

**Safe prescribing practices  
for addictive medications  
and management of  
substance use disorders in  
primary care: A pocket  
reference for family  
physicians**

Meldon Kahan, MD

Edited by Kate Hardy, MSW and Sarah Clarke, PhD

  
META:PHI

  
WOMEN'S COLLEGE HOSPITAL  
Health care for women | REVOLUTIONIZED

Version date: April 3, 2017

© 2017 Women's College Hospital

All rights reserved.



# Table of Contents

<b>Acknowledgments</b> .....	1
<b>Part I: Alcohol</b> .....	2
Introduction.....	2
Diagnostic continuum of alcohol problems .....	3
Screening and identification .....	7
Diagnosis: At-risk drinking, mild AUD, moderate AUD, severe AUD .....	11
Management of at-risk drinking and mild AUDs .....	12
Management of moderate and severe AUDs .....	14
Management of alcohol withdrawal.....	15
Anti-alcohol medications.....	22
Management of common outpatient alcohol-related problems .	27
Reporting to the Ministry of Transportation.....	32
<b>Part II: Opioids</b> .....	34
Introduction.....	34
Initiating opioid therapy .....	34
Opioid prescribing protocol.....	36
Opioid tapering.....	41
Opioid switching.....	44
Opioid misuse .....	45
Opioid use disorder (OUD).....	46
Prescribing buprenorphine.....	54
<b>Part III: Cannabis</b> .....	62
Introduction.....	62
Harms associated with cannabis use .....	63

Screening and assessment.....66

Managing cannabis use .....67

Cannabis use disorder .....68

Cannabis therapy .....72

Authorizing cannabis therapy .....74

**Part IV: Benzodiazepines**.....76

Introduction .....76

Benzodiazepine therapy.....76

Benzodiazepine tapering.....81

Benzodiazepine use disorders.....84

**References**.....87

# Acknowledgments

Mentoring, Education, and Clinical Tools for Addiction: Primary Care–Hospital Integration (META:PHI) is an ongoing initiative to improve the experience of addiction care for both patients and providers. The purpose of this initiative is to set up and implement care pathways for addiction, foster mentoring relationships between addiction physicians and other health care providers, and create and disseminate educational materials for addiction care. This handbook is intended as a quick-reference tool for family physicians to assist them in implementing best practices for prescribing potentially addictive medications and managing substance use disorders in primary care.

We wish to thank Dr. Jessika Schaman, who co-authored the cannabis section. We also extend our thanks to the physicians who have given feedback on this handbook, including Dr. Mark Ben-Aron, Dr. Peter Butt, Dr. Delmar Donald, Dr. Mike Franklyn, Dr. Melissa Holowaty, and Dr. Anita Srivastava.

We gratefully acknowledge funding and support from the following organizations:

- Adopting Research to Improve Care program (Health Quality Ontario & Council of Academic Hospitals of Ontario)
- The College of Family Physicians of Canada
- Toronto Central Local Health Integration Network
- Women’s College Hospital



# Part I: Alcohol

## Introduction

Until recently, primary care physicians' role has been restricted to treating medical complications of alcohol misuse and referring patients for specialized alcohol treatment. However, primary care is an ideal setting for the long-term management of alcohol disorders. Primary care practitioners can provide ongoing advice (1); there is evidence that the length of treatment has a greater impact on outcome than the intensity of treatment (2). Surveys suggest that patients would much prefer to receive treatment in a primary care setting than in a formal addiction setting. Addiction treatment in a primary care setting also enables the provision of ongoing medical care to the addicted patient. Controlled trials, cohort studies, and a systematic review have demonstrated that patients with a substance-related medical condition had reductions in hospitalizations, emergency room visits, health care costs, and possibly mortality if their primary care practitioner had addiction medicine training, or if addiction treatment was integrated with primary care (3-6). However, despite compelling evidence for physician involvement with alcohol use disorders, physicians do not consistently screen for alcohol or drug problems, counsel their addicted patients, or refer patients to formal treatment (7). A strong and growing body of evidence indicates that these interventions are effective, easily learned, and practical in a primary care setting. What follows is a brief overview of these interventions.

# Diagnostic continuum of alcohol problems

Alcohol use occurs along a spectrum of severity: abstinence, low-risk drinking, at-risk drinking, and alcohol use disorder (AUD).

## Low-risk drinking

The Canadian Centre for Substance Abuse released these low-risk drinking guidelines in 2010 (8):

*Note: These guidelines are not intended to encourage people who choose to abstain for cultural, spiritual or other reasons to drink, nor are they intended to encourage people to commence drinking to achieve health benefits. People of low bodyweight or who are not accustomed to alcohol are advised to consume below these maximum limits.*

### **Guideline 1**

Do not drink in these situations:

- When operating any kind of vehicle, tools, or machinery
- Using medications or other drugs that interact with alcohol
- Engaging in sports or other potentially dangerous physical activities
- Working
- Making important decisions
- If pregnant or planning to be pregnant
- Before breastfeeding
- While responsible for the care or supervision of others
- If suffering from serious physical illness, mental illness, or alcohol dependence

## Guideline 2

If you drink, reduce *long-term* health risks by staying within these average levels:

**Women:** 0-2 standard drinks\* per day, no more than 10 standard drinks per week

**Men:** 0-3 standard drinks\* per day, no more than 15 standard drinks per week

Always have some non-drinking days per week to minimize tolerance and habit formation. Do not increase drinking to the upper limits as health benefits are greatest at up to one drink per day. Do not exceed the daily limits specified in Guideline 3.

## Guideline 3

If you drink, reduce *short-term* risks by choosing safe situations and restricting your alcohol intake:

- Risk of injury increases with each additional drink in many situations. For both health and safety reasons, it is important not to drink more than three standard drinks\* in one day for a woman and four standard drinks\* in one day for a man.
- Drinking at these upper levels should only happen *occasionally* and always be consistent with the *weekly* limits specified in Guideline 2. It is especially important on these occasions to drink with meals and not on an empty stomach; to have no more than two standard drinks\* in any three-hour period; to alternate with caffeine-free, non-alcoholic drinks; and to avoid risky situations and activities. Individuals with reduced tolerance, whether due to low bodyweight, being under the age of 25 or over 65 years old, are advised to never exceed Guideline 2 upper levels.

#### **Guideline 4**

When pregnant or planning to be pregnant:

*The safest option during pregnancy or when planning to become pregnant is to not drink alcohol at all.* Alcohol in the mother's bloodstream can harm the developing fetus. While the risk from light consumption during pregnancy appears very low, there is no threshold of alcohol use in pregnancy that has been definitively proven to be safe.

#### **Guideline 5**

Alcohol and young people:

*Uptake of drinking by youth should be delayed at least until the late teens and be consistent with local legal drinking age laws.* Once a decision to start drinking is made, drinking should occur in a safe environment, under parental guidance and at low levels (i.e., one or two standard drinks\* once or twice per week). From legal drinking age to 24 years, it is recommended women never exceed two drinks per day and men never exceed three drinks in one day.

\*A **standard drink** is defined as a 341 ml (12 oz.) bottle of 5% strength beer, cider, or cooler; a 142 ml (5 oz.) glass of 12% strength wine; or a 43 ml (1.5 oz.) shot of 40% strength spirits.

### **At-risk drinking**

At-risk drinkers have the following properties:

- (a) Patient drinks above recommended guidelines.
- (b) Patient may have alcohol-related problems.
  - Psychological problems: insomnia, anxiety, depression
  - Social problems: spending inadequate time with family, reduced work performance, impaired driving charges
  - Physical problems: gastritis, hypertension, fatty liver, recurrent trauma, sexual dysfunction
- (c) Patient does not meet the DSM-V criteria for an alcohol use disorder.

## **Alcohol use disorder (AUD)**

The DSM-V gives the following criteria for an AUD (9):

- (a) Alcohol taken in larger amounts or over a longer period of time than intended.
- (b) Repeated unsuccessful efforts to reduce use.
- (c) Great deal of time spent obtaining or using alcohol, or recovering from its effects.
- (d) Strong cravings or urges to drink.
- (e) Recurrent use resulting in a failure to fulfill major responsibilities.
- (f) Continued use despite alcohol-related social or interpersonal problems.
- (g) Reduction of major activities because of alcohol (e.g., missing work, spending less time with children or spouse).
- (h) Repeatedly drinking in situations or activities where intoxication is dangerous.
- (i) Continued use despite knowledge of alcohol-related physical or psychological problems.
- (j) Tolerance (need to drink more to achieve the same effect, or diminished effects with continued use of the same amount of alcohol).
- (k) Withdrawal (e.g., tremors, sweating and/or anxiety in morning or afternoon, relieved by drinking; withdrawal seizures).

Patients who meet two or three of these criteria have a **mild** AUD, four to five criteria indicate a **moderate** AUD, and six or more indicate a **severe** AUD.

# Screening and identification

## Alcohol consumption history

- Ask all adolescent and adult patients at baseline and annual physical.
- Elicit a specific weekly consumption.
- Convert responses into standard drinks: 12 oz. of beer, 5 oz. of wine, or 1.5 oz. of spirits.
- Ask about patients' maximum consumption on one day in the past one to three months.

## Common errors in alcohol history

- Not asking.
- Accepting vague answers (e.g., "I just drink socially").
- Not converting to standard drinks (most people pour large drinks at home).
- Missing binge consumption (many patients do not mention periodic heavy consumption when asked about "average" or "typical" drinking).

