Methadone and Buprenorphine/Naloxone Toolkit for Pharmacists

Part B: Buprenorphine/Naloxone
## Table of Contents

Addiction Management Principles ................................................................. 3

Initiating a Buprenorphine/Naloxone Program in Your Pharmacy ..................... 4

Dispensing Buprenorphine/Naloxone at A Glance ........................................... 8

Buprenorphine/Naloxone Combination Product Dosing Guide ......................... 10

Buprenorphine/Naloxone Drug Interactions .................................................... 112

Buprenorphine/Naloxone FAQs ....................................................................... 14

---

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.

### 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; and the Ontario College of Pharmacists.

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

**Full update: Dec 2015**
**Last revised: Mar 2017**
**Addiction Management Principles**

Disclaimer: This tool has been developed by the Ontario Pharmacists Association as a resource to support pharmacists wishing to initiate a methadone program in their pharmacy setting. It is not a substitute for established clinical practice guidelines or regulatory requirements. The information provided is not a substitute for sound clinical judgement from the health care professional. While we strive 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.

**Pathophysiology of Addiction**

![Diagram showing the relationship between Biogenetic Predisposition, Individual Psychologic Traits, Socio-Cultural Context, and Addiction Substance or Behaviour, leading to the release of Dopamine.]

**Fundamentals and Key Concepts in Addiction**

<table>
<thead>
<tr>
<th>Concept</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviours. Addiction is characterized by inability to consistently abstain, impairment in behavioural control, craving, diminished recognition of significant problems with one’s behaviours and interpersonal relationships, and a dysfunctional emotional response.</td>
</tr>
<tr>
<td>Physical Dependence</td>
<td>Physical dependence an adaptive physiological state that occurs with regular drug use and results in a withdrawal syndrome when drug use is stopped. It is usually associated with increased tolerance. Physical dependence tends to be a characteristic of substance use disorders, but alone does not imply addiction.</td>
</tr>
<tr>
<td>Tolerance</td>
<td>Tolerance is a condition in which higher doses of a drug are required to produce the same effect experienced during initial use. It is often associated with physical dependence.</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Withdrawal is a characteristic of substance use disorders, but does not necessarily imply addiction. With regular use of a substance, biochemical and structural adaptations take place in the brain. Withdrawal is the group of symptoms and signs that a person experiences after a period of regular use, when the quantity of the substance in the brain is reduced.</td>
</tr>
</tbody>
</table>
Initiating a Buprenorphine/Naloxone Program in Your Pharmacy

Disclaimer: This tool has been developed by the Ontario Pharmacists’ Association as a resource to support pharmacists wishing to initiate a buprenorphine/naloxone program in their pharmacy setting. It is not a substitute for established clinical practice guidelines or regulatory requirements. The information provided is not a substitute for sound clinical judgement from the health care professional. While we strive 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.

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

Information to provide to OCP

- There is no requirement to report the decision to dispense buprenorphine/naloxone for opioid dependence, as there is with methadone.

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

Recommended Resources:
Ontario College of Pharmacists
- OCP Article – Buprenorphine for the Treatment of Opioid Dependence:
- Opioid Dependence Education: Suboxone® Education Program
  - www.suboxonecme.ca
- OPA complimentary online and live program
  - https://www.opatoday.com/professional/resources/education
- Ontario Pharmacists Association’s Methadone and Buprenorphine/Naloxone Toolkit for Pharmacists
  - https://www.opatoday.com/professional/resources/for-pharmacists/programs/methadone
- CAMH ODT Core course

  - http://www.camh.ca/en/education/about/AZCourses/Pages/BUP.aspx
- CPSO “MMT Program Standards and Clinical Guidelines (2011) also covers buprenorphine
- Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline provides clinical recommendations for the initiation, maintenance and discontinuation of buprenorphine/naloxone maintenance treatment in the ambulatory treatment of adults and adolescents with opioid dependence in Ontario.
- Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline

Information for physicians
CPSO expects all physicians who prescribe buprenorphine to treat opioid-dependent patients, will have training/education on addiction medicine generally, prior to initiating buprenorphine treatment

Previously, CPSO had a policy outlining expectations for physicians who wish to prescribe buprenorphine / naloxone. CPSO has transitioned information still considered important for members to know when considering prescribing buprenorphine from a policy into an FAQ document.
Required Documentation

