh.ca/COVID19-OAT-Protocols

Minimizing risk

- Use tamper evident-tape or self-sealing bottles
- Best practice is to have all measurements checked by at least two pharmacy staff (one of whom must be registered with the College)
- Positively identify all patients; call them by name and use picture ID
- Confirm the dose with the patient by asking them their dose before it is consumed
- If a patient is receiving methadone from two different pharmacies, have an effective communication system to confirm last dose or missed doses.

Pharmacology of Methadone

- Readily absorbed, onset of effect is within 30 minutes
- Usual peak plasma levels: two to four hours after ingestion
- Elimination half-life is 22-48 hrs
- Steady state levels in 5-7 days
- Metabolism: primarily by cytochrome P450-3A4 in liver; minor roles for CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6. Primary metabolite is EDDP which is inactive and is used as a marker in urine drug screens

Methadone Adverse Effects
Note: This is a list of the more common side effects or symptoms and is not intended to be all-inclusive

Common with All Opioids:
- sweating (dose related) is exacerbated by heat and social situations (can be misinterpreted as withdrawal)

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- constipation
- sexual dysfunction and neuroendocrine effects
- weight changes (usually weight gain)
- drowsiness/sedation (slurred speech, cognitive impairment, 'nodding off' or ataxia) sleep disturbances-insomnia (may also be related to other causes such as depression, anxiety, PTSD or rumination of past trauma) or sleep apnea
- Dental problems caused by or related to dry mouth (there may be other medications, such as anti-depressants, used by a methadone client that may also cause increased dryness of the mouth). With low saliva, generalized bacterial plaque accumulates as a result of poor oral health

Less Common-Methadone specific:
- psychoactive changes (mood or cognitive impairment)
- cardiovascular effects (QTc prolongation and cases of TdP-torsades de pointes)
- urinary hesitancy or retention

Rare-Methadone specific:
- cutaneous effects (flushing, itchiness, skin rash)
- peripheral edema (swelling of feet or ankles)
- dental problems (including dry mouth)

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Methadone Drug Interactions

Methadone can interact with other medications. Pharmacists should always ask about all other drugs the patient is taking including prescription medications and herbal remedies.

Mixing methadone with other drugs that depress the central nervous system ca be extremely dangerous. Other opioids, alcohol and benzodiazepines should be avoided. This is especially risky when you first start OAMT. Using other drugs while taking methadone can also cause your dose of methadone to affect you differently.

Pharmacists are encouraged to regularly access the most up-to-date information on drug interactions from reliable drug information sources as part of their clinical assessment and new information is becoming known daily.

Pharmacists and Methadone Drug Interactions

- Keep an accurate, updated medication profile, including OTC, herbal and illicit drugs
- Develop a working knowledge of methadone drug interactions
- Watch for additive toxicity, particularly with CNS depressants and drugs known to increase QT interval
- Need quick access to a current list of interactions
- Determine clinical significance of drug interaction.
- Use alternative, non-interacting drugs when possible
- If potentially interacting drug must be used, adjust methadone dose based on patient response
- Make dose adjustments slowly and in small increments to avoid toxicity or symptoms of withdrawal. Severity of signs/symptoms of withdrawal or over sedation may help determine extent of dose change required
- If potential increase in methadone levels, advise patient in advance of signs or symptoms to watch for and what to do
- When possible, avoid concurrent administration of drugs with overlapping side effect profiles
- Consider pre-existing disease states as an alternative cause for symptoms, other than a drug interaction.
- Consider complexity of prescribed regimens on patient adherence
- Patients should be carefully monitored when starting or discontinuing a medication that may interact with methadone.
- Many interactions can be managed by monitoring for symptoms (e.g., Opioid withdrawal symptoms or excess sedation) and making dose adjustments as needed.

Patients and Methadone Drug Interactions

- Provide all health care providers with an updated list of all medications used (including OTC, herbal and illicit)
- Carry a list of all medications (Best Possible Medication Record)
- Consult with their doctor or pharmacist before taking any new prescription, OTC, herbal or dietary supplements.
- Be advised of hazards of using illicit substances or drugs intended for someone else
- Patients who are on an interacting medication should be educated about the importance of adhering to their medication regimen.
- Counselled to quickly report any sudden or unexpected signs/symptoms of methadone withdrawal or overmedication
- If potential increase in methadone levels, advise patient in advance of signs or symptoms to watch for and what to do.
- Verbally instructed on what the drug is for, how to take it, and how to reduce risk of side effects or interactions
- Adherence to prescribed medications emphasized
- Special consideration for patients with liver or kidney disorders, pulmonary or heart ailments, pregnancy
- Instructed in advance on what to do in an emergency if their supply of methadone and/or other medications runs out

Pharmacodynamic Interactions of Methadone

Additive Effects: When methadone is combined with a medication or illicit drug that has similar pharmacological profile, the effects may be additive – e.g., Potentiation of CNS or respiratory depressant effects, constipation, nausea or urinary retention. CNS depressant effects of alcohol and benzodiazepines are additive when combined with methadone – putting patients at increased risk of respiratory depression and sedation. This can result in death.

OTC medications containing dimenhydrinate and diphenhydramine can be abused and are problematic when used by patients on methadone. They also have CNS depressant effects.
Anticholinergic medications can potentiate the effects on the bowel, causing increased risk of severe constipation, possibly leading to paralytic ileus. It can also increase the risk of urinary retention.

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Patients taking drugs that are associated with a prolonged QT interval are at risk of developing an arrhythmia (Torsade de Pointes – TdP) which may be fatal (reference www.crediblemeds.org). Avoid medications known to prolong QT interval in patients taking methadone. Methadone, especially at higher doses (greater than 150mg) is an independent risk factor for QTc prolongation.

Pharmacokinetic Interactions

Many of the interactions with methadone occur through involvement of the microsomal P450 system – especially those that are also metabolized by CYP3A4. Methadone may also be metabolized to a lesser extent by the CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 enzymes.

Effects of induction of methadone metabolism tend to occur slowly. Maximal effects generally occur at one to two weeks and can result in methadone withdrawal symptoms.

Inhibition of methadone metabolism occurs rapidly, and toxic effects (sedation, respiratory distress) can present in 1-2 days – patients need to be monitored for a longer time.

Chronic use of alcohol can enhance hepatic metabolism of methadone through enzyme induction. However, acute alcohol use reduces methadone metabolism by competing for metabolic enzyme activity. Patients presenting as intoxicated or smelling of alcohol must be refused their dose and referred to the prescriber.

Theoretically, grapefruit juice could cause elevated plasma levels of methadone – clinical significance is unknown

Medications that can decrease plasma levels/effects of Methadone	**Medications that can increase plasma levels/effects of Methadone**	**Medications that may be affected by Methadone**
Amprenavir Barbiturates Efavirenz Fusidic acid Indinavir Lopinavir Nelfinavir Nevirapine Phenytoin Primidone Rifampin Risperidone Ritonavir Somatostatin St. John's Wort Urinary acidifiers	Amitriptyline Benzodiazepines Cimetidine Ciprofloxacin Clarithromycin Delavirdine Disulfiram Erythromycin Fluconazole Fluoxetine Fluvoxamine Indinavir Ketoconazole Paroxetine Sertraline Etc.	Abacavir Amprenavir Desipramine Didanosine MAOI's Nifedipine Stavudine AZT

Check with your Drug Information Centre or an online reference for current, up to date information.

Resources:

CAMH Opioid Agonist Treatment: A pharmacist's guide to methadone and buprenorphine for opioid disorder 3rd edition
NB: Appendix 2 is not exhaustive.