## Screening questionnaires

- Three common surveys: CAGE (10-12), binge drinking question (13), AUDIT (14).
- Best as waiting room questionnaire, but can be incorporated into clinical interview.
- Sensitivity for detecting alcohol problems in primary care 70–80%.
- Positive screens require further assessment.

## (1) CAGE questionnaire

Have you ever felt you ought to **CUT DOWN** on your drinking?  
Have people **ANNOYED** you by criticizing your drinking?  
Have you ever felt bad or **GUILTY** about your drinking?  
Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**EYE-OPENER**)?

\* A positive screen is 2/4 for men, 1/4 for women.

\* CAGE is retrospective; it may indicate a past problem rather than a current one.

## (2) Binge-drinking question

How many times in the past year have you had five (men) / four (women) or more drinks in one day?

\* Once or more is a positive screen.

### (3) Alcohol use disorders identification test (AUDIT)

<i>1. How often do you have a drink containing alcohol?</i>				
<b>0</b> Never	<b>1</b> Monthly or less	<b>2</b> 2–4 times per month	<b>3</b> 2–3 times per week	<b>4</b> 4+ times per week
<i>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</i>				
<b>0</b> 1–2	<b>1</b> 3–4	<b>2</b> 5–6	<b>3</b> 7–9	<b>4</b> 10+
<i>3. How often do you have 6 or more drinks on one occasion?</i>				
<b>0</b> Never	<b>1</b> Less than monthly	<b>2</b> Monthly	<b>3</b> Weekly	<b>4</b> Daily or almost daily
<i>4. How often during the last year have you found that you were not able to stop drinking once you had started?</i>				
<b>0</b> Never	<b>1</b> Less than monthly	<b>2</b> Monthly	<b>3</b> Weekly	<b>4</b> Daily or almost daily
<i>5. How often during the last year have you failed to do what was expected of you because of drinking?</i>				
<b>0</b> Never	<b>1</b> Less than monthly	<b>2</b> Monthly	<b>3</b> Weekly	<b>4</b> Daily or almost daily
<i>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</i>				
<b>0</b> Never	<b>1</b> Less than monthly	<b>2</b> Monthly	<b>3</b> Weekly	<b>4</b> Daily or almost daily
<i>7. How often during the last year have you had a feeling of guilt/remorse after drinking?</i>				
<b>0</b> Never	<b>1</b> Less than monthly	<b>2</b> Monthly	<b>3</b> Weekly	<b>4</b> Daily or almost daily
<i>8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?</i>				
<b>0</b> Never	<b>1</b> Less than monthly	<b>2</b> Monthly	<b>3</b> Weekly	<b>4</b> Daily or almost daily
<i>9. Have you or someone else been injured because of your drinking?</i>				
<b>0</b> No	<b>2</b> Yes, but not in the past year		<b>4</b> Within the past year	
<i>10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested that you cut down?</i>				
<b>0</b> No	<b>2</b> Yes, but not in the past year		<b>4</b> Within the past year	

\* A score of 8+ suggests at-risk drinking or a mild AUD.

\* The higher the score, the greater the likelihood of AUD. A score of 20+ indicates a strong chance of AUD.

## Laboratory measures

Laboratory measures can be used to confirm clinical suspicion and monitor response to treatment (15, 16).

<b>GGT</b>	<ul style="list-style-type: none"> <li>• 35–50% sensitive for detecting 4+ drinks/day</li> <li>• Half-life four weeks</li> <li>• Also elevated by hepatic enzyme inducers (e.g., phenytoin), diabetes, obesity, etc.</li> </ul>
<b>MCV</b>	<ul style="list-style-type: none"> <li>• Somewhat less sensitive than GGT</li> <li>• At least three months to return to baseline</li> <li>• Also elevated by medications, folic acid and B12 deficiency, liver disease, hypothyroidism, etc.</li> </ul>

## Identification of alcohol problems in primary care

System	Presenting complaint	Clue that problem may be alcohol-related
Musculo-skeletal	Trauma	<ul style="list-style-type: none"> <li>• Recurrent</li> <li>• Not related to sports activities</li> <li>• Occurs during/after social event</li> </ul>
GI	Gastritis and esophagitis	<ul style="list-style-type: none"> <li>• Resolved with abstinence or reduced drinking</li> <li>• Not triggered by usual risk factors (fatty meals, NSAIDs)</li> </ul>
Hepatic	Fatty liver Elevated GGT/AST Signs of liver dysfunction	<ul style="list-style-type: none"> <li>• Not explained by other conditions (obesity, diabetes, viral hepatitis, medication use)</li> </ul>
Cardio-vascular	Hypertension	<ul style="list-style-type: none"> <li>• 3+ standard drinks consumed daily</li> <li>• Relatively resistant to anti-hypertensive meds</li> <li>• BP improves with abstinence or reduced drinking</li> </ul>

System	Presenting complaint	Clue that problem may be alcohol-related
Sleep	Sleep apnea Insomnia	<ul style="list-style-type: none"> <li>• Resolves with abstinence or reduced drinking</li> <li>• No trouble falling asleep but disturbed by vivid dreams in middle of night and/or early morning</li> </ul>
Social	Problems with relationships at home and at work	<ul style="list-style-type: none"> <li>• Fails to meet work or family obligations because of drinking or recovering from drinking</li> <li>• Is argumentative, emotionally labile, or sleepy after 4+ standard drinks</li> </ul>
Psychiatric	Anxiety and depression	<ul style="list-style-type: none"> <li>• Rapid improvement in anxiety or mood with first 1–3 drinks (though mood often worsens with 4+ standard drinks)</li> <li>• Worse during periods of drinking, better with reduced drinking/abstinence</li> <li>• Relatively unresponsive to medical or counselling interventions to improve anxiety/mood</li> </ul>

## Diagnosis: At-risk drinking, mild AUD, moderate AUD, severe AUD

Most heavy drinkers are **at-risk drinkers** or have a **mild AUD**. They drink above the low-risk guidelines, but are often able to drink moderately, have not suffered serious social consequences of drinking, and do not go through withdrawal. They often respond to brief physician advice and reduced drinking strategies.

Patients with **moderate to severe AUDs** often have withdrawal symptoms, rarely drink moderately, continue to drink despite knowledge of social or physical harm, and spend a great deal of time drinking, neglecting other responsibilities. They generally require abstinence and more intensive treatment.

	<b>At-risk drinking or mild AUD</b>	<b>Moderate or severe AUD</b>
Withdrawal symptoms	No	Often
Standard drinks	14+ per week	40–60+ per week
Drinking pattern	Variable; depends on situation	Tends to drink a set amount
Daily drinker	Less likely	More likely
Social consequences	None or mild	Often severe
Physical consequences	None or mild	Often severe
Socially stable	Usually	Often not
Neglect of major responsibilities	No	Yes

## **Management of at-risk drinking and mild AUDs**

### **Patient intervention (17, 18)**

- Review low-risk drinking guidelines.
- Link alcohol to patient’s own health condition if possible.
- Review non-specific sedative effects of alcohol (fatigue, insomnia, low mood).
- Ask patient to commit to a drinking goal: reduced drinking or abstinence.
- If unwilling to commit, continue to ask about drinking at every office visit.
- If reduced drinking goal chosen:
  - Have patient specify when, where and how much they intend to drink.
  - Give tips on avoiding intoxication (see below).
  - Ask patient to keep a daily record of drinking.

- Monitor GGT and MCV at baseline and follow-up.
- Identify triggers to drinking (e.g., emotions, social events) and develop plan to deal with triggers.
- Have regular follow-ups.
- Consider referral to alcohol treatment program if problem persists.

## **Tips to reduce alcohol intake**

- Set a goal for reduced drinking. The goal should specify the amount and circumstances of each drinking day (e.g., no more than three standard drinks on Thurs, Fri, Sat; no drinking alone). The goal should include non-drinking days.
- Record drinks on a calendar, log book, or app.
- Arrive and leave drinking events at a pre-determined time (e.g., only stay at a pub or party for three hours). If this is unlikely to work, avoid drinking events altogether.
- Avoid people and places associated with heavy drinking.
- Eat before and while drinking.
- Start drinking later in the evening or night.
- Switch to a less preferred alcoholic drink.
- Pace your drinking (e.g., no more than one drink per 45–60 minutes).
- Sip drinks slowly.
- Alternate alcoholic drinks with non-alcoholic drinks.
- Dilute drinks with mixer.
- Wait for 20 minutes between deciding to drink and actually having a drink.

# Management of moderate and severe AUDs

## Patient intervention

- Explain health effects of alcohol, linking them to patient's condition; reversible with abstinence.
- Explain that within days or weeks of abstinence, most patients have improved sleep, mood, and energy level.
- Explain that alcohol use disorder is a chronic illness, that it can happen to “good” people, that effective treatments are available, and that prognosis is good with treatment.
- Ask whether patient is willing to commit to a drinking goal (abstinence or reduced drinking).
- If the patient is not ready to commit, ask about drinking and readiness to change at each visit.
- If ready to commit, negotiate a written drinking goal:
  - Abstinence is more likely to be successful.
  - If reduced drinking goal is chosen, encourage a time-limited trial.
- Consider planned detoxification if at risk for withdrawal (6+ standard drinks/day, morning or afternoon tremor/anxiety).
- Treat concurrent conditions (e.g., anxiety, depression, hypertension, liver disease).
- Routinely offer pharmacotherapy: disulfiram, naltrexone, acamprostate, baclofen, gabapentin, topiramate.
- Encourage patient to make healthy lifestyle choices:
  - Avoid people and places associated with drinking.
  - Spend time with supportive family and friends.
  - Take daily walks (if health permits).
  - Maintain regular sleeping/waking schedule.
  - Plan regular activities outside the house as feasible.