- A written/faxed prescription from any prescriber who is eligible to prescribe narcotics, and has undertaken training in compliance with CPSO Standards and Guidelines
- Best practice:
  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, if requested, they will be required to provide photo ID before receiving their buprenorphine/naloxone dose(s)
  - Record of dispensing of daily doses and take home doses
  - Tracking of missed doses of buprenorphine/naloxone must be 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.
  - 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 doses
- Patient lockbox, if applicable

Web Resources

- Centre for Addiction and Mental Health (www.camh.net)
  - https://www.porticonetwork.ca/
- Ontario Pharmacists Association Professional Development Website
  - https://www.opatoday.com/professional/resources/education
- Addiction Treatment Forum
  - www.atforum.com
- Opioid Addiction & Dependence Recovery (ORbeOK)
  - http://www.orbeok.ca/opioid_addiction_recovery_find_help_now
- Ontario Pharmacists Association Opioid Substitution Therapy Discussion Forum
  - www.opioiddruginteractions.com
- PCCM Scientific Drug-Drug Interactions in Opioid Therapy
  - http://methadoneforum.opatoday.com/

Telephone Resources

- CAMH Addiction Clinical Consultation Service
  - 416-535-8501, press 2 (open Mon – Fri 8:30AM-5PM)
- Ontario Pharmacists Association Opioid Substitution Therapy Drug Information Line
  - 1-888-519-6069 (open M-F 9AM-5PM)
  - 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 days and hours of operation
- Pharmacy layout and work flow
- Need for a private area for counseling and witnessing doses
- Staffing Impact: Adequate personnel, training and competency, professional satisfaction
- Business Impact: Impact on new clients, current patients and clientele
- 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
- Harm reduction assessment
- Assess staff competence to deliver buprenorphine/naloxone services
- 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 lockbox if necessary)
- Dosing documentation logs
- Establish patient care process for patient assessment, dispensing, witnessed administration, and management of difficult situations

Role of Pharmacist in Buprenorphine/Naloxone Program

- Assess patient care issues for the safe dispensing of daily doses or take home doses
- Monitor for signs and symptoms of intoxication or overdose
- Decline in patient’s appearance
- Unusual patient behaviours
- Social and housing issues that may require special dispensing needs
- Process for missed, lost, stolen or vomited doses
- Monitoring of drug interactions
- Positive identification of the patient (e.g. correct patient for the dose prescribed)
- Observe witnessed daily doses
- Provide take home doses
- Awareness of when buprenorphine/naloxone doses must be withheld and physician immediately contacted

(e.g. 5 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. inform of 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 (eg. Email, cell phone etc.)
- 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
- Report discrepancies to supervising pharmacist (e.g. missing patient documentation, identification discrepancies, interaction codes, unusual patient behaviour etc.)
- Billing/administrative issues as assigned by the pharmacy
- Maintain stock and required supplies

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

- Dissolve tablet under tongue
- Total daily dose in mg
- Ingest date(s) when specified on prescription order (e.g., patients that receive dose every other day)
- Child-resistant cap for take home doses

Initiating a New Patient

- Copy of picture identification
- Current contact information
- Treatment Agreement (Best Practice): 2 way (pharmacist-patient) or 3 way (prescriber-pharmacist-patient) agreement signed by all parties
- Explain hours of operation, usual process/procedure
- Lock box policy (as necessary; considered best practice)
- Establish and discuss with MD that patient is in at least moderate opioid withdrawal prior to administering first dose
- Counsel on safety and harm reduction

Initiating a Buprenorphine/Naloxone Program in Your Pharmacy

The Ontario Pharmacists Association wishes to acknowledge the Ministry of Health and Long term care for funding this initiative.
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 best practice)
- How to notify prescriber about missed doses

Patient Treatment Agreement (Best practice)

2 way agreement (pharmacist-patient) or 3 way (prescriber-pharmacist-patient)

- 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 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 in order to safely administer 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 3-5 minutes, ask patient to lift tongue to display partially dissolved tablet
- Paper cup to be disposed behind pharmacy counter
- Pharmacist and/or patient sign record of administration (best practice)
- Patient may leave once tablet is fully dissolved

Documentation

- Document on hard copy of Rx (or another record) the time of administration noting if a witness or take home dose given
- Record of administration
- No Shows/Missed doses to be communicated to 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

Disclaimer: This tool has been developed by the Ontario Pharmacists Association as a resource to support pharmacists wishing to initiate a buprenorphine/naloxone program in their pharmacy setting. It is not a substitute for established clinical practice guidelines or regulatory requirements. The information provided is not a substitute for sound clinical judgement from the health care professional. While we strive 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.