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To order- https://www.camh.ca/en/camh-news-and-stories/get-the-latest-on-opioid-agonist-guidelines

Drugs.com
https://www.drugs.com/drug-interactions/methadone.html

Addiction Treatment Forum 2005
https://atforum.com/documents/Drug_Interactions.pdf

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Initiating a Methadone Program in Your Pharmacy

Ontario College of Pharmacists Opioid Policy, 2018
(*Formerly Methadone Maintenance Treatment (MMT) and Dispensing Policy June 2014)*
http://www.ocpinfo.com/regulations-standards/policies-guidelines/opioid-policy/

Abbreviations: Ontario College of Pharmacists (OCP); College of Physicians and Surgeons of Ontario (CPSO); Centre for Addiction and Mental Health (CAMH); Designated Manager (DM)

Information to provide to OCP:

Notify OCP within seven days of initiating methadone dispensing practice (for MMT) by submitting completed Methadone Dispensing Notification Form – send by email to pharmacyapplications@ocpinfo.com, or fax to 416-847-8399, or mail to the attention of Pharmacy Applications & Renewals at 483 Huron St. Toronto, ON M5R 2R4

http://www.ocpinfo.com/library/forms/download/Methadone%20Dispensing%20Form.pdf

Hours and days of operation for your pharmacy (including holidays)
Does pharmacy accept new patients?
Date(s) that DM and staff pharmacist(s) trained (or will be trained) to dispense methadone
Does the pharmacy transfer custody of methadone doses to an exempted physician or his/her delegate for administration at a clinic?

NB: OCP must be notified of any changes to the information specified above (e.g., change in hours)

Training Requirements

Designated Manager must take the CAMH Opioid Use Disorder Treatment (OUDT) Course (or comparable course) within 6 months of beginning methadone dispensing.

https://www.camh.ca/en/education/continuing-education-programs-and-courses/continuing-education-directory/opioid-use-disorder-treatment-course

In addition to the DM, within one year, at least one staff pharmacist must take the CAMH OUDT Course (or comparable course) within one year.

Training must be updated every five years.
One of the following would be acceptable as a training update:

OPA one-day live program
or
OPA opioid addictions and substitution therapy online modules - completion of 5 online modules including Policies Guiding Methadone Dispensing in Ontario module
https://www.opatoday.com/224161

Although not mandatory, OPA methadone training courses would be beneficial for all pharmacists involved with methadone dispensing.

All pharmacists (regular and casual) who dispense methadone must be familiar with the principles and guidelines outlined in the current CAMH Opioid Agonist Maintenance Treatment: A pharmacist's guide to methadone and buprenorphine for opioid disorder 3rd edition

Required Documentation

Pharmacists should record relevant and pertinent details with regards to opioid therapy in an accessible and standardized manner in accordance with OCP Documentation Guidelines.

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https://www.ocpinfo.com/regulations-standards/practice-policies-guidelines/documentation-guidelines/

Documentation of decision that requires professional or clinical judgment that involves a change in therapy (holding dose, what to do when dose vomited etc.), Documentation should include: the decision, the rationale for the decision, expected patient outcome and plan for monitoring and follow up.

Treatment Agreement

A written two-way (pharmacist-patient) OR three-way (prescriber-pharmacist-patient) agreement serves as best practice to outline expectations and prevent miscommunication.
Items to be addressed in agreement may include:

- Expectations of all parties involved (hours of operation, consequences of inappropriate behaviour of patient)
- Patient's consent to access and share personal health information with other health professionals involved in their care
- Notice to the patient that methadone dose will be withheld if the patient appears to be intoxicated or under the influence of other substances
- Patient's acknowledgement that, if requested, they will be required to provide photo ID before receiving their dose
- Signature of Designated Manager (or delegated pharmacist) and the patient

NB: This agreement should be reviewed and re-signed when the pharmacy makes substantial changes to their policies or procedures regarding methadone

Record of dispensing of daily observed/witnessed and take-home/carry doses. This record of administration for MMT to include patient's name, daily dose, date, time, and place of observed administration.

When a physician or delegate administers the methadone in a clinic/treatment location (i.e., if transferring custody of doses), the dispensing pharmacist must be provided with copies of the daily administration record. Record of daily reconciliation of methadone dispensed to and received from a clinic/treatment location under transfer of custody agreements.

Record of destruction of unused doses in accordance with applicable laws and standards of practice.

If applicable, written institution[1]-specific policies for dispensing methadone (e.g., hospital, licensed nursing homes, correctional facilities)

1 Institution is a facility that is licensed, approved or designated by a province in accordance with the laws of that province to provide care or treatment to persons or animals suffering from any form of disease or illness; or is owned or operated by the Government of Canada or the government of a province that provides health service. This would include correctional facilities-both federal and provincial.

Note: these are not to be considered transfer of custody scenarios

Dosage Form

All doses (observed/witnessed and take-home/carry doses) must be prepared using a manufactured product (10mg/mL solution) diluted to at least 100mL with a vehicle that does not lend itself to injection (e.g., Tang®)

Equipment Needed

- An appropriate measuring device (e.g., calibrated pump) that can accurately deliver 0.1 mL increments.
- Note that graduated cylinders are not suitable.
- Disposable cups (approx.100ml) for observed doses,
- 100mL bottles for carry doses
- Childproof safety caps are required; tamper proof caps are recommended.

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- A lock box is recommended for take home/carry doses. The necessity for a lockbox should be discussed in collaboration with the prescriber and patient. Consideration should be given to the risks. Unsecured methadone doses may pose a risk while under the patient's custody – both in transit and at home.

Required auxiliary labelling for take home doses

- "Methadone may cause serious harm to someone other than the intended patient. Not to be used by anyone other than the patient for whom it was intended. MAY BE FATAL TO CHILD OR ADULT."
  OR "Methadone may cause serious harm to someone other than the intended patient. MAY BE FATAL TO CHILD OR ADULT."
- "Keep Refrigerated" auxiliary label for take home doses (may be typed as part of the prescription label)

Required References

The pharmacy must have access to the current text:

CAMH Guide Opioid Agonist Maintenance Treatment, 3rd edition
- To order - https://store-camh.myshopify.com/products/p6500

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Initiating MMT Services: A Brief Overview

Things to Consider Before Starting to Dispense Methadone

Pharmacy hours of operation – hours for methadone administration? Open seven days per week?
Pharmacy layout and workflow – private area for preparing methadone doses without distraction
A private area/alcove for counseling and witnessing methadone dose self-administration
Staffing Impact - adequate personnel, training and competency, professional satisfaction
Business Impact -impact on new clients, current patients and clientele
Impact on the surrounding community
Collaborations with methadone prescribers
Reimbursement

Develop policies on:

- Hours when methadone is dispensed
- Number of methadone clients
- Number of methadone clients in pharmacy at one time
- Service to methadone clients who are regularly serviced by other facilities (i.e., guest dosing)
- Assess staff competence to deliver methadone services in a non-stigmatizing environment
- Procedures to minimize dosing errors and optimize work processes
- Appropriate equipment (e.g., dispensing tools, measuring equipment, labels and labeling as regulated, child proof liquid bottles, tamper evident caps or seals [best practice])
- Documentation logs with information as regulated
- Establish patient care process for patient assessment, dispensing, witnessed administration, and management of difficult situations

Role of Pharmacist in MMT Program

- Assess patient care issues for the safe dispensing of observed/witnessed and carry/take-home doses.
- Monitor for signs and symptoms of withdrawal, intoxication and/or overdose.
- Observe for changes in patient's appearance or behaviour
- Aware of social and housing issues that may require special dispensing needs
- Ensure a process is in place for handling missed, lost, stolen or vomited doses
- Identify and address drug interactions
- Positive identification of the patient
- Observe ingestion of witnessed/observed doses
- Provide carry/take-home doses
- Awareness of when methadone doses must be withheld and physician immediately contacted (e.g., 3 or more missed doses in a row or as pre-established with prescriber; symptoms of intoxication such as slurred speech, stumbling gait, confusion, disorientation)
- Provide patient advice and information as necessary (e.g., signs and symptoms requiring immediate attention at various phases of methadone treatment and dosing, harm reduction education)
- Diversion alertness
- Determine physician's preferred method of communication (e.g., email, cell phone, etc.) especially after office hours
- Be familiar with the required guidelines for methadone dispensing
- Ensure all regulations are met in accordance with the pharmacist's assigned role
- Dispensing and billing roles pending staffing