- Review options for formal treatment (residential, day, outpatient).
- Encourage access to local addiction services through the Connex DART database or through a local directory.
- Recommend AA for group support, practical advice, and as a way to overcome loneliness and boredom; suggest Al-Anon for families or caregivers (19).
- Arrange follow-up; routinely monitor drinking through self-report, GGT, MCV.
- Acknowledge successes, even if partial or temporary.
- If patient relapses, encourage contact and reconnection with treatment.

## **Management of alcohol withdrawal**

### **Clinical features of withdrawal**

- Starts 6–12 hours after last drink
- Peaks at 24–72 hours
- Resolves in 3–10 days (or longer)
- Tremor is most reliable feature (postural, intention, not a resting tremor)
- Other features: sweating, vomiting, anxiety, tachycardia, hypertension, ataxic gait

### **Risk factors for withdrawal**

- 6+ standard drinks/day for 1+ weeks; risk increases with amount consumed
- Past seizures/DTs risk factor for future seizures/DTs

## **Withdrawal management options**

### **Indications for office management of withdrawal:**

- Reports frequent withdrawal symptoms
- Committed to abstinence and willing to start psychosocial treatment and/or anti-alcohol medications
- No history of seizures, DTs, or ED visits or hospitalizations due to withdrawal
- Not on high doses of opioids or sedating medications.
- Does not have cirrhosis with liver dysfunction
- Has supports at home

### **Indications for home management of withdrawal:**

- Office management not feasible
- A spouse, relative, or friend agrees to dispense the medication
- No history of severe withdrawal (seizures, delirium, hospital admissions)
- Treatment plan in place (anti-alcohol medication, ongoing counselling, AA, etc.)
- Age < 65
- No hepatic decompensation (ascites, encephalopathy)
- Patient agrees not to drink while taking medication

### **Indications for ED management of withdrawal:**

- History of seizures, DTs, or ED visits or hospitalizations due to withdrawal
- On high doses of opioids or sedating medications
- Has advanced cirrhosis
- Lacks supports at home
- No treatment plan in place
- Age  $\geq$  65

## **Office withdrawal protocol**

### **Before treatment:**

- Advise patient to have their last drink the night before the morning appointment.
- If patient shows up intoxicated, reschedule and/or admit to withdrawal management.

### **Withdrawal severity scales:**

1. Sweating, Hallucination, Orientation, Tremor (SHOT) scale (20): Simple scale validated in the ED
2. Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) (21): Standard monitoring scale, strong evidence of validity

### **Diazepam vs. lorazepam:**

- Diazepam is first-line medication.
- Use lorazepam instead if patient is 60 or older, is on opioids or other sedating medications, has low serum albumin from any cause, or has liver dysfunction (i.e., clinical or laboratory signs of cirrhosis, e.g., low albumin, high bilirubin/INR).

**Treatment:**

- Administer CIWA-Ar or SHOT every 1–2 hours.
- Give diazepam 10–20 mg (PO/IV) or lorazepam 2–4 mg (SL/PO/IM/IV) for CIWA-Ar  $\geq 10$  or SHOT  $\geq 2$ .
- Treatment is complete when CIWA-Ar  $< 8$  or SHOT  $\leq 1$  on 2 consecutive occasions and patient has minimal or no tremor.
- Send the patient to ED if patient has not improved or has worsened despite 3–4 doses; if they display marked tremor, vomiting, sweating, agitation, or confusion; or if they have risk factors for electrolyte imbalance or arrhythmias (e.g., diuretics, heart disease, diabetes).

**On discharge:**

- Initiate anti-alcohol medication.
- Advise patient to attend AA or other psychosocial treatment program.
- Arrange follow-up in a few days (1–2 days if lorazepam was used).
- Ensure patient leaves accompanied by friend or relative.
- If uncertain whether withdrawal is resolved, give diazepam 10 mg q4h (4–5 10 mg tablets) or lorazepam 1–2 mg q4h (10–12 1 mg tablets) for tremor, to be dispensed by partner if possible.

# Withdrawal severity scales

## (1) SHOT scale

<b>Sweating</b>	0 – No visible sweating 1 – Palms moderately moist 2 – Visible beads of sweat on forehead
<b>Hallucinations</b> “Are you feeling, seeing, or hearing anything that is disturbing to you? Are you seeing or hearing things you know are not there?”	0 – No hallucinations 1 – Tactile hallucinations only 2 – Visual and/or auditory hallucinations
<b>Orientation</b> “What is the date, month, and year? Where are you? Who am I?”	0 – Oriented 1 – Disoriented to date by one month or more 2 – Disoriented to place or person
<b>Tremor</b> Extend arms and reach for object. Walk across hall (optional).	0 – No tremor 1 – Minimally visible tremor 2 – Mild tremor 3 – Moderate tremor 4 – Severe tremor

\* False positives: Interpret SHOT with caution if patient has a febrile illness, cerebellar disease or benign essential tremor, psychosis, dementia, impaired consciousness, or delirium not related to alcohol.

## Discontinuation

- Discontinue H and O if zero at baseline.
- If either H or O are greater than zero, assess and treat for delirium, encephalopathy, and/or psychosis.

## History of seizures

- Diazepam 20 mg (PO/IV) or lorazepam 2–4 mg (SL/PO/IM/IV) q 1–2H x 3 doses, regardless of SHOT score.

**(2) CIWA-Ar scale**

<p><b>TREMOR</b> Arms extended and fingers spread apart Observation 0 no tremor 1 not visible, but can be felt fingertip to fingertip 2 3 4 moderate, with patient's arms extended 5 6 7 severe, even with arms not extended</p>	<p><b>NAUSEA AND VOMITING</b> Ask "Do you feel sick to your stomach? Have you vomited?" Observation 0 no nausea and no vomiting 1 2 3 4 intermittent nausea with dry heaves 5 6 7 constant nausea, frequent dry heaves and vomiting</p>
<p><b>TACTILE DISTURBANCES</b> Ask "Have you any itching, pins and needles sensations, any burning or numbness, or do you feel bugs crawling on your skin?" Observation 0 none 1 very mild itching, pins and needles, burning or numbness 2 mild itching, pins and needles, burning or numbness 3 moderate itching, pins and needles, burning or numbness 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations</p>	<p><b>AGITATION</b> Observation 0 normal activity 1 somewhat more than normal activity 2 3 4 moderately fidgety and restless 5 6 7 paces back and forth during most of the interview, or constantly thrashes about</p>

<p><b>HEADACHE, FULLNESS IN HEAD</b> Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or light-headedness. Otherwise, rate severity.</p> <p>Observation 0 not present 1 very mild 2 mild 3 moderate 4 moderately severe 5 severe 6 very severe 7 extremely severe</p>	<p><b>ANXIETY</b> Ask "Do you feel nervous?" Observation 0 no anxiety, at ease 1 mildly anxious 2 3 4 moderately anxious, or guarded, so anxiety is inferred 5 6 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions</p>	<p><b>PAROXYSMAL SWEATS</b> Observation 0 no sweat visible 1 barely perceptible sweating, palms moist 2 3 4 beads of sweat obvious on forehead 5 6 7 drenching sweats</p>
<p><b>ORIENTATION AND CLOUDING OF SENSORIUM</b> Ask "What day is this? Where are you? Who am I?" Observation 0 oriented and can do serial additions 1 cannot do serial additions or is uncertain about date 2 disoriented for date by no more than 2 calendar days 3 disoriented for date by more than 2 calendar days 4 disoriented for place and/or person</p>	<p><b>VISUAL DISTURBANCES</b> Ask "Does the light appear to be too bright? Is its colour different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation 0 not present 1 very mild sensitivity 2 mild sensitivity 3 moderate sensitivity 4 moderately severe sensitivity 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations</p>	<p><b>AUDITORY DISTURBANCES</b> Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation 0 not present 1 very mild harshness or ability to frighten 2 mild harshness or ability to frighten 3 moderate harshness or ability to frighten 4 moderately severe hallucinations 5 severe hallucinations 6 extremely severe hallucinations 7 continuous hallucinations</p>

# Home management of withdrawal

## Protocol

- Instruct patient to have last drink the night before
- Instruct patient to take diazepam 10 mg every 4 hours as needed for tremor (dispensed by spouse, relative, or friend)
- Prescribe no more than 60 mg diazepam
- Reassess the next day (by phone or in person)
- Clinic visit within 2–3 days

# Anti-alcohol medications

## Medication overview

- Anti-alcohol medications should be routinely offered to patients with AUDs. They reduce alcohol use, have a good safety profile, and help retain patients in psychosocial treatment.
- Medications:
  - Level I evidence of effectiveness: naltrexone, acamprosate
  - Level II evidence of effectiveness: topiramate, gabapentin, baclofen
- Level I medications have the strongest evidence of effectiveness; Level II medications are not officially indicated for alcohol use disorders, but have been shown to be effective in controlled trials.
- Choice of medication is based on individual considerations (such as side effects or cost).
- Titrate dose until cravings are mild and patient is abstinent, or until troublesome side effects emerge.

- If effective, prescribe for at least six months (all medications are safe for long-term use). The medication can be discontinued when patient is abstinent or has markedly reduced drinking for at least several months, has minimal cravings, has social supports and non-drug ways of coping with stress, and is confident that he or she no longer needs it to prevent relapse. The medication can be restarted again if patient does relapse.