New patient presents a prescription for buprenorphine/naloxone for Opioid Dependence

A Controlled Drugs and Substances Act (CDSA) Prescriber Exemption is not required. The College of Physicians and Surgeons of Ontario (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/carrries’
- Confirm Narcotics Monitoring System (NMS) requirements and evaluate NMS alerts

NB: Buprenorphine/naloxone is not 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

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 (best practice)

Take home doses

- Do not dispense buprenorphine/naloxone take home doses unless authorized by prescriber
- May only be given to the patient
- 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

Dispensing Buprenorphine/Naloxone at A Glance

Initiating a new patient

- Request a copy of picture identification
- Ensure correct contact information is recorded (home, work, cell)
- Collect a signed two way agreement (pharmacist-patient) as a minimum, but a three 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 to the new pharmacy

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 close by the pharmacy area while the tablet dissolves. After 3-5 minutes, have the patient show the partially dissolved tablet. Patient may leave once 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 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 buprenorphine¹

- 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
- May be associated with fewer and less severe drug interactions when compared with methadone.

Pharmacology of naloxone

- An opioid antagonist with a relatively short half-life that is included with buprenorphine to deter misuse of buprenorphine through crushing and injecting of the sublingual tablets.
- Poor oral bioavailability; no clinically significant effects when taken sublingually
- Naloxone is used intravenously to treat opioid overdose.

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Withdrawal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>dose related to other opioids</td>
<td>head-ache</td>
</tr>
<tr>
<td>constipation</td>
<td>GI upset</td>
</tr>
<tr>
<td>head-ache</td>
<td>nausea</td>
</tr>
<tr>
<td>CNS depression (sedation)</td>
<td>diarrhea</td>
</tr>
<tr>
<td>euphoria</td>
<td>runny nose</td>
</tr>
<tr>
<td>sweating</td>
<td>sweating</td>
</tr>
<tr>
<td>nausea</td>
<td>insomnia</td>
</tr>
<tr>
<td>insomina</td>
<td>orthostatic hypotension</td>
</tr>
</tbody>
</table>

Toxic Effects/Severe Symptoms

- Respiratory depression (delayed and prolonged)

References:

- Opioid Agonist Treatment: A pharmacist’s guide to methadone and buprenorphine for opioid use disorder (CAMH) 3rd edition
- Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline (Handford 2012)
- OCP Pharmacy Connection 2014: Buprenorphine for the Treatment of Opioid Dependence

¹ Unless otherwise specified, information on dosing, pharmacology, pharmacokinetics, and drug interactions refer to the buprenorphine component. When the drug is taken as prescribed, naloxone absorption is negligible.
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 absolutely safe for all patients. Health professionals are advised to use their professional judgment and refer to available literature when dosing buprenorphine/naloxone.

Buprenorphine Pharmacokinetics*

- Poor oral bioavailability due to extensive first-pass metabolism by intestine and liver, however its bioavailability sublingually is extensive enough to be used for opioid dependence.
- Dose administered sublingually once per day or every other day or three times weekly once patient is stabilized.
- Absorption: rapid with sublingual administration
- Time to peak concentration: 3 to 4 hours
- Steady state: 3 to 7 days
- Elimination Half-life: Average of 37 hours (May range from 24 to 69 hours)

Naloxone Pharmacokinetics

- Naloxone is a pure opioid antagonist.
- Short half-life
- When administered sublingually, it is largely unabsorbed and does not exert pharmacological activity
- Does not appear to influence the pharmacokinetics of buprenorphine

Some important dosing facts about buprenorphine/naloxone*

- Most deaths with opioid agonist therapy occur during the initiation phase as the dose is adjusted.
- 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 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 6-12 hrs (best is 12 hrs) after use of short-acting opioids; or at least 12-24 hrs or longer (best is 24 hrs) after use of long-acting opioid; or wait at least 48 hrs after using Fentanyl®.
- For those patients switching from methadone to buprenorphine, they need to wait 3 or more days after last dose of methadone; and after having tapered methadone dose to 30mg or less.

Prior to first dose:

- Patients must be in at least moderate withdrawal prior to receiving their first dose.
- Some objective signs of opioid withdrawal (agitation, restlessness, tearing, yawning, runny nose, vomiting, sweating, goosebumps, tachycardia, hypertension) should be apparent, especially if there is some question of last use.
- Pharmacists who are concerned that sufficient withdrawal is not present should communicate with the prescriber.
- Advise patients that relief of opioid withdrawal symptoms usually begins 20-40 min. after the initial dose of buprenorphine.