Role of Pharmacy Technician in MMT Program

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- Enter/process prescriptions pending staffing
- Check prescriptions for technical accuracy
- Prepare individual patient doses
- Monitor return of empty bottles from carry doses
- Report discrepancies to supervising pharmacist (e.g., missing patient documentation, patient identification discrepancies, interaction codes, discoloration of solutions, unusual patient behaviour etc.)
- Billing/administrative issues as assigned by the pharmacy
- Maintain stock and required supplies

Methadone Label Requirements
(in addition to DPRA requirements for all prescriptions)

- Directions for use: "Drink entire contents of bottle"
- Dose in mg.
- A notation that the drug product has been diluted (i.e., "in orange drink")
- Date of ingestion for carry/take-home doses

Required auxiliary labels as per OCP Policy

- Methadone may cause serious harm to someone other than the intended patient. Not to be used by anyone other than the patient for whom it was intended. MAY BE FATAL TO CHILD OR ADULT."
  OR "Methadone may cause serious harm to someone other than the intended patient. MAY BE FATAL TO CHILD OR ADULT."
- "Keep Refrigerated" auxiliary label for take home doses (may be typed as part of the prescription label)

Preparing Methadone Dose

- Accurately measure commercially available methadone solution using an appropriate measuring device accurate to 0.1ml increments
- Diluents for methadone doses (witnessed/observed and take home/carry) may include Tang®, Crystal Light®, Kool-Aid®, and other brands of artificially sweetened crystals. It is important to note that stability data is lacking for the mixture of Methadose® in these drinks. The vehicle component will develop microbial contamination; therefore, it is recommended to refrigerate take home doses. In the absence of clinical stability and sterility data, USP 795 recommends a maximum beyond use date of 14 days for oral non-sterile preparations containing water, when stored at controlled cool temperature (i.e., Temperature thermostatically maintained between 2 and 8 degrees Celsius)
- Take-home/carry doses prepared in these diluents must be protected from extremes in temperature when transferring custody to a physician's clinic under delegation

Initiating a New Patient

- Copy of picture identification
- Current contact information (keep updated)
- Two or three-way treatment agreement signed by all parties
- Explain hours of operation and usual process/procedure
- Lock box and take-home/carry dose bottle return policy (as necessary)
- Counsel on safety and harm reduction

Physician - Pharmacist Collaboration

- Pharmacy and clinic hours of operation
- After hours contact information for physician and pharmacist
- Consistency in patient messaging and counseling for patient care issues
- Is a lock box required by the prescriber/clinic?

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

- Tamper proof caps/seals required by the prescriber/clinic?
- Return take home dose bottles?
- Procedures for missed appointments and missed doses?
- How to notify prescriber of missed doses?

Patient Treatment Agreement

2-way (pharmacist-patient) or 3-way (prescriber-pharmacist-patient)
Expectation of all parties and consequences may include:

- Consent to access and share personal health information among health care professionals involved in their care
- Pharmacy and clinic hours of operation
- Consequences of inappropriate behaviour
- Need for lock box and returned take home dose bottles (if applicable)
- Inability to have methadone dose if patient appears to be intoxicated and/or under the influence of other substances
- Notice to the patient that missed, lost, stolen or wasted doses will not be replaced without a prescription
- Patient's acknowledgement that, if requested, they will be required to provide photo ID before receiving their dose
- Sample patient-pharmacist agreement: https://www.porticonetwork.ca/documents/204049/0/Sample+MMT+Pharmacist-Patient+Agreement.pdf/53a7bad2-e344-49a1-b838-558663d26e3e

Witnessing a Dose

- Positive identification of patient (photo ID)
- Only the pharmacist can assess the patient in order to safely administer the dose
- Confirm the dose with the patient
- Prepare the dose and administer it in a container that will hold at least 100 mL of liquid (disposable cup or bottle)
- Ensure total volume is consumed and converse with patient to ensure dose was swallowed
- Cup is to be disposed of in the pharmacy
- Pharmacist and/or patient sign the record of administration

Documentation

Documentation of methadone ingestion must include the patient's name, daily dose, date, time and place where the administration was observed
All 'No-shows' (missed doses) communicated to prescriber
Patient receipt given, with dose documented- especially important when a patient is guest-dosing at another pharmacy.

Provision of Naloxone kits:
Naloxone is a Schedule II medication that can be provided by a pharmacist through funding from the Ontario Ministry of Health and Long-Term Care for 'emergency use' to temporarily prevent overdoses from opioids including methadone. Pharmacists must do a patient assessment and get the appropriate training to provide patient/agent education.
https://www.ocpinfo.com/library/practice-related/download/Naloxone.pdf

Resources

https://www.ocpinfo.com/library/practice-related/download/Methadose%20Article.pdf

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

Methadone Maintenance Dosing Guide

Methadone is prescribed in a way that balances the risk of adverse effects to the patient and people in their environment while optimizing the benefits, including retention in treatment and decreased health and quality-of-life harms related to substance abuse.

Methadone Pharmacokinetics

- Methadone is a long-acting, orally effective full mu-opioid receptor agonist – it exhibits no ceiling effect. Ceiling effect is the point at which the increasing effects of partial agonists reach maximum levels and do not increase further, even if doses continue to rise. Therefore, dosing must be managed in a manner to always minimize risk of overdose.
- Administration once per day mixed with orange drink (e.g., Tang®) or another suitable drink which does not lend itself to injection - QS to 100mL
    - Note: Split daily dosing may be beneficial to patients with the following conditions: chronic pain, pregnancy, rapid metabolism (due to genetics or drug interactions)
- Onset of Action: 30 minutes
- Time to peak plasma concentration after ingestion: 2 to 4 hours
- Steady state: 5 to 7 days
- Elimination half-life 22-48 hrs.

Some important dosing facts about Methadone Maintenance Therapy

- Most deaths with methadone treatment occur during the initiation phase or within the first two weeks as the dose is adjusted.
- Accidental overdoses in adults of as little as a starting dose of 40 mg have led to deaths after 3 days of treatment.
- For non-tolerant adults, a single day's maintenance dose as low as 50-100 mg can be lethal.
- For children, an accidental overdose of 10 to 20 mg can be fatal.
- The effectiveness of methadone maintenance therapy is tied to adequacy of methadone dosing. Adequate dosing can result in treatment retention and reduction in illicit opioid use.
- Patients should be on same dose for at least three consecutive days; although the frequency of dose adjustment ranges are based on various clinical parameters (stage of titration, base dose, risks of toxicity etc.). There should be no missed dose before a dose increase.
- All missed doses must be communicated to the prescriber.

Phases in Methadone Dosing

Induction (or Initiation) Doses 'Start Low'
Goal is to reduce withdrawal or abstinence symptoms safely.

An initial dose of 10mg or less should be prescribed; then doses increased by no more than 5mg every 5 days (as necessary) for patients who:

- Are recently abstinent or use intermittently
- Have unknown tolerance to opioids due to unclear history or lack of collateral information
- Use low-potency opioids (e.g., codeine)

An initial dose of 5-20mg should be prescribed; then doses increased by 5-10mg every 3-5 days (as necessary) for patients who:

- Have established tolerance via patient history or collateral information (e.g., UDT results)
- Have risk factors that include:
    - High or multiple CNS depressant use (e.g., alcohol, antipsychotic, benzodiazepine, gabapentoid)
    - Medical illness involving respiratory compromise (e.g., chronic obstructive pulmonary disease)
- Have changes in drug metabolism

An initial dose of 5-30mg should be prescribed; then increase doses by 5-15mg every three to five days (as necessary) for patients who both:

- Have high tolerance of high-potency opioids from daily use and have UDT confirmation of recent opioid use

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- Do not have risk factors for excessive CNS depression (as listed above)

Exercise extreme caution if you are considering rapid and high dose titration (increasing the methadone dose by more than 10mg at a time in a period under five days).