### **Availability of medication**

- For patients on Ontario Drug Benefits, the physician must apply to the Exceptional Access Program (EAP) to obtain coverage for naltrexone and acamprosate.
- Early initiation of treatment is important because patients are at high risk for relapse and treatment drop-out in the first few weeks of abstinence; therefore, gabapentin, topiramate, or baclofen may be prescribed while waiting for EAP approval.
- Disulfiram is only available in Canada as a compounded medication. The patient can ask his/her pharmacy to arrange for compounding.

# Medications

## 1. Disulfiram (22-26)

### Action

- Acetaldehyde accumulates when alcohol consumed, causing toxic reaction.
- Most effective when taken with supervision of pharmacist or family member

### Side effects

- *With alcohol:* Vomiting, flushed face, and headache lasting several hours.
- *Without alcohol:* Headache, anxiety, fatigue, garlic-like taste, acne, peripheral neuropathy (with prolonged use). May cause depression.

### Contraindications and precautions

- Alcohol reaction can cause severe hypotension and arrhythmias, especially in patients with heart disease or on antihypertensives.
- To avoid reaction: Wait at least 24–48 hours between last drink and first pill. Wait at least 7–10 days between last pill and first drink.
- May trigger psychosis at higher doses (500 mg). Recommended dose appears safe in schizophrenia.
- Can cause toxic hepatitis.
- Contraindicated in cirrhosis, pregnancy, and unstable cardiovascular disease.

### Dose

- 125 mg PO OD usual dose.
- Increase to 250 mg if patient reports no reaction to alcohol.

## 2. Naltrexone (27)

### **Action**

- Blocks opioid receptor; reduces euphoric effect of drinking.

### **Side effects**

- Nausea, headache, dizziness, insomnia, anxiety, sedation.
- Blocks analgesic action of opioids.

### **Contraindications and precautions**

- Pregnancy.
- Will trigger severe withdrawal in patients on opioid medications.
- Can cause reversible elevations in AST and ALT; if pre-existing liver disease, order AST and ALT at baseline and at 3-4 weeks, and discontinue naltrexone if levels rise more than 3x baseline.

### **Dose**

- 25 mg OD x 3 days to reduce GI side effects; then 50 mg PO OD.
- Titrate to 100–150 mg per day if 50 mg has minimal effect on craving.
- Patients do not need to abstain before starting.

## 3. Acamprosate (28, 29)

### **Action**

- Glutamate antagonist.
- Relieves subacute withdrawal symptoms (insomnia, dysphoria, cravings).
- Works best if abstinent several days prior to initiation.

### **Side effects**

- Diarrhea.

### **Contraindications and precautions**

- Renal insufficiency.
- Pregnancy.

### **Dose**

- 666 mg tid; 333 mg tid if renal impairment or BW < 60 kg.

#### 4. Topiramate (30-32)

**Action**

- Modulates GABA system.
- May improve sleep and mood disturbance in early abstinence.

**Side effects**

- Sedation, dose-related neurological effects (dizziness, ataxia, speech disorder, etc.) resolve over time.

**Contraindications and precautions**

- Can cause weight loss (risk for underweight patients).
- Lower dose needed in renal insufficiency.
- Can cause glaucoma or renal stones.

**Dose**

- Initial dose 50 mg OD; titrate by 50 mg to a maximum dose of 200–300 mg daily.

#### 5. Gabapentin (33-35)

**Action**

- Modulates dopamine.

**Side effects**

- Dizziness, sedation, ataxia, nervousness.

**Contraindications and precautions**

- Can cause suicidal ideation (rare).

**Dose**

- Initial dose 300 mg bid–tid. Optimal dose is 600 mg tid.

## 6. Baclofen (36, 37)

### **Action**

- GABA agonist.

### **Side effects**

- Drowsiness, weakness, can cause or worsen depression.
- Safe in patients with liver disease.

### **Contraindications and precautions**

- Lower dose with renal insufficiency.
- Use with caution in patients on tricyclic anti-depressants or MAO inhibitors.

### **Dose**

- Initial dose 5 mg tid, increase to 10 mg tid. Maximum daily dose 80 mg.

## **Management of common outpatient alcohol-related problems**

### **Alcohol-related mood and anxiety disorders (38)**

- May be primary or alcohol-induced. Alcohol-induced disorders tend to resolve within weeks of abstinence or reduced drinking, whereas primary disorders remain the same or improve only marginally.
- Always ask patients with alcohol problems about mood, and ask patients with mood problems about alcohol.
- Treat alcohol and mood disorders concurrently.
- Consider a trial of antidepressant medication if:
  - Symptoms persist after four weeks of abstinence.
  - Unable to sustain abstinence for several weeks.
  - Possible primary mood disorder: depression precedes drinking; strong family history.
  - Severe depression (e.g., suicidal ideation).
- Long-term benzodiazepine use in heavy drinkers creates risk of accidents, overdose, and misuse.

## Insomnia, non-restorative sleep

Cause	Comment	Management
Sleep apnea	May contribute to hypertension, accidents, arrhythmias.	Abstinence
Alcohol withdrawal	Can cause night-time seizures.	Abstinence Treat withdrawal
Subacute alcohol withdrawal	Common in first few weeks of abstinence.	Acamprosate, topiramate, gabapentin
Chronic night-time alcohol use	Causes rebound REM and fitful sleep.	Abstinence Trazodone, tryptophan Avoid benzodiazepines

## Alcoholic liver disease

### (1) Fatty liver

- First and most common phase of alcohol liver disease
- Usually asymptomatic, reversible with abstinence
- Large liver on exam and ultrasound
- Elevated GGT

### (2) Alcoholic hepatitis

- Usually asymptomatic but occasionally very severe
- Diagnose elevated AST > ALT
- Advise patient that repeated and prolonged hepatitis may lead to cirrhosis

### **(3) Cirrhosis (39)**

#### **Risk**

- Over 10–20 years, 10–20% risk of cirrhosis with 6 (men) or 3 (women) standard drinks per day

#### **Physical signs**

- Spider nevi, gynecomastia (estrogen not metabolized)
- Ascites, peripheral edema, right heart failure (low albumin, portal hypertension)
- Firm liver edge
- Splenomegaly (portal hypertension)
- Asterixis, signs of encephalopathy

#### **Diagnostic tests**

- ↑GGT (enzyme induction)
- ↑AST > ALT (alcoholic hepatitis)
- ↑INR, ↑bilirubin, ↓albumin (liver unable to synthesize protein)
- ↑bilirubin, low platelets (due to splenomegaly and portal hypertension)
- U/S unreliable, except if splenomegaly present (portal hypertension)
- Check for other cause of cirrhosis (e.g., hepatitis B, C)
- If concerned about encephalopathy, check serum ammonia
- Biopsy if cause uncertain

## Outpatient management

- a. Prevent progression
  - Abstinence
    - 5-year survival in cirrhosis with complications: abstainers 60%, non-abstainers 34%.
    - Risk of variceal bleed 10 times greater with recent heavy drinking than with abstinence
    - Abstinence crucial if hepatitis C positive
  - Avoid NSAIDs and limit acetaminophen to 2–3 g daily (only as necessary; patient must be abstinent).
- b. Liver transplant
  - Most effective treatment for cirrhosis
  - To get on transplant list, patients require 6 months to 2 years of abstinence as well as a treatment program
- c. Encephalopathy
  - Avoid benzodiazepines; use caution with other sedating drugs
  - Lactulose (30–45 mL orally 3 times a day) if at high risk or early signs: poor concentration, day-night reversal, inattention, slow responses.
  - Urgent intervention for triggers: electrolyte imbalance, blood loss, high protein meal, benzodiazepines, infection
- d. Ascites
  - Low salt diet
  - Moderate fluid intake
  - Judicious use of diuretics (e.g., spironolactone)
- e. Portal hypertension
  - Regular endoscopic measurement of portal pressures
  - Nadolol if portal hypertension

## **Hypertension**

- Consumption of 3+ standard drinks/day can cause or exacerbate hypertension.
- Patients with alcohol-induced hypertension tend to be refractory to antihypertensive medication.
- Hypertension resolves within weeks of abstinence or reduced drinking.

## **Neurological conditions**

- Alcohol-induced dementia, cerebellar ataxia, peripheral neuropathy, parkinsonism
- Conditions often improve with abstinence over weeks/months

## **Dilated cardiomyopathy**

- Presents with heart failure and arrhythmias
- Excellent prognosis; sometimes completely resolves within months of abstinence

## **GI bleed**

- Gastritis, esophagitis: abstinence, PPI
- Esophageal varices: abstinence, treatment of portal hypertension, treatment of cirrhosis

## **Prescribing benzodiazepines and opioids (40)**

- Risk of overdose and accidents greatly increased when combining benzodiazepines or opioids with alcohol.
- Both medications should be routinely tapered to the lowest effective dose in the elderly.

# Reporting to the Ministry of Transportation

## Suggested criteria for reporting

- Patient admits to drinking and driving.
- Family member informs physician that patient is drinking and driving.
- Patient drinks steadily throughout the day and regularly drives.
- Patient drove to your clinic while intoxicated.
- Patient regularly drives and has recently experienced severe withdrawal or complication of withdrawal (e.g., seizure).
- Patient has blackouts caused by alcohol consumption.
- Patient has other alcohol-related complications that impair driving ability (e.g., cerebellar ataxia, recurrent trauma, sleep apnea, on high doses of opioids or benzodiazepines, hepatic encephalopathy).