Initial Dose (day 1)

- Start buprenorphine/naloxone treatment in the morning and early in the week to allow sufficient time to assess the patient for adequacy of dose and adverse effects.
- Initial dose of buprenorphine/naloxone is 2-4 mg sublingually under observation (max dose 6mg of buprenorphine); and reassess the patient after one hour to evaluate for precipitated withdrawal
- Reassess after 3 hrs. and a second dose of 2-4mg can be given later in the day to a maximum of 8mg on the first day depending on the individual patient’s response. NB: this second dose may be given as a take-home dose if significant withdrawal begins to occur later in the day.
Day 2 to Week 2

- Reassess the patient's response to the first day's dose.
- If opioid withdrawal symptoms are fully suppressed, the first day's dose can be given in a single daily dose; however, if the patient is feeling 'intoxicated', the dose should be decreased by 2mg.
- If the patient is not yet stabilized, the dose can be increased by 2-4mg on subsequent days or alternate days.
- Because of buprenorphine's long half-life the full effect of a dose increase can be only assessed 3-5 days after a dose increase.
- Goal is to reach a suitable dose in one to two weeks.

Maintenance

- The optimal dose relieves withdrawal symptoms and craving for 24 hrs. (or more) without causing side effects.
- The dose can be increased progressively depending on patient response to a max of 24mg. (as per Canadian Suboxone® monograph). Average dose is 8-12mg/day.
- Daily doses should be separated by at least 15 hrs.
- Due to buprenorphine's long half-life, alternate daily dosing is an option. Regimens include giving double the daily dose every other day or using a three times weekly dosing schedule - Monday and Wednesday at double the daily dose and Friday at three times the daily dose.
- Pharmacists should communicate all missed doses to the prescriber.
- If more than five daily doses are missed during the stable phase, patient should not be medicated until they are assessed by the prescriber; alternate day dosing is a more complicated situation - consult the prescriber
- Doses should be held and the prescriber contacted if a patient appears to be intoxicated (e.g. symptoms of slurred speech, ataxia, drowsiness, smell of alcohol, other unusual behaviours)
- If patient is receiving buprenorphine/naloxone from two different pharmacies, it is necessary to have a communication system to ensure both pharmacies are aware of any missed doses and/or dose changes.
- Once at the maintenance dose and more clinically stable, patient visits become gradually less frequent. Even a highly stable patient should be assessed at least every 12 weeks. Visits will again be more frequent during periods of instability.

Take Home Doses:

- Take home doses are considered based on assessment of clinical stability, length of time in treatment and patient's ability to store drug safely.
- After the first two months, patients can qualify for one take-home dose depending on clinical stability. Take home doses should be increased gradually depending on patient, up to a recommended maximum of one to two weeks (special considerations can be made for vacations or those working in remote areas for extended periods). Physicians must document rationale if they decide to give take home doses early and document their discussion with the patient.
- Patients may receive take home doses if the pharmacy is closed on Saturday, Sunday and/or Holidays.
- Patients receiving take home doses must be closely monitored.

References:

- CAMH: Opioid Agonist Maintenance Treatment – A pharmacist’s guide to methadone and buprenorphine for opioid disorder 3rd edition
- CAMH : Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline 2011
- CPSO: MMT Program Standards and Clinical Guidelines 2011 (also covers buprenorphine)
- CPSO: FAQ’s on Buprenorphine
- OCP Pharmacy Connection 2014: Buprenorphine for the Treatment of Opioid Dependence

* Unless otherwise specified, information on dosing, pharmacology, pharmacokinetics, and drug interactions refer to the buprenorphine component. When the drug is taken as prescribed, naloxone absorption is negligible.
Buprenorphine/Naloxone Drug Interactions

Disclaimer: This tool has been developed by the Ontario Pharmacists' Association as a resource to support pharmacists wishing to initiate a buprenorphine/naloxone program in their pharmacy setting. It is not a substitute for established clinical practice guidelines or regulatory requirements. The information provided is not a substitute for sound clinical judgement from the health care professional. While we strive 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.

Appendix 2 in the 3rd edition—Opioid Agonist Treatment: A pharmacist’s guide to methadone and buprenorphine for opioid disorder (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.