Reassess patients frequently during the first two weeks of treatment because they are at the highest risk of fatal overdose during this period. Discuss the risks and strategies to reduce it (e.g., use only small amounts of additional opioids; do not use alone; have a naloxone kit available).

Reassess the patient with every subsequent dose increase.

Titration and stabilization Phase

The dose should be increased 5-10mg every five to seven days to manage withdrawal symptoms and cravings.

Maintenance Phase
An appropriate maintenance dose is determined through clinical judgment i.e., one which provides 24hours without opioid withdrawal and reduction of opioid cravings while not causing sedation or toxicity.

Consideration should be given to tapering down the dose for patients experiencing opioid-induced side effects (e.g., sweating, hypogonadism, severe constipation, adrenal insufficiency. Also, collaborate with the patient to balance the benefits, disadvantages and risks of methadone treatment.

Rapid metabolism is confirmed with serum methadone levels and/or observing emergence of withdrawal after an observed dose.

There is no consensus on the best way to assess the need for split dosing. Consideration should be given to clinical stability before offering split dosing. It often requires providing evening doses as take-home doses as most patients are unavailable to attend a pharmacy for witnessed dosing.

Assessment of post-dose sedation at peak serum levels should be done for patients on high doses of methadone.

Missed doses
- One or two doses: the dose is not reduced unless there are concerns about loss of tolerance or adverse events
- Three doses: the dose should be decreased by 50 percent
- Four or more doses: the dose should be decreased to 30mg or less

A stable methadone dose should be re-established after several missed doses. This may not be the same as the previous dose,
One replacement dose of methadone (no more than 50 percent of the regular dose) should be offered if the patient has emesis witnessed by a health care professional occurring withing 15 minutes of an observed dose. If emesis occurs during pregnancy, the dose should be spread over 30 minutes and consider observing for 15-20 minutes after dosing.
https://www.ocpinfo.com/library/practice-related/download/Importance%20of%20Missed%20Doses.pdf

Signs of Opioid Intoxication
- Sedation ('nodding off')
- Slowed or slurred speech
- Motor retardation
- Euphoria
- Dysphoria
- Pinpoint pupils

Opioid intoxication occurs when opioids are taken in excess of the individual's level of tolerance and may progress into overdose. Medical attention is required if patients exhibit signs of sedation, motor retardation or slurred speech

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Signs of Overdose

- Respiratory depression – infrequent or shallow breathing, change in skin colour
- Circulatory collapse – slow pulse and low blood pressure
- Severe sedation, including stupor and coma
- Cardiac arrest
- Death

Opioid overdose is considered a medical emergency as it can be fatal.

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Resources

OCP Opioid Policy
https://www.ocpinfo.com/regulations-standards/practice-policies-guidelines/opioid-policy/

OPA Methadone and Buprenorphine/Naloxone Toolkit for Pharmacists
https://opatoday.com/download/methadone-and-buprenorphine-toolkit/

OPA Opioid Addictions and Substitution Therapy Online Modules (FREE)
https://opatoday.com/product/opioid-substitution/

CAMH Methadone Maintenance Treatment: Recommendations for Enhancing Pharmacy Services-2009
https://www.porticonetwork.ca/documents/77404/475940/mmt_enhancing_pharmacy_services.pdf/52d1a5d9-8a42-4b23-964c-c0bba6ccc8ae

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain
https://www.cmaj.ca/content/cmaj/suppl/2017/05/03/189.18.E659.DC1/170363-guide-1-at-updated.pdf

Naloxone dispensing and training resources
http://www.ocpinfo.com/regulations-standards/policies-guidelines/naloxone-guidance/

Canada's Mental Health & Addiction Network
https://www.porticonetwork.ca/web/opioid-toolkit

Addiction Treatment Forum
http://atforum.com/

Connex Ontario: Addiction, Mental Health, and Problem Gambling Treatment Services
https://www.connexontario.ca/en-ca/

OPA Opioid Substitution Therapies Discussion Forum
http://methadoneforum.opatoday.com/

CAMH Making the Choice, Making It Work, Treatment for Opioid Addiction 2nd edition
(Formerly Methadone Maintenance Treatment: Client Handbook)
https://www.porticonetwork.ca/web/knowledgex-archive/amh-specialists/mmt-client-handbook

CAMH Opioid Agonist Maintenance Treatment 3rd edition 2015. Available for purchase at-
https://store-camh.myshopify.com/products/p6500

CAMH Primary Care Addiction Toolkit
https://www.porticonetwork.ca/tools/toolkits/pcat

CRISM National Guideline for the Clinical Management of Opioid Use Disorder
https://crism.ca/projects/opioid-guideline/

NAPRA Model Standards for Pharmacy Compounding of Non-sterile Preparations
https://napra.ca/general-practice-resources/model-standards-pharmacy-compounding-non-sterile-preparations

CAMH Opioid Agonist Therapy: A Synthesis of Canadian Guidelines for Treating Opioid Use Disorder May 2021
https://www.camh.ca/-/media/files/professionals/canadian-opioid-use-disorder-guideline2021-pdf.pdf

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

Live Telephone Resources

CAMH Addiction Clinical Consultation Service
- 416-535-8501, press 2
- (M-F 8:30AM - 5PM)

OPA Opioid Substitution Therapy Drug Information Line
- 1-888-519-6069 (M-F 9AM-5PM)
- Email: methadone@opatoday.com

CPSO Methadone Infoline (for prescribing)
- 416-967-2600 ext. 603

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

ONTARIO PHARMACISTS ASSOCIATION

Advocating Excellence in Practice and Care

Methadone and Buprenorphine/Naloxone Toolkit for Pharmacists

Part B: Buprenorphine/Naloxone

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Disclaimer

These tools have been developed by the Ontario Pharmacists Association (OPA) for pharmacists in Ontario as a general guide to support those wishing to initiate a buprenorphine/naloxone program in their pharmacy setting. The resource materials provided in this toolkit are for general information purposes only and are NOT meant to be used "as is".

This toolkit is complementary and is not inclusive of all recommendations and considerations. The information provided is not a substitute for sound clinical judgement from the health care professional. Pharmacists are to exercise their professional judgment in accordance with the Ontario College of Pharmacists (OCP) Standards of Pharmacy Practice. This tool is not a substitute for established clinical practice guidelines or regulatory requirements. It is not intended to supersede or replace guidelines, practice standards, policies or procedures issued by OCP, the Ministry or corporate employers. It is also not intended, and should not be construed, as legal or professional advice or opinion.

While OPA strives to ensure the accuracy of the information provided in this document, information may be subject to change, and it is the responsibility of the user of this document to ensure they have the most up-to-date and complete information from available resources.

Note: During the COVID-19 pandemic, modifications to the standard guidelines have been made in order to reduce community transmission. Please refer to the CAMH document "COVID-19 Opioid Agonist Treatment Guidance" for further information on these modifications to treatment delivery.

Acknowledgement

Compilation of this toolkit required the dedicated effort of many individuals. The Ontario Pharmacists Association would like to thank the following for their tireless work in revising and reviewing the toolkit for the benefit of all Ontario pharmacists and the patients they serve: Rose Fitzgerald, B.Sc.Phm., RPh; Satinder Sanghera, B.Sc.Phm., RPh; Andrew Tolmie, B.Sc.Phm., RPh; Shamim Rajan; Dr. Alice Ordean, MD, CCFP, M.H.Sc, FCFP ; Mohammad-Usman Imran, B.Sc.Phm., RPh; and the Ontario College of Pharmacists.

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health for funding this initiative.

Full update: October 2021

Opioid Agonist Maintenance Treatment (OAMT)

What is Opioid Agonist Maintenance Treatment (OAMT)?

It involves the prescribing of methadone or buprenorphine as part of a comprehensive program which includes counselling to help the person in treatment reduce or stop the harmful use of opioids. (Kleber, 2008).
Currently, methadone and buprenorphine are the most prescribed treatment options. Methadone is the most studied and longest used pharmacological treatment for opioid dependence. A third option, oral slow-release morphine (e.g., Kadian®) may be used as OAMT in individuals who have not benefited from treatment with first line and second line treatment options (i.e., buprenorphine/naloxone and methadone). In Canada, this use is considered **off-label**, and requires careful review of the risks and benefits, fully informed consent of the patient and rigorous clinical documentation.