## Management of patients with suspended licenses

- Explain to the patient that you have a legal obligation to report.
- Patients may ask you to give them a chance to abstain and attend treatment before deciding to report them.
- However, trusting the patient to comply with your instructions is not considered an adequate reason for failing to report. Therefore, take the following precautions when delaying reporting:
  - Inform the patient that you will report if patient misses follow-up appointments or if monitoring or history suggests ongoing drinking.
  - Order GGT and MCV regularly.
  - Consider urine ethyl glucuronide every 1–2 weeks.
  - EG detects alcohol consumption for several days after last drink.
  - Check urine creatinine to detect tampering.
- To lift the suspension, the patient must have attended treatment and maintained abstinence or low-risk drinking for a specified number of months (usually one year).
- Monthly appointments are recommended. At each appointment:
  - Ask about alcohol consumption and attendance at AA and treatment programs.
  - Order GGT and MCV.
  - With the patient's permission, ask the spouse/partner or close family member to corroborate the patient's reported alcohol consumption.
- Write follow-up letter to Ministry if patient is abstinent at 6 months and at one year.

## Part II: Opioids

### Introduction

Since the 1990s, Canadian physicians have dramatically increased their opioid prescribing. This has benefited many patients with chronic non-cancer pain (CNCP), but it has also been associated with substantial increases in opioid overdose deaths and opioid use disorders (41, 42). Evidence suggests that physicians' prescribing practices are a major contributor to these harms. The medical profession has responded to this public health crisis by developing a set of evidence-based guidelines and best practices on opioid prescribing for chronic pain (43). However, these guidelines have had little appreciable effect: many family physicians continue to overprescribe opioids, while some are extremely uncomfortable prescribing opioids at all. What follows outlines the role of opioids in CNCP management, provides a clear protocol for prescribing opioids, and advises on how to reduce, mitigate, or prevent the harms associated with chronic opioid use.

### Initiating opioid therapy

#### Indications for opioid trial

- Patient has a well-defined pain condition (nociceptive or neuropathic) that (a) has been shown to respond to opioids, and (b) causes both **pain and disability**.
- Diagnosis is confirmed on physical examination, diagnostic imaging, and/or consultation.
- Non-opioid treatments are contraindicated, have intolerable side effects, or are found to be ineffective after an **adequate trial** (e.g., one month for NSRIs).

- Note: Opioids are not indicated for common pain conditions such as fibromyalgia, low back pain, and headaches.

## Contraindications to opioid trial

Avoid long-term opioid therapy in patients who are at high risk for opioid overdose and addiction:

- Patients with a current or past history of problematic use of alcohol, opioids, cannabis, or other substances
- Patients with a current, active psychiatric disorder (i.e., anxiety disorder, mood disorder, post-traumatic stress disorder)

## Prior to prescribing opioids

- Ask about current and past use of alcohol and drugs.
- Ask about mood. Depressed patients tend to have a heightened perception of pain and are less responsive to opioid therapy.
- Check renal and respiratory status, especially risk of sleep apnea.
- In elderly patients, assess risk of falls.
- Consider tapering benzodiazepines (see page 81).
- Ask about the impact of pain on activities of daily living, e.g., walking, cooking, visits to family and friends.
- Have the patient rate the severity of their pain on a 0–10 scale, at rest and with activity.
- Reassess their response to non-opioid treatments:
  - Nociceptive pain: acetaminophen, NSAIDs, SNRIs
  - Neuropathic pain: anticonvulsants, SNRIs, TCAs
  - All pain: Mindfulness programs, graded exercise
- Inform patients that opioid therapy will be a **trial**, to be discontinued if side effects outweigh benefits.

- Advise patients not to drink alcohol during titration.
- Warn patients to avoid driving for at least two hours after a dose in the first 1–2 weeks of treatment initiation and the first week of dose increase.
- Warn patients to keep their opioids safely stored, and not to give any opioid medications to relatives or friends.

## **Office visits**

- See the patient frequently during initiation and titration.
- At each office visit, ask about changes in:
  - Work, school, social activities, daily activities
  - Pain ratings on a 0–10 scale, at rest and with activity
  - Mood
- Ask about side effects:
  - Sedation, dizziness, and other CNS effects
  - Constipation, nausea

## **Opioid prescribing protocol**

### **Immediate release (IR) vs. controlled release (CR)**

- Initiate opioid trial with IR preparations.
- Maintain on IR for brief pain (less than 4 hours) or incident pain (triggered by activity).
- For constant pain throughout the day, switch to CR.
- In long-term therapy for constant pain throughout the day, IR preparations should not exceed 10–30% of total daily opioid dose.

## Opioid selection

- Always initiate opioid treatment with “weak” opioids, i.e., oral preparations of codeine, tramadol (e.g., Tramacet<sup>®</sup>, Ultram<sup>®</sup>, Zytam XL<sup>®</sup>), or buprenorphine patch (BuTrans<sup>®</sup>). These medications are effective, and they have a much lower risk of overdose, addiction, sedation, and falls than the potent opioids.
- If insufficient analgesia with first-line opioids, prescribe morphine (various generics), oxycodone (various generics, OxyNEO<sup>®</sup>), or hydromorphone (e.g., Dilaudid<sup>®</sup>, Hydromorph Contin, Journista<sup>®</sup>).
- Morphine is contraindicated in patients with renal insufficiency.
- Evidence suggests that hydromorphone and oxycodone have fewer cognitive effects than morphine in the elderly.
- Transdermal fentanyl (various generics, Duragesic<sup>®</sup>) should be avoided if possible in the elderly and in patients with less severe pain. It is very easy to overdose on the patch. Use only if the patient has taken at least 60–100 mg morphine equivalent daily (MED) for at least 2 weeks.

## Opioid initiation and dose titration

Opioid	Max initial dose*	Max dose increase	Min # of days between increases	Min IR dose before moving to CR
Codeine	200 mg/d	50 mg/d	7 days IR, 14 days CR	150 mg
Transdermal buprenorphine	5 µg/7d	5 µg/7d	7 days	-----
Morphine**	40 mg/d	10 mg/d	7 days IR, 14 days CR	30 mg
Oxycodone**	30 mg/d	5 mg/d IR, 10 mg/d CR	7 days IR, 14 days CR	20 mg
Hydromorphone**	8 mg/d	1–2 mg/d IR, 2–4 mg/d CR	7 days IR, 14 days CR	6 mg
Tapentadol**	IR 700 mg/d, CR	100 mg/d CR	3 days CR	-----

\* Starting dose is 40 mg MED (less for seniors).

\*\* Potent opioids should only be dispensed to patients currently taking weak opioids daily. All dose increases should be based on an individual assessment.

## Morphine equivalency

Opioid	Analgesic equivalence value
Morphine (reference)	30 mg
Codeine	200 mg
Oxycodone	20 mg
Hydromorphone	6 mg
Tapentadol	No equivalence to morphine established, but CR has demonstrated comparable pain relief to oxycodone CR (dose ratio 5:1)
Transdermal buprenorphine	No equivalence to morphine established
Transdermal fentanyl	25 µg/hr = 60–134 mg oral morphine per day

## Optimal dose

- Effective opioid therapy causes gradual improvement in pain and function as dose increases.
- Optimal dose reached if:
  - Pain relief at least 2 points on 10-point scale, with no benefit from 1–2 additional increases.
  - Improved functioning at work, school, and with family; increased physical activities.
  - No major side effects.
- Most patients respond to a dose of **50 mg MED or less**; doses above 90 mg MED are rarely needed.

## Ongoing vigilance

- Opioids have dose-related complications, including overdose, sleep apnea, and falls and fractures.
- Any patient with an ongoing opioid prescription of 40 mg MED or more should have **monthly visits** to assess:
  - Pain levels, at rest and with activity
  - Function (mood, activities of daily living)
  - Adverse effects
- At doses of 90+ mg MED, the physician should reassess the opioid's analgesic effectiveness and side effects, and decide whether to maintain the dose or taper.

## Minimizing adverse effects

### (a) Falls in the elderly

- Do not prescribe opioids to cognitively impaired patients unless dispensed and overseen by a caregiver.
- Taper benzodiazepines (see page 81).
  - Benzodiazepines increase risk and severity of opioid-induced fatigue, sedation, inattention and overdose.

- Avoid use of opioids at night if possible.
  - If pain wakes the patient up, prescribe the smallest IR opioid dose and warn patients to take extra precautions when getting out of bed.

### **(b) Sedation during initiation or dose increase**

- Sedation, slowed speech, or “nodding off” are all early signs of an impending overdose.
- The patient may appear relatively alert in conversation, yet have respiratory arrest at night while asleep.
- Family members should contact the doctor or call emergency services at the first sign of an overdose.

### **(c) Fatigue**

- Opioids can cause fatigue either through a direct sedating effect or by contributing to sleep apnea.
- Patients who report daytime fatigue and/or reduced function should be assessed for sleep apnea. Their opioid dose should be reduced or discontinued, or the opioid should be switched.

### **(d) Constipation**

- Increase fibre, fluid, and activity.
- If laxatives are needed, consider polyethylene glycol (Restorolax), sodium picosulphate (Dulcolax) or lactulose. Polyethylene glycol is most effective for opioid-induced constipation.

# Opioid tapering

## Rationale for opioid tapering

- Tapering is an **active therapeutic decision** made for the patient's benefit when they have failed at opioid therapy.
- Evidence suggests that when a patient has failed at opioid therapy, tapering the dose improves pain, mood, and functioning.
- Tapering is a **far safer option** than abrupt cessation of opioid prescribing:
  - Abrupt cessation will trigger severe withdrawal, and patients will lose their opioid tolerance within days, creating a heightened risk of overdose.