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.
- 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 Buprenorphine/Naloxone 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 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
- Counselling 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
- Adherence to prescribed medications emphasized
- Special consideration for patients with liver or kidney disorders, pulmonary or heart ailments, pregnancy
- 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. This can result in death.

OTC medications containing dimenhydrinate and diphenhydramine can be abused and are problematic when used in 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 them 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 CAMH-Opioid Agonist Treatment 3rd edition - Appendix 2, Table A2-2 and A2-3, pg. 106-116. NB: This list is current as of that publication.

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

Medications that can decrease buprenorphine levels/effects
- Efavirenz

Medications that can increase buprenorphine levels/effects
- Atazanavir
- Delavirdine
- Erythromycin
- Fluoxetine
- Indinavir
- Itraconazole
- Ketoconazole
- Nelfinavir
- Ritonavir

Buprenorphine effects on other drugs
- Lopinavir
- Nelfinavir

References:
Opioid Agonist Maintenance Treatment: A pharmacist’s guide to methadone and buprenorphine for opioid use disorder (CAMH) 3rd edition

* Unless otherwise specified, information on dosing, pharmacology, pharmacokinetics, and drug interactions refer to the buprenorphine component. When the drug is taken as prescribed, naloxone absorption is negligible.
**Buprenorphine/Naloxone FAQs**

**Disclaimer:** This tool has been developed by the Ontario Pharmacists' Association as a resource to support pharmacists wishing to initiate a buprenorphine/naloxone program in their pharmacy setting. It is not a substitute for established clinical practice guidelines or regulatory requirements. The information provided is not a substitute for sound clinical judgement from the health care professional. While we strive 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.

<table>
<thead>
<tr>
<th><strong>BUPRENORPHINE/NALOXONE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Do physicians require an exemption to prescribe buprenorphine/naloxone?</strong> (Ref <a href="http://www.cpso.on.ca">www.cpso.on.ca</a>)</td>
<td>Buprenorphine/naloxone does not require an exemption. The CPSO expects that prescribers will undertake training in buprenorphine/naloxone prescribing and in the treatment of opioid dependence and/or addictions prior to prescribing this drug. Also a one-day clinical observer-ship of opioid dependence practice is suggested.</td>
</tr>
<tr>
<td><strong>Can buprenorphine/naloxone prescriptions be accepted from prescribers out of province?</strong> (Ref 1)</td>
<td>Yes, any prescription can be accepted from out of province as long as the prescriber is authorized to practice in the province or territory in which the prescription was written. As with any prescription, the authenticity should be confirmed, as well as the appropriateness of the drug and dose. The prescriber's compliance with Provincial requirements for buprenorphine/naloxone prescribing must be confirmed with the prescriber.</td>
</tr>
</tbody>
</table>
| **What resources are available to guide pharmacists in the safe and effective dispensing of buprenorphine/naloxone?** | The following resources are available to guide pharmacists in the safe, effective, and appropriate dispensing of buprenorphine/naloxone:  
| **Is buprenorphine/naloxone subject to the same Ontario College of Pharmacists (OCP) reporting requirements before a pharmacy can start dispensing?** | No. There are no specific OCP reporting requirements prior to dispensing buprenorphine/naloxone. As with any treatment paradigm, pharmacists are expected to have trained in the provision of treatment for substance dependence before dispensing. |
| **Can buprenorphine/naloxone be removed from the foil and dispensed in a vial?** (Ref 4) | It is not recommended to remove the tablets from the foil until the time of administration. Take home doses should be dispensed in foil strips in a child proof vial. |
| **A buprenorphine/naloxone patient has missed 3 doses and presents to the pharmacy on the fourth day for a dose. Should the pharmacy cancel the prescription after 3 missed doses, or can the patient receive a dose?** (Ref 4,5) | Clinically, buprenorphine/naloxone can be missed up to 5 days without requiring a dose change. After more than 5 days of missed doses, prescriptions should be cancelled and the patient referred to the physician for reassessment. For patients on other day dosing schedules, dose readjustment will be required after missing 2 consecutive dosing days. Pharmacists should communicate missed doses with the prescriber daily and work with the prescriber to establish protocols for missed doses. |

**References:**
1. Drug and Pharmacies Regulation Act (1990), s. 1 and s. 158  
3. Controlled Drugs and Substances Act - S.C. 1996, c. 19 (Sec. 56).  
4. CAMH – Buprenorphine/Naloxone Clinical Practice Guideline, 2012  

Buprenorphine/Naloxone FAQs

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