OAMT as a Harm Reduction Approach

Any program or policy designed to reduce drug-related harm without requiring the cessation of drug use. Interventions may be targeted at the individual, the family, community or society (Erickson et al, 2002).

Harm reduction includes both strategies that focus on reducing drug use and those that focus on reducing the harm of drug use.

OAMT has been shown to reduce:

- Use of other opioids (Brand et al., 2003; Davioli et al., 2007; Gibson et al., 2008)
- Criminal activity (Lind et al, 2005) as OAMT is legal and may keep patients away from the harmful consequences of acquiring and possessing illicit opioids and prescription opioids
- Patient mortality rates (Degenhardt et al., 2011; Gibson et al., 2008; Soyka et al., 2011) compared to people who continue to use opioids
- Injection-related risk (including behaviours and transmission of HIV and sexually transmitted infections (Hart, 2007)
- Cost of law enforcement, health care and social services for patients who are unemployed, homeless or in other difficulties (Hart, 2007)

OAMT improves (Brands et al., 2002)**:**

- Physical and mental health
- Social functioning
- Quality of life
- Pregnancy outcomes

In contrast to many short-acting opioids (e.g., heroin), methadone and buprenorphine:

- Are well absorbed and effective orally (methadone) or sublingually (buprenorphine)
- Take longer (e.g., 30 minutes vs. instantaneously) to produce an effect than opioids that are injected, smoked or snorted
- Are longer acting than other opioids (24 to 36 hours or longer vs. three to six hours) and are administered less frequently (once daily vs. three or more times daily)
- Do not cause drowsiness or euphoria in patients on an appropriate dose
- Do not cause significant impairment in thinking, behaviour or functioning when taken at an appropriate dose
- Do not dull normal emotions and physical sensations
- Diminish opioid craving
- Decrease drug-seeking behaviour
- Reduce the likelihood of euphoria from other opioids in stable patients

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- Continue to be effective with long-term use without dose increases

Limitations to the use of OAMT

- Methadone is a high-risk medication with a narrow therapeutic range that can result in opioid overdose, especially at the beginning of treatment. It may prolong QT interval, leading to an increased risk of fatal arrhythmias.
- Buprenorphine has a lower overdose mortality risk but can still have severe health consequences including death – especially, if misused or combined with other CNS depressants or alcohol.
- People (including health professionals) may inadvertently or inappropriately label patients as 'still addicted', thus stigmatizing them further.
- Program practices may be experienced by patients as demeaning (e.g., observed urine collection, waiting in line at the pharmacy for their dose).
- OAMT requires regular visits to the pharmacy, physician and counsellor.
- Cost may be a barrier for some patients.
- Both buprenorphine and methadone can produce adverse side-effects and may interact with other medications.
- OAMT practices may limit patient's 'flexibility' for work or travel.
- There may be limited availability of physicians and pharmacies that offer OAMT.
- Pharmacists can aid their patient's recovery by supervising drug administration, monitoring their dosage, communicating with the treatment team, dispensing take-home doses in accordance with established guidelines and providing encouragement and support.

CAMH Opioid Agonist Maintenance Treatment: A pharmacist's guide to methadone and buprenorphine for opioid use disorder. Third edition 2015

Information on Buprenorphine/Naloxone

CPSO expects all physicians who prescribe buprenorphine for opioid use disorder treatment to have training/education on addiction medicine generally, prior to initiating buprenorphine treatment. Physicians should collaborate with pharmacists and other members of the patient's interprofessional health care team.

There is no policy governing the prescribing or dispensing of buprenorphine/naloxone.

Buprenorphine/naloxone is rapidly available as the first-line treatment for patients with Opioid Use Disorder. It is recognized that for many patients, any opioid agonist treatment carries a substantially lower risk of adverse events than no opioid agonist treatment.

Consider treatment intensity when determining the most appropriate opioid agonist treatment option. Adjust the treatment to accommodate the changing circumstances and preferences of the patient.

Initiate opioid agonist treatment with buprenorphine/naloxone whenever it is assessed to carry a lower risk than other agonist therapies because of its pharmacological characteristics and the advantages of more flexible take-home dosing.

Consider long-acting preparations of buprenorphine - monthly injections (Sublocade®) or Probuphine® six-month subdermal implants when appropriate to facilitate integration into society and reduce health care burden.
https://pharmacyconnection.ca/opioid-use-disorder-treatment-spring-summer-2020/

Initiate opioid agonist treatment with methadone when treatment with buprenorphine/naloxone is not preferable (e.g., intolerance, patient preference, challenging induction, inadequate response to buprenorphine/naloxone).

Some patients who show a successful and sustained response to methadone may wish to transition to buprenorphine/naloxone. This is an option for patients who:

- Request more treatment flexibility with increased take-home doses
- Are seeing a better side-effect and drug-interaction profile
- Wish to withdraw from opioid agonist treatment but have difficulty tapering off methadone and might better tolerate a taper from buprenorphine/naloxone

The decision to transition to buprenorphine/naloxone must be balanced with potential risks of destabilization, which may increase when transitioning from higher methadone doses. To mitigate risk, the methadone should be slowly reduced before making the transition, microdose buprenorphine/naloxone or switch to slow-release oral morphine for five days after stopping methadone and before initiating buprenorphine/naloxone.

Induction Phase

Prescribe 2-4mg of buprenorphine/naloxone as an initial supervised dose when the patient is in moderate to severe withdrawal (COWS >13). U to 6mg is acceptable in clinically required situations but may increase the risk of precipitating withdrawal.

Reassess the patient after one to three hours and prescribe additional observed doses if necessary (COWS >8), symptoms of withdrawal).

- Be careful not to precipitate withdrawal by giving too high a dose or by medicating in the absence of observable withdrawal
- One or two 2mg tabs to take home may be provided if repeated observation is not feasible in the clinical setting, with clear instructions on timing the dose to avoid precipitating withdrawal

Avoid prescribing more than 12mg total on the first day.

Consider alternative induction approaches such as 'microdosing' or 'rapid microdosing'.
https://pharmacyconnection.ca/opioid-use-disorder-treatment-spring-summer-2020/

Titration and Stabilization Phase

Titrate based on withdrawal symptoms and side effects until an optimal dose has been reached, typically on day 3. Doses may be doubled every day, up to a maximum of 24mg on day 3.

Consider an alternative approach: add up the dose given on day 1 and administer it as the first dose of day 2, followed by additional doses based on the re-emergence of withdrawal symptoms. On day 3, add up the doses administered on day 2 and provide additional doses as necessary. Repeat daily until the patient is stable (no withdrawal, or COWS scores <8 for 24 hrs.) or until a maximum of 24mg per day is achieved.

Use slow titration with older adults, patients taking other CNS depressants and patients with questionable opioid tolerance, balancing the risk of lower treatment retention with the risk of over-sedation:

- Increase buprenorphine/naloxone by 2-6mg per day until an optimal dose has been reached (24hrs with no withdrawal symptoms, extinction of cravings to use opioids, absence of toxicity).

The patient should be seen by a member of the health care team to assess effectiveness and safety (e.g., excess sedation). Base reassessment frequency on the intensity of induction.

Maintenance Phase

Use clinical judgment to maintain an optimal individualized daily dose, which is up to a max of 24mg per day.

- If exceeding 24mg in exceptional circumstances, inform the patient that this is a departure from approved doses (Limited evidence of a benefit for higher doses & an increased risk of adverse events).

Recognize alternate-day dosing as an option for patients who are clinically stable at doses less than or equal to 12mg per day (i.e., 24mg every other day) and who require less frequent visits to the pharmacy for dosing.

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

- Balance this with the challenges in managing missed doses. The patient should be reassessed for toxicity/sedation when given this higher dose. Communicate between pharmacist and prescriber is critical.
- Take-home doses or switching to an extended-release formulation may be a better approach than alternate-day dosing.