## Indications for opioid tapering

- Patient has persistent severe pain and pain-related disability despite an adequate opioid dose (e.g., 60 mg/d MED), and the patient has already failed on a trial of at least one opioid previously.
- Patient is on an unusually high dose for the pain condition (well above 90 mg MED in a patient with mechanical low back pain).
- Patient has a complication from opioid therapy, such as sleep apnea, sedation, or dysphoria.
- Patient has suspected opioid use disorder and opioid maintenance therapy with methadone or buprenorphine is not an option.

## Reluctance to taper

If patient expresses reluctance to taper their opioid dose:

- Explain **why** you are tapering the opioid dose: to prevent future harms (e.g., falls) and to improve the patient's mood and well-being (e.g., energy and sleep).
- Explain that tapering does not usually increase pain, and may actually improve it:
  - Opioids often stop working after many months or years.
  - Opioids can even make pain worse by lowering the pain threshold.
- Explain that you are not necessarily going to stop the opioids altogether, but lower it to a safer dose that improves mood and function while still keeping the pain manageable.
- Explain that you will be lowering the dose **gradually**, and that you will adjust the rate of the taper according to how the patient is doing.

## Tapering protocol

<b>Formulation</b>	CR preferred (until low dose reached).
<b>Dosing interval</b>	Scheduled doses rather than PRN Keep dosing interval the same for as long as possible (bid or tid). Advise patients not to skip doses.
<b>Rate of taper</b>	Taper slowly, typically 10% of the total daily dose at each office visit, no more than 10% of total daily dose <b>every 1–2 weeks</b> . Adjust rate of taper according to patient's pain and withdrawal symptoms. If patient experiences mild withdrawal symptoms, reassure them they will resolve after 1–2 weeks. Let patient choose which dose is decreased (AM, PM, or HS). Taper even more slowly when 1/3 of total dose is reached.
<b>Dispensing interval</b>	If patient runs out early, increase frequency to weekly, alternate day, or daily.
<b>Endpoint of taper</b>	Dose well below 90 mg MED. Controls pain with minimal side effects. Similar or improved mood and function.
<b>Frequency of visits</b>	If possible, see patient prior to each dose decrease.
<b>Approach at each visit</b>	Ask not just about withdrawal symptoms but benefits of tapering: more alert, less fatigued, improved mood, improved pain, etc.

# Opioid switching

## Indications for opioid switching

- Inadequate analgesic response to the current opioid (< 2/10 pain relief, no improvement in function) despite a reasonable dose (e.g., 60 mg MED). Patients who have had minimal analgesic response to a moderate dose are unlikely to benefit from further dose increases.
- Adverse effects with the current opioid, e.g., constipation, sedation, falls.

## Opioid switching protocol

- Because the patient will not be fully tolerant to the new opioid, its MED should be 50% of the MED of original.
- *Example:* When switching a patient from 40 mg/d of oxycodone to hydromorphone:
  - 40 mg/d oxycodone = 60 mg MED
  - 60 mg MED = 12 mg/d hydromorphone
  - 50% of hydromorphone 12 mg = 6 mg
  - Therefore, start patient on 6 mg/d in divided doses.
- Emphasize that taking extra doses is dangerous.
- Titrate dose as described on page 38.

# Opioid misuse

## Limiting diversion

- Warn patients to store their medication in a locked box or other secure location, not to show them to younger relatives, and not to share them with anyone.
- Avoid using fentanyl patches in elderly patients with younger adults at home (used patches contain a large amount of fentanyl, and patches can be easily lifted off the skin of a sleeping patient).
- Consider a fentanyl patch exchange program at the pharmacy (<http://www.patch4patch.ca>): patients place their used patch on a piece of paper so the pharmacist can make sure it has not been cut or manipulated.
- Without anyone else in the office, ask parents and grandparents on opioids if younger relatives could be using their medication, especially if the patient requires high doses, runs out early, or is accompanied by a younger adult to the office visits.

## Monitoring for misuse

- Any patient with an ongoing opioid prescription of 40 mg MED or more should be monitored for signs of opioid misuse.
- At each visit, the physician should assess the patient for:
  - Changes in their mood, relationships, or functioning
  - Concerns expressed by family or close friends
  - Unauthorized changes to the dose, schedule (i.e., binge use), or route of delivery (i.e., biting oral tablets, etc.) of their medication
  - Euphoric effects (e.g., relaxation, confidence, energy) immediately after taking a dose

- Withdrawal symptoms (see pages 55–56)
- Drug-seeking behaviours: running out of medication early, frequent requests for dose increases, etc.
- These features may indicate that the patient is at risk for an **opioid use disorder** (see below).

## Opioid use disorder (OUD)

The DSM-V gives the following criteria for an OUD (9):

- (a) Opioids taken in larger amounts or over a longer period of time than intended.
- (b) Repeated unsuccessful efforts to reduce use.
- (c) Great deal of time spent obtaining or using opioids, or recovering from their effects.
- (d) Strong cravings or urges to use opioids.
- (e) Recurrent opioid use resulting in a failure to fulfill major responsibilities.
- (f) Continued use despite opioid-related social or interpersonal problems.
- (g) Reduction of major activities because of opioids (e.g., missing work, spending less time with children or spouse).
- (h) Repeatedly using opioids in situations or activities where intoxication is dangerous.
- (i) Continued use despite knowledge of opioid-related physical or psychological problems.
- (j) Tolerance (need to use more to achieve the same effect, or diminished effects with continued use of the same amount).
- (k) Withdrawal (e.g., myalgias, chills, sweating, nausea/vomiting, cramps, diarrhea, insomnia, anxiety, dysphoria).

Patients who meet two or three of these criteria have a **mild** OUD, four to five criteria indicate a **moderate** OUD, and six or more indicate a **severe** OUD.

## Symptoms, signs, and behaviours

OADs are difficult to diagnose; patients are often reluctant to disclose key symptoms and behaviours for fear that the physician will discontinue the opioid. A diagnosis often requires collateral information from family members and observation of a pattern of behaviour over time. The following patterns tend to emerge in patients with an OAD:

- Patient's opioid dose high for underlying pain condition
- Aberrant behaviours: Running out early, crushing or biting oral tabs, or accessing opioids from other sources
- Strong resistance to tapering or switching current opioid
- Importance patient attaches to the drug far outweighs its analgesic benefit (e.g., "pain is 10/10, hydromorphone only takes edge off, but I would die if you stopped it")
- Binge rather than scheduled opioid use
- May be currently addicted to other drugs, e.g., alcohol
- Depressed and anxious
- Deteriorating mood and functioning
- Concerns expressed by family members
- Reports recurrent, frightening withdrawal symptoms
- May acknowledge that they experience immediate improvement in mood after taking the opioid

## Harm reduction advice

All patients with a suspected OAD should be given advice on harm reduction and reducing the chance of a fatal overdose:

- Never use opioids alone; always use with a friend and make sure you are both aware of the signs of overdose (pinpoint pupils, falling asleep, slowed or stopped breathing, bluish skin around lips or under nails).

- If a friend has overdosed:
  - Shake them and call their name.
  - Call 911.
  - Administer naloxone and start chest compressions.
  - If they are drowsy and nodding off but not unconscious, do not let them fall asleep; keep talking to them until they are awake and alert for at least an hour without slurred speech/nodding off. If they cannot remain alert, take them to the ED.
- If you are taking opioids after a period of abstinence of any length, take a much smaller dose than you used to.
- Be aware that drug dealers often add fentanyl to their product without informing their customers. Only medications obtained from a doctor's prescription and purchased at a pharmacy are guaranteed to be free of fentanyl.
  - Fentanyl is many times more potent than heroin.
  - Even a tiny amount can kill a heavy and experienced opioid user.
- Do not inject opioids.
- Do not mix opioids with other substances, especially alcohol or benzodiazepines.
- Always carry naloxone (see page 49).
- The only sure way to prevent overdose is to stop using. The most effective way to do this is through opioid maintenance therapy (see page 53).

## **Take-home naloxone**

Naloxone is a competitive opioid antagonist with a duration of action of 15-30 minutes. Take-home naloxone is available in two bioequivalent formulations: parenteral naloxone 0.4 mg and intranasal naloxone 4 mg. The latter is much more expensive but is more acceptable to oral opioid users. In most provinces, public health departments offer naloxone kits and training through their needle exchange programs, and some provinces have made parenteral and/or intranasal naloxone available at community pharmacies at no charge and without a prescription.

### **Indications for naloxone**

- On a high dose of prescription opioids (200+ mg MED)
- On prescription opioids and also taking benzodiazepines or drinking heavily.
- Previous overdose
- Suspected OUD
- Intermittent recreational use or illicit opioids
- Has regular contact with friends or relatives who have OUD
- Heavy users of cocaine or other non-opioid drugs (drug dealers sometimes add fentanyl to non-opioid drugs)

When giving or recommending naloxone, the clinician should spend a few minutes advising the patient on overdose prevention (see pages 47–48). This advice will reinforce the education they will receive from the public department or pharmacy.

## **Options for management of OUDs**

### **(a) Abstinence-based psychosocial treatment**

Abstinence-based treatment is the cessation of all alcohol and drugs, including methadone and buprenorphine; it is usually accompanied by psychosocial interventions, such as counselling or self-help groups (e.g., Narcotics Anonymous). This form of treatment is less effective than opioid maintenance but often preferred by patients. Patients are at increased risk for opioid overdose after leaving abstinence-based programs, so it is crucial that they are given harm reduction advice and overdose prevention strategies (see pages 47–48).

### **(b) Structured opioid therapy**

Structured opioid therapy is continued opioid prescribing under conditions that limit misuse. Preliminary evidence suggests it is effective, convenient for patients, and easier to organize than opioid substitution therapy. Refer patients for opioid substitution therapy if structured therapy fails.

### **Indications**

- Has or is at high risk for opioid use disorder (younger, personal or strong family history of addiction, anxiety or mood disorder).
- Has pain condition requiring opioid therapy.
- Only uses opioids supplied by one physician.
- Does not alter route of delivery (inject or crush oral tabs).
- Is not currently addicted to alcohol or other drugs.

### **Protocol**

- Perform taper (see pages 41–43).
- Dispense small amounts frequently (e.g., 1–2 times per week).

- Do not refill if patient runs out early.
- Monitor closely with urine drug screens, pill counts, office visits.
- Switch to buprenorphine or methadone treatment if structured opioid therapy fails (e.g., patient continues to access opioids from other sources).

### **(c) Involuntary taper**

Opioid tapering is often difficult for people with moderate to severe OUDs; they usually experience intense and frightening withdrawal symptoms along with powerful cravings, leading them to access illicit opioids. Although opioid maintenance therapy with methadone or buprenorphine (see page 53) is indicated in these cases, patients may be resistant to this treatment. In this situation, the patient should be slowly tapered off their opioid.

Tapering gives the patient several weeks or months to consider and make an informed decision about the need for opioid substitution treatment. As well, tapering is safer to the patient and the public than ongoing prescribing of high doses or abrupt cessation. The former allows the patient to put off treatment indefinitely, maintaining the risk of diversion and overdose; the latter will cause the patient to lose tolerance, increasing their risk of overdose.

Note that you should not discharge patients with OUDs from your practice unless they have been abusive towards you, your staff, or other patients, or if you have concrete evidence that they have been selling your medications.

## Indications

- Has an opioid use disorder (if you are unsure about the diagnosis, consult with an addiction physician or pain physician who is knowledgeable about OUDs).
- Does not have a pain condition requiring long-term opioid therapy.
- Suspected of injecting, crushing, or snorting oral tabs.
- Suspected of accessing opioids from more than one physician (either double-doctoring or purchasing from the street) or of selling their medication.

## Patient reluctance

If the patient expresses resistance to an involuntary taper, deliver the following message:

You have an opioid use disorder. The opioid I am prescribing may be making it harder for you to function and may be worsening your mood. It is also putting you at risk of serious harm, including death from overdose.

The most effective treatment for opioid use disorder is opioid maintenance treatment. This treatment will result in improved mood, function, and pain. It will eliminate your cravings and withdrawal symptoms. However, since this is not an option at this time, your opioid dose needs to be lowered for safety reasons. As you will lose tolerance as the dose is lowered, it is important that you take steps to prevent opioid overdose (see pages 47–48).

If you change your mind about opioid maintenance therapy at any point, I will arrange treatment for you, either with me or at an addiction clinic. If you disagree with this decision, please feel free to find another doctor. Until then, we will proceed with the taper.

## Protocol

- Provide patient with naloxone and advice on harm reduction.
- Dispense frequently (as often as daily).
- Taper by 10% of total baseline dose per week (e.g., if patient is on 600 mg MED, taper by 60 mg per week).
- Slow taper to 10% every 2 weeks once dose of 200 mg MED is reached.
- See the patient frequently, every 1–2 weeks.
  - During each visit, emphasize that opioid maintenance therapy with methadone or buprenorphine will relieve their withdrawal symptoms while improving their mood and function.
  - If patient agrees to opioid maintenance therapy, refer to addiction physician or initiate buprenorphine treatment (see below).
- Taper completely off opioid.
  - If patient has a severe biomedical pain condition that warrants opioid therapy, prescribe once-daily long-acting morphine, daily dispensed, at a maximum dose of 50 mg.

### **(d) Opioid maintenance therapy**

Opioid maintenance therapy is substituting an illegal and/or euphoria-inducing opioid with a longer-acting, less euphoric opioid (i.e., methadone or buprenorphine). While family physicians cannot prescribe methadone unless they have a special exemption from the CPSO, they can prescribe buprenorphine, which is now available as a General Benefit on the Ontario Drug Benefit Formulary.

## Indications

- Has an OUD.
- Failed at or not a candidate for structured opioid therapy.
- Acquires opioids from multiple sources (e.g., other doctors, friends and relatives, the street).
- Injects or crushes oral tablets.
- Currently misusing alcohol or other drugs.

## Prescribing buprenorphine

### Buprenorphine

- Partial opioid agonist with a ceiling effect.
  - Unlike full agonists such as morphine, even very high doses rarely cause respiratory depression unless combined with alcohol or sedating drugs.
- When taken in the appropriate dose, relieves withdrawal symptoms and cravings for 24 hours without causing euphoria.
- Binds very tightly to the opioid receptors, displacing other opioids that occupy the receptor site; this minimizes the psychoactive effect of other opioids taken concurrently.
- Has a slow onset and long duration of action because it dissociates very slowly from the receptors.
- Side effects similar to those of other opioids: nausea, constipation, and sedation.
- Buprenorphine is often combined 4:1 with naloxone, an opioid antagonist, in order to prevent misuse: the naloxone in the preparation has no effect when taken sublingually, but will trigger severe withdrawal if injected.

## Initiation protocol

- Physician must ensure that patient has no opioid in their serum before taking the first dose.
  - Buprenorphine is very safe, even in patients who have never taken it before, but it does displace opioids currently attached to the receptor.
  - This precipitates opioid withdrawal in patients who are physically dependent on those opioids.
  - Precipitated withdrawal is rarely severe or dangerous, but patients who experience it are reluctant to try buprenorphine again.
  - Use the Clinical Opioid Withdrawal Scale (COWS) to gauge the patient's withdrawal:

## Clinical Opioid Withdrawal Scale (COWS) (44)

	Interval	0	30m	2h	4h
Date	Time	Score	Score	Score	Score
<b>Resting heart rate (measure after lying or sitting for one minute):</b> 0 HR ≤ 80                      2 HR 101–120 1 HR 81–100                  4 HR > 120					
<b>Sweating (preceding 30m and not related to room temp/activity):</b> 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face					
<b>Restlessness (observe during assessment):</b> 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds					
<b>Pupil size:</b> 0 pupils pinned or normal size for room light 1 pupils larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible					

Interval	0	30m	2h	4h
Date	Time			
	Score	Score	Score	Score
<b>Bone or joint pain (not including existing joint pains):</b> 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints / muscles plus unable to sit still due to discomfort				
<b>Runny nose or tearing (not related to URTI or allergies):</b> 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks				
<b>GI upset (over last 30 minutes):</b> 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhoea 5 multiple episodes of vomiting or diarrhoea				
<b>Tremor (observe outstretched hands):</b> 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching				
<b>Yawning (observe during assessment):</b> 0 no yawning 1 yawning once or twice during assessment 2 yawning 3+ times during assessment 4 yawning several times/minute				
<b>Anxiety or irritability</b> 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult				
<b>Gooseflesh skin</b> 0 skin is smooth 3 piloerection (goosebumps) of skin can be felt or hairs standing up on arms 5 prominent piloerection				
<b>SCORE INTERPRETATION</b>  5–12 MILD 13–24 MODERATE 25–36 MODERATELY SEVERE > 36 SEVERE	Total	Total	Total	Total
	Initials	Initials	Initials	Initials

- Office induction is preferred, as it will ensure patient does not go into precipitated withdrawal.
- Home induction may be necessary in certain situations:
  - Patient is unable to abstain from opioids long enough to attend the office in withdrawal.
  - Patient is at high risk for treatment drop-out (e.g., younger, injection opioid user, unstable housing).
  - Patient is in an acute care setting (e.g., ED, withdrawal management), is not yet in withdrawal, and is unlikely to keep a clinic appointment.
- **Office induction protocol:**
  - At least 12 hours since last oral IR dose, 24 hours since last oral CR dose.
  - Patient reports typical withdrawal symptoms.
  - COWS score of 12+
  - First dose: 4 mg SL. Dose may take several minutes to dissolve.
  - Reassess in 2 hours. If patient improved but still in withdrawal, give another 4 mg to take in office or at home. **Maximum dose first day is 12 mg.**
- **Home induction protocol:**
  - Prescribe 2 mg SL q4H PRN, up to 6 tabs over 24 hours, x 1–3 days (e.g., 18 tabs all as take-home or 6 tabs daily dispensed for 3 days).
  - Warn patient to wait at least 12 hours after last opioid use and be in at least moderate withdrawal before taking first dose.
  - Take 2 mg x 2 tabs SL.
  - If still in withdrawal after 2 hours, take another 2 mg x 2 tabs SL. **Maximum dose is 12 mg** in 24 hours.

## Titration

- Reassess in 1–3 days. Increase dose by 2–4 mg at each visit if patient reports withdrawal symptoms or cravings towards the end of a dosing interval. Each dose increase should increase duration of relief from withdrawal and cravings.
- **Optimal maintenance dose** is usually **8–16 mg SL OD**; **maximum dose** is **24 mg SL OD**. The optimal dose should relieve withdrawal symptoms and cravings for 24 hours without causing significant sedation or other side effects.
- If feasible, at the beginning of therapy, buprenorphine should be dispensed daily under observation by the pharmacist.
  - This is particularly important if the patient has been accessing opioids from other sources.
  - If the patient is unable to attend daily because of limited mobility, lack of transportation, or work or family commitments, arrange supervised dispensing at home by a nurse or reliable relative.
  - Take-home doses may be prescribed once patient is at optimal dose and has stopped unauthorized use.
- The physician should arrange frequent office visits for counseling and urine drug screen monitoring.