There is an option of switching to buprenorphine extended-release monthly injection (Sublocade®) or the six-month subdermal implant (Probuphine®) to enhance medication adherence and convenience for patients who are clinically stable.
Discuss switching to buprenorphine injection or implant if the patient also:

- Requires less frequent medication administration
- Is comfortable with an invasive procedure or device
- Does not want to administer medications sublingually
- Has drug coverage

Take Home Doses

Urine drug screens should be done at least monthly during induction and dose escalation until the patient has achieved a stable dose. Urine screens are useful to determine take-home dosing

Missed Doses

For missed doses with no relapse to full opioid agonist use:

- <5 days – resume previous dose
- >6 days – adjust the dose based on the total daily dose and the number of missed doses
- 2 alternate-day doses – suspend buprenorphine/naloxone until the patient can be reassessed. Then return the patient to a daily dose schedule, possibly at a lowered dose, to restabilize them before resuming an alternate-day schedule.

For missed doses due to relapse or return to full agonist opioid use – advise the patient to stop using buprenorphine/naloxone until they are ready to resume opioid agonist treatment. Schedule a new induction date and return to the process in the 'induction phase'.

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Initiating a Buprenorphine/Naloxone Program in Your Pharmacy

Abbreviations:
Ontario College of Pharmacists (OCP); College of Physicians and Surgeons of Ontario (CPSO); Centre for Addiction and Mental Health (CAMH); Clinical Opiate Withdrawal Scale (COWS)

Information to provide to OCP

Unlike methadone, there is no requirement to report the decision to dispense buprenorphine/naloxone for opioid use disorder treatment.

Training Information for staff

Designated manager and all pharmacists (regular and casual) should be familiar with the principles and practice guidelines on buprenorphine/naloxone. There is no OCP Policy for specific mandatory training, as there is with methadone.

Information for physicians

CPSO expects all physicians who prescribe buprenorphine for opioid use disorder treatment to have training/education on addiction medicine generally, prior to initiating buprenorphine treatment.

Required Documentation

- A written/faxed prescription from any prescriber who is eligible to prescribe narcotics.
- Best practice is a 2-way (Pharmacist-Patient) or 3- way (Pharmacist-Patient-Physician) Treatment Agreement which may include:
    - Expectations of all parties involved
    - Circumstances under which treatment agreement will be in place - "Pharmacy's rules"
    - Consent to access and share personal health information as it relates to buprenorphine/naloxone treatment
    - Signature of Designated Manager or delegated pharmacist as determined by written policy
    - Signature of the patient
- Patient's acknowledgement that they may be required to provide photo ID before receiving their buprenorphine/naloxone dose(s)
- Record of dispensing of witness/daily doses and take home/carry doses
- Tracking of missed doses of buprenorphine/naloxone must be readily retrievable, using a tracking tool/record of dose administration
- All missed doses should be communicated to the prescriber
- Record of administration to include patient's name, daily dose*, date, time, and place of observed administration.
  *daily doses can be prepared using different combinations - document for future reference
  e.g., for 12mg, can use [8mg + 2 x 2mg] or [1.5 x 8mg]
- Record of destruction of unused doses must be handled in accordance with applicable laws, standards of practice, and OCP policy

Supplies

- Childproof vial for take home/carry doses
- Patient lockbox, if applicable

Recommended Resources:

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

OCP Article – Buprenorphine for Opioid Use Disorder Treatment: Focus on New Formulations and Alternative Induction Protocols

- https://pharmacyconnection.ca/opioid-use-disorder-treatment-spring-summer-2020/

OPA Methadone, Buprenorphine and the Community complimentary online and/or live program

- https://opatoday.com/product/methadone-buprenorphine-and-the-community-march-2021/

OPA Methadone and Buprenorphine/Naloxone Toolkit for Pharmacists

- https://opatoday.com/download/methadone-and-buprenorphine-toolkit/

CAMH Opioid Use Disorder Treatment (OUDT) Course

- http://www.camh.ca/en/education/continuing-education-programs-and-courses/continuing-education-directory/opioid-use-disorder-treatment-course

CAMH Buprenorphine-Naloxone Treatment for Opioid Use Disorder

- http://www.camh.ca/en/education/continuing-education-programs-and-courses/continuing-education-directory/buprenorphine-naloxone-treatment-for-opioid-use-disorder

CPSO Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline

- http://www.cpso.on.ca/admin/CPSO/media/Documents/physician/your-practice/quality-in-practice/cpgs-other-guidelines/buprenorphine-naloxone-guidelines.pdf

CAMH Opioid Agonist Maintenance Treatment, 3rd edition

- To order - https://store-camh.myshopify.com/products/p6500

Web Resources

- Canada's Mental Health & Addiction Network
  - https://www.porticonetwork.ca/web/opioid-toolkit/treatment/buprenorphine-naloxone
- OPA Professional Development Website
  - https://www.opatoday.com/professional/resources/education/learn
- Addiction Treatment Forum
  - http://atforum.com/
- OPA Opioid Substitution Therapies Discussion Forum
  - http://methadoneforum.opatoday.com/

Telephone Resources

- CAMH Addiction Clinical Consultation Service
  - 416-535-8501, press 2
  - Open Mon – Fri 8:30AM-5PM
- OPA Methadone Drug Information Line
  - 1-888-519-6069 (open M-F 9AM-5PM)
  - Email: methadone@opatoday.com

OPA resources are made possible with the support of the Ontario Ministry of Health and Long-Term Care

Things to Consider Before Starting to Dispense Buprenorphine/Naloxone

- Pharmacy layout and workflow
- Need for a private area for counseling and witnessing doses
- Staffing impact: adequate personnel, training and competency, professional satisfaction
- Collaborations with buprenorphine/naloxone prescribers
- Reimbursement: will patients pay cash or bill to third party plan?
- Service policies and limitations on:
    - hours when buprenorphine/naloxone is dispensed
    - number of buprenorphine/naloxone clients
    - number of buprenorphine/naloxone clients in pharmacy at one time
- Service to buprenorphine/naloxone clients, regularly serviced by other facilities (i.e., guest dosing)
- Harm reduction assessment
- Assess staff competence to deliver buprenorphine/naloxone services in a non-stigmatizing environment
- Procedures to minimize dosing errors and optimize work processes
- Appropriate equipment (e.g., dispensing labels and labeling as regulated, child proof bottles, Information resources, and lockboxes if necessary)
- Dosing documentation logs
- Establish patient care process for patient assessment, dispensing, witnessed administration, and management of difficult situations
- Witnessing buprenorphine/naloxone ingestion requires longer time than methadone ingestion, so, staffing levels will need to be adjusted – where will the patient wait?

Role of Pharmacist in Buprenorphine/Naloxone Program

- Assess patient care issues for the safe dispensing of witness doses or take-home doses
    - Monitor for signs and symptoms of intoxication or overdose
    - Observe change in patient's appearance or behaviour
    - Social and housing issues that may require special dispensing needs
    - Process for missed, lost or stolen doses
    - Monitoring of drug interactions
- Positive identification of the patient (e.g., correct patient for the dose prescribed)
- Observe witnessed daily dose
- Provide take-home dose(s)
- Awareness of when buprenorphine/naloxone doses must be withheld, and physician immediately contacted (e.g., symptoms of intoxication such as slurred speech, stumbling gait, confusion, disorientation)
- Provide patient advice and information as necessary (e.g., signs and symptoms requiring immediate attention at various phases of buprenorphine/naloxone use and dosing) – reinforce safety risks
- Diversion alertness
- Determine physician's preferred method of communication especially after hours (e.g., email, cell phone)
- Be familiar with best practices and guidelines for buprenorphine/naloxone dispensing
- Ensure all regulations are met in accordance with the pharmacist's assigned role
- Dispensing and billing roles pending staffing

Role of Pharmacy Technician in Buprenorphine/Naloxone Program

- Enter/process prescriptions
- Prepare individual patient doses

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- Report discrepancies to supervising pharmacist (e.g., missing patient documentation, identification discrepancies, interaction codes, unusual patient behaviour)
- Billing/administrative issues as assigned by the pharmacy
- Maintain stock and required supplies
- Check prescriptions for technical accuracy

Buprenorphine/Naloxone Label Requirements
-best practices in addition to DPRA requirements for regular prescriptions

- Specify to "Dissolve tablet under the tongue"
- Total daily dose in mg.
- Ingestion date(s) when specified on prescription order (e.g., patients that receive dose every other day)
- Child-resistant cap for take home doses
- Required auxiliary label as per OCP Opioid Policy

Initiating a New Patient

- Copy of picture identification
- Current contact information
- Treatment Agreement (Best Practice): 2-way (pharmacist-patient) or 3way (prescriber-pharmacist-patient) agreement signed by all parties
- Explain hours of operation, usual process/procedure
- Lock box policy (considered best practice)
- Establish and discuss with prescribers (including nurse practitioners) whether patient is in at least moderate opioid withdrawal (i.e., COWS >13) prior to administering first dose
- Counsel on safety and harm reduction including how to recognize and temporarily reverse an opioid overdose by using a Naloxone Kit
- Notify patient that witnessing dissolving of buprenorphine/naloxone tabs takes longer than methadone ingestion – patient should be prepared to schedule visits to the pharmacy to accommodate

Physician/Pharmacist Collaboration

- Pharmacy and clinic hours
- After hours contact information for physician and pharmacist
- Pharmacy and clinic procedures
- Consistency in patient messaging and counseling
- Patient care issues
- Is a lock box required? (Considered as best practice)
- How to notify prescriber about missed doses (fax, cell number, email etc.)

Patient Treatment Agreement (Best practice)

- 2-way agreement (pharmacist-patient) or 3-way (prescriber-pharmacist-patient) https://www.porticonetwork.ca/documents/489955/0/Buprenorphine+and+Naloxone+-+Clinical+Practice+Guidelines+2012+PDF/fd1eee5d-fd7f-4b58-961f-b45350a8b554 page 91
- Optional but best practice
- Expectation of all parties and consequences may include:
    - Consent to access and share personal health information among health care professionals involved in their care.
    - Pharmacy and clinic hours of operation and procedures
    - Consequences of inappropriate patient behaviour

- Patient care issues
- Need for consistency in timing of doses
- Need for lock box (considered best practice)
- Notice to the patient that missed, lost, stolen or wasted doses will not be replaced without a new prescription
- Inability to have dose if patient appears to be intoxicated
- Procedures for traveling
  Patient's acknowledgement that, if requested, they will be required to provide photo ID before receiving their dose

Witnessing a Dose

- Positive identification of patient (photo ID)
- Pharmacist must assess the patient for signs of intoxication prior to administering the dose
- Press sublingual tab out of foil and into a medicine cup (avoid handling tab)
- Ensure total dose is consumed (be aware of potential for diversion)
- After 1 to 2 minutes, discreetly and respectfully ask patient to lift tongue to display partially dissolved tablet.
- Advise patient not to talk or drink while the tablets are dissolving, as this can result in less of the tablet being absorbed sublingually
- Paper cup to be disposed of in secure pharmacy area
- Pharmacist and/or patient sign record of administration (best practice)
- Patient may leave once the tablet is fully dissolved
- To minimize the risk of diversion, the pharmacist may consider "chunking" or "crushing" the dose to speed up dissolution time – there may be a difference in effect in patients receiving crushed or chunked tabs when attending different pharmacies

Documentation

- Document on the observed dose record, or on the hard copy of Rx, the patient's name, daily dose, date, place and the time of administration noting if a witness or take-home dose was given
- Record of administration
- No shows/ missed doses to be communicated to the prescriber
- Patient receipt is given, with the dose documented-important when patient is guest - dosing at another pharmacy. (i.e., receipt) may be used as evidence of last dose)

Dispensing Buprenorphine/Naloxone at A Glance

New patient presents a prescription for buprenorphine/naloxone for opioid use disorder treatment

A Controlled Drugs and Substances Act (CDSA) Prescriber Exemption is not required.
The CPSO expects physicians to undertake training in addictions medicine and buprenorphine/naloxone prescribing.

Prescription should include:
- Dose written in numbers and words
- Directions "dissolve under the tongue"
- Start and stop dates (use the word "inclusive" to minimize ambiguity)
- Specific details for days to be observed, or days patient may have take-home doses
- Confirm Narcotics Monitoring System (NMS) requirements and evaluate NMS alerts

NB: Buprenorphine/naloxone is not officially approved for treatment of pain in Canada

Wastage and Destruction

Health Canada no longer requires prior authorization requests for the local destruction of Narcotics and Controlled Drugs
- http://www.ocpinfo.com/practice-education/practice-tools/fact-sheets/destruction/

Prescription Labelling Requirements

Label must include:
- "Dissolve under the tongue"
- Total daily dose in mg.
- Usual prescription labelling requirements

For take home doses include:
- Child resistant vial
- Lockbox (best practice)
- Usual auxiliary labelling for opioid narcotics
- Ingestion dates for take home doses

Take-Home Doses

- Do not dispense buprenorphine/naloxone take home doses unless authorized by prescriber
- Usually, can initiate take homes after 2 months of clinical stability
- Provide tablets to patient in childproof vial
- Once patient qualifies, the take home dose schedule is defined by the prescriber. The usual number of take-home doses can range from one to a recommended maximum of one to two weeks.
- If applicable, explain benefits of a locked box to the patient

Initiating a New Patient

NOTE: ALL staff in a pharmacy that serves methadone/buprenorphine patients should be trained to communicate effectively and are given the necessary skills to reason, deescalate, and be empathetic to patients that have unique needs. The needs of such patients may differ from those that they may be used to interacting with.

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long-term care for funding this initiative.

- Collect patient information including date of birth, drug allergies, medical history, current medications including OTC's, use of alcohol and cannabis
- Request a copy of picture identification
- Ensure correct contact information is recorded (home, work, cell phone number, address)
- Collect a signed 2-way agreement (pharmacist-patient), but a 3-way agreement (physician-pharmacist-patient) is preferred if possible – Best practice
- Explain the pharmacy's hours of operation, usual process and procedures
- If the pharmacy is closed on a given day, other arrangements must be made, and proof of last dose must be presented

Witnessing a Buprenorphine/Naloxone Dose

- Positively identify the patient (using picture ID if necessary)
- Pharmacist to assess the safety of administering a dose - note the visual appearance, eyes, gait) - do not give a dose if the patient appears to be intoxicated or under the influence of substances
- All tablets should be administered at the same time. You may split tablets to speed up dissolution. (Do not crush tablets.) Provide water to the patient before dosing to moisten mouth and potentially decrease time it takes for tabs to dissolve
- Press sublingual (SL) tablet(s) out of foil and into a medicine cup (avoid handling tablet)
- Have the patient wait within view of the pharmacy area while the tablet dissolves. After 1 to 2 minutes, have the patient show the partially dissolved tablet. Patient may leave once the tablet is fully dissolved.
  NB: May take up to 10 min. to fully dissolve
- Patient should not eat or drink for approx. 5 min. before and after dose
- Document the time of ingestion and have the patient and/or pharmacist sign the record of dispensing

Minimizing Risk

- Use childproof vials for take home doses
- Positively identify all patients (photo ID)
- Confirm the dose with the patient before it is consumed
- If a patient is receiving buprenorphine/naloxone from two different pharmacies, have an effective communication system to ensure communication of all doses received, dose changes or missed doses.
- Advise patients that relief of opioid withdrawal symptoms usually begins 20-40 min. after the initial dose of buprenorphine
- Advise patients that serious respiratory depression has occurred when combined with CNS depressants including other opioids, alcohol, benzodiazepines, certain antidepressants, sedating antihistamines and barbiturates

Pharmacology of Buprenorphine (sublingual tablets)

- Buprenorphine is a synthetic opioid, acting as a partial mu agonist at the mu-opioid receptors of the CNS and peripheral tissues
- As a partial agonist, buprenorphine has a ceiling effect to its opioid agonist effects at higher doses, making it safer in overdose & reducing its potential for abuse
- Poor oral bioavailability due to extensive first-pass metabolism
- Administration sublingually once per day or every other day
- Absorption: rapid with sublingual administration
- Onset of effects: 30-60 minutes
- Time to peak plasma concentration: 90 minutes
- Peak clinical effects: 1-4 hrs.

- Duration of effects: 48-72 hrs.
- Time to steady state: 5-10 days
- Elimination Half-life: 28-37 hrs.
- May be associated with fewer and less severe drug interactions when compared with methadone.
- Metabolized primarily by CYP 3A4; lesser by CYP 2C8

Pharmacology of Naloxone

- An opioid antagonist with a relatively short half-life that is included with buprenorphine to deter misuse of buprenorphine through injecting or snorting of the sublingual tablets.
- Poor oral bioavailability. No clinically significant effects when taken sublingually
- Naloxone is used intravenously, intramuscularly or intranasally to treat opioid overdose.

Adverse Effects	Withdrawal Symptoms
• dose related-similar to other opioids • constipation • headache • CNS depression (sedation) • euphoria • sweating • nausea • insomnia • orthostatic hypotension	• headache • GI upset • nausea • diarrhea • runny nose • sweating

Toxic Effects/Severe Symptoms
- Respiratory depression (delayed and prolonged)

Buprenorphine/Naloxone Combination Product Dosing Guide

Disclaimer: Individual variability in buprenorphine/naloxone effect and pharmacokinetics need to be considered when dosing buprenorphine/naloxone. There is no induction dose considered to be absolute safe for all patients. Health professionals are advised to use their professional judgment and refer to available literature when dosing buprenorphine/naloxone.

Some Important Dosing Facts About Buprenorphine/Naloxone*

- Buprenorphine is a partial mu agonist at opioid receptors
- Buprenorphine is a partial agonist and has a 'ceiling effect' to its opioid agonist effects at higher doses, therefore making it safer in overdose and reducing its potential for abuse
- Serious respiratory depression has occurred when combined with CNS depressants including other opioids, alcohol, benzodiazepines, certain antidepressants, sedating antihistamines and barbiturates
- For patients with children, the use of child proof vials and lockboxes for take home doses can prevent accidental overdoses
- The effectiveness of opioid maintenance therapy is tied to adequacy of dosing. Adequate dosing can result in treatment retention and reduction in illicit opioid use.
- Buprenorphine has a very high binding affinity for the opioid receptor and can precipitate withdrawal in patients who have recently used other opioids with lower affinities, including morphine or methadone.
- Wait to initiate therapy with buprenorphine/naloxone until at least 6 to12 hours (best is 12 hours) after use of short-acting opioids; or at least 12 to 24 hours or longer (best is 24 hrs.) after use of slow release opioid; 36-72 hours after long-acting opioid (e.g. transdermal Fentanyl®, methadone)
- For those patients switching from methadone to buprenorphine, it is preferable to wait 3 or more days after last dose of methadone; in addition, the transition should occur after having tapered methadone dose to 30mg or less to minimize risk of precipitated withdrawal
- Note: A microdosing approach in which buprenorphine/naloxone initiation overlaps with administration of initial opioid may be used in patients who prefer to avoid withdrawal symptoms.

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Adverse Effects	Withdrawal Symptoms
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Toxic Effects/Severe Symptoms

- Respiratory depression (delayed and prolonged)

Buprenorphine/Naloxone Drug Interactions

Pharmacists are encouraged to regularly access the most up-to-date information on drug interactions from reliable drug information sources as part of their clinical assessment and new information is becoming known daily.

Appendix 2 in the 3rd edition of Opioid Agonist Maintenance Treatment (CAMH) is not exhaustive. Pharmacists are encouraged to regularly access the most up-to-date information on drug interactions from reliable drug information sources as part of their clinical assessment and new information is becoming known daily.

An additional resource is the mobile APP – Opioid Drug Interactions by PCM Scientific.

Pharmacists and Buprenorphine/Naloxone Drug Interactions

- Keep an accurate, updated medication profile, including OTC, herbal and illicit drugs
- Develop a working knowledge of buprenorphine/naloxone drug interactions
- Watch for additive toxicity, particularly with CNS depressants
- Need quick access to current list of interactions
- Determine clinical significance of drug interaction.
- Use alternative, non-interacting drugs when possible
- If potentially interacting drug must be used, adjust buprenorphine/naloxone dose based on patient response
- Make dose adjustments slowly and in small increments to avoid toxicity. Severity of signs/symptoms of withdrawal or over sedation may help determine extent of dose change required
- If potential increase in buprenorphine/naloxone levels, advise patient in advance of signs or symptoms to watch for and what to do
- When possible, avoid concurrent administration of drugs with overlapping side effect profiles
- Consider pre-existing disease states as an alternative cause for symptoms, other than a drug interaction.
- In some cases, adverse drug reactions can be resolved by altering dosing schedule
- Consider complexity of prescribed regimens on patient adherence
- Patients should be carefully monitored when starting or discontinuing a medication that may interact with buprenorphine/naloxone

Patients and Buprenorphine/Naloxone Drug Interactions

- Provide all health care providers with an updated list of all medications used (including OTC, herbal and illicit drugs)
- Carry a list of all current medications on a Medication Record
- Consult with their doctor or pharmacist before taking any OTC, herbal or dietary supplements
- Advised of hazards of using illicit or drugs intended for someone else
- Patients who are on an interacting medication should be educated about the importance of adhering to their medication regimen
- Counselled to quickly report any sudden or unexpected signs/symptoms of buprenorphine/naloxone withdrawal or overmedication
- If potential increase in buprenorphine/naloxone levels, advise patient in advance of signs or symptoms to watch for and what to do.
- Verbally instruct on what the drug is for, how to take it, and how to reduce the risk of side effects or interactions
- Special consideration for patients with liver or kidney disorders, pulmonary or heart ailments, pregnancy
    - Note: buprenorphine is contraindicated in patients with severe hepatic impairment
- Instruct in advance on what to do in an emergency if their supply of buprenorphine/naloxone and/or other medications runs out

Pharmacodynamic Interactions of Buprenorphine/Naloxone

Additive Effects:

- When combined with a medication or illicit drug that has similar pharmacological profile, the effects may be additive – e.g., Potentiation of CNS or respiratory depressant effects, constipation, nausea or urinary retention.
- CNS depressant effects of alcohol and benzodiazepines are additive when combined with buprenorphine – putting patients at increased risk of respiratory depression and sedation which can result in death.

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- OTC medications containing dimenhydrinate and diphenhydramine can be abused and are problematic when used by patients on buprenorphine.
- Anticholinergic medications can potentiate the effects on the bowel, causing increased risk of severe constipation, possibly leading to paralytic ileus. It can also increase the risk of urinary retention.
- Due to buprenorphine's powerful affinity for the mu-opioid receptor, when it is used in the presence of other opioids it may cause these opioids to be displaced leading to acute withdrawal symptoms (precipitated withdrawal).

Pharmacokinetic Interactions

- Buprenorphine is metabolized by CYP3A4 and to a lesser extent by CYP2C8.

A list of medications that can increase or decrease plasma levels/effects of buprenorphine is detailed in Opioid Agonist Maintenance Treatment (CAMH) 2016- Appendix 2, Table A2-5, A2-6 and A2-7, pg. 117-119.

Medications that can decrease buprenorphine levels/effects

- Efavirenz

Medications that can increase buprenorphine levels/effects

- Atazanavir
- Delaviridine
- Erythromycin
- Fluoxetine
- Indinavir
- Itraconazole
- Ketoconazole
- Nelfinavir
- Ritonavir

Buprenorphine effects on other drugs

- Lopinavir
- Nelfinavir

Check with your Drug Information Centre or an online reference for current, up to date information.