## **Buprenorphine prescriptions**

Prescription should include:

- Patient's name, date of birth, and health card number
- The pharmacy address and fax number
- The dose
- Start and end dates
- Day(s) of the week the patient takes a dose at the pharmacy under the observation of the pharmacist, and days of the week the patient takes the dose at home. Stable patients usually attend the pharmacy once a week to take a single dose under the observation of a pharmacist and receive 6 tablets to take home.

## **Follow-up visits for stable patients on buprenorphine**

- Ask about withdrawal symptoms or cravings; sometimes patients require minor dose adjustments of 2–4 mg/day.
- Ask about alcohol and cannabis use.
- Ask about overall mood and functioning.
- Manage chronic medical conditions (e.g., hepatitis C) or psychiatric conditions (e.g., anxiety, depression).
- Perform regular screening and health maintenance (e.g., pap tests, mammograms, immunizations, etc.).
- Identify any new medical or psychiatric conditions.
- Review urine drug screen results.
  - Stable patients should leave at least one urine sample per month.
  - Review unexpected results with patient and, if necessary, with addiction physician.

## Interpretation of unexpected urine drug screen results

<b>Result</b>	<b>Interpretation</b>	<b>Action</b>
Absence of norbuprenorphine	Noncompliance or diversion	If diversion suspected, resume daily supervised dispensing. Consider consult with addiction physician.
Presence of opioids or benzodiazepines	Innocent slip Early relapse	If inadvertent, warn patients not to take meds from family or friends. Increase testing frequency. If relapse: <ul style="list-style-type: none"><li>• Assess adequacy of buprenorphine dose.</li><li>• Counsel about avoiding triggers.</li><li>• Assess mood.</li><li>• Increase testing frequency.</li><li>• If persists, reduce number of take-home doses.</li></ul>
Presence of cocaine or crystal methamphetamine	Possible stimulant use disorder	Consider consult with addiction physician

## Indications for buprenorphine tapering

- Patient wants to taper.
- Patient has at least six months without any substance use.
- Patient is socially stable and has a supportive family or social network.
- Patient has a stable mood and good coping strategies.
- Patient has minimal contact with drug users.

## **Buprenorphine tapering protocol**

- Decrease by small amounts, e.g., 2 mg or even 1 mg (half of a 2 mg tablet) at a time.
- Leave at least two weeks, preferably longer, between dose decreases.
- Put the taper on hold at the patient's request, or if the patient experiences withdrawal symptoms or cravings.
- Return to the original dose if the patient begins using opioids again, even in small amounts or intermittently.
- Provide regular support and encouragement.
- Emphasize that it is not a "failure" if the taper has to be held or reversed, and it is safe and acceptable to remain on buprenorphine for long periods when necessary.

## **Part III: Cannabis**

### **Introduction**

Cannabis is the most widely used illicit substance worldwide. In Canada, cannabis is second only to alcohol as the most widely used psychoactive substance. Among adolescents, Canadian teens have the highest use of cannabis, with more than 20% reporting use in the past year, compared to 10% in other developed countries (45). There has been an increase in cannabis use disorder in the United States over the last ten years, especially in states where cannabis use has been decriminalized (46). It is estimated that 9% of people who use marijuana will become dependent on it at some point in their lives (45).

An additional factor is the Health Canada regulation allowing physicians to authorize the use of cannabis for medical purposes. This, combined with the high number of users, the risk of dependency, and the possible legislative changes that may be on the horizon in Canada, makes it crucial for family physicians to be able to communicate with their patients about cannabis. This section outlines the essentials of managing patients' cannabis use, both medical and recreational.

# Harms associated with cannabis use

## Route of delivery

- Smoking is most common route.
  - Smoking creates hundreds of chemical by-products, some of which are carcinogenic and atherogenic.
- Vaporizing avoids the toxic byproducts of smoking.
- With both smoking and vaporizing, THC rapidly enters the CNS in high concentrations, increasing the risk of cognitive impairment.
- THC absorption is slow with the oral route, but food products sometimes contain large amounts of THC, which can cause severe intoxication.

## Long-term effects and complications

- Cognitive impairment
  - Can impact impulse control, working memory, decision-making, executive function (47)
- Psychiatric
  - Can trigger and exacerbate psychosis (48)
  - Cannabis use disorder (49)
  - Association between cannabis use and anxiety and mood disorders, though directionality is not entirely clear (50)
  - Risks greater under the age of 25

- Cannabis hyperemesis syndrome (51)
  - Difficult to diagnose, but often characterized by long-term cannabis use, cyclical vomiting, and a compulsive need for hot bathing
  - Can also be accompanied by reduced oral intake, abdominal pain, weight loss, dehydration
  - Condition resolves within 1–3 months of cannabis cessation; a return to cannabis can lead to recurrence
- Respiratory
  - Chronic bronchitis
  - Possible risk factor for lung cancer
- Cardiac
  - Tachyarrhythmias
  - Very high doses can precipitate myocardial infarction
- Reproductive
  - Neurodevelopmental delays in infants of women who use cannabis during pregnancy

## **Cannabis use during adolescence**

- Canadian adolescents (age 11–15) have highest rate of cannabis use among 29 most developed countries (52).
- French study showed that a positive first exposure to cannabis may increase risk of developing cannabis dependence at age 18–21 (53).
- Other risks of cannabis use during adolescence:
  - Increase in social dysfunction (54).
  - Vulnerability of the adolescent brain to regular cannabis exposure (drop in IQ by 5–8 points) with changes persisting into midlife even after cessation (55, 56).
  - Heavy use may increase risk for developing psychosis (57).

## **Cannabis use and driving**

- Cannabis use impairs performance of cognitive and motor tasks that are necessary for driving safely.
- Use of cannabis increases risk of a motor vehicle collision, with the risk increasing with driving after cannabis use and with using more than once weekly (58, 59).
- A meta-analysis of studies that looked at acute cannabis use and motor vehicle collisions found an almost doubling of risk for drivers involved in a collision that resulted in serious injury or death (60).
- Inform your patients that you have a duty to report to the Ministry of Transportation if you have concerns about safety and driving.
- Criteria for reporting to the Ministry of Transportation:
  - Patient or family member reports that patient is using cannabis before driving.
  - Patient reports that they are using cannabis throughout the day and also reports that they are driving.

# Screening and assessment

## Drug history

- Ask all adolescent and adult patients at baseline and annual physical about their use of all recreational substances, including cannabis.
- Ask about weekly **frequency** of cannabis use and typical **amount** they use in a day.
  - An average joint contains about 500 mg of dried cannabis; an average bowl contains about 250 mg of dried cannabis.
  - If patient is not sure how much they smoke in a week, ask them how much they purchase at a time and how long it takes them to go through it.
- Patients who use cannabis more than **3 times per week** or use more than **2 g per day** should have further assessment.

## Screening questionnaire

- The CAGE-AID (CAGE Adapted to Include Drugs) questionnaire has been validated as a screening tool for substance use disorders (61).
- CAGE-AID is well suited to use in primary care, as it is quick and can be easily incorporated into a medical history or office visit.
- A score of 1+ indicates a need for further evaluation for cannabis use disorder (CUD).

## CAGE-AID

In the last three months...

- Have you felt you ought to **CUT DOWN** or stop drinking or using drugs?
- Has anyone **ANNOYED** you or gotten on your nerves by telling you to cut down or stop drinking or using drugs?
- Have you felt **GUILTY** or bad about how much you drink or use drugs?
- Have you been waking up wanting to have an alcoholic drink or use drugs (**EYE-OPENER**)?

## Managing cannabis use

Patients in certain risk categories should be discouraged from using cannabis regularly, whether or not they are identified as having a cannabis use disorder. Other patients who are not identified as having a cannabis use disorder should be given advice on harm reduction and reducing their use.

### Discourage regular use

The following patients should be strongly discouraged from engaging in regular cannabis use:

- Patients under the age of 25.
- Patients who are pregnant or trying to become pregnant.
- Patients with a current, past, or strong family history of psychosis.
- Patients with a current, past, or strong family history of problematic substance use.
- Patients with a current anxiety or mood disorder.
- Patients with a respiratory or cardiac illness.

## **Advice on reducing cannabis use and avoiding cannabis-related harms**

- Do not combine cannabis with alcohol or opioids.
- Do not drive for at least 6 hours after using (or at least 8 hours if you experience a subjective high).
- Use a vaporizer rather than smoking.
- Use very small amounts of edibles, as they can contain large amounts of THC.
- Abstain from cannabis at least 2 days per week.
- Set a weekly goal for cannabis use and keep a daily record of the amount used.
- Purchase smaller amounts and make smaller joints.
- Wait 10 minutes between puffs and 20–30 minutes between joints.
- Do not inhale deeply or hold your breath.

## **Cannabis use disorder**

Patients scoring 1+ on the CAGE-AID screening questionnaire should be assessed for cannabis use disorder (CUD).

### **Diagnostic criteria**

The DSM-V gives the following criteria for a CUD (9):

- (a) Cannabis taken in larger amounts or over a longer period of time than intended.
- (b) Repeated unsuccessful efforts to reduce use.
- (c) Great deal of time spent obtaining or using cannabis, or recovering from its effects.
- (d) Strong cravings or urges to use cannabis.
- (e) Recurrent use resulting in a failure to fulfill major responsibilities.

- (f) Continued cannabis use despite recurrent social or interpersonal problems.
- (g) Reduction of major activities because of cannabis use (e.g., missing work, spending less time with children or spouse).
- (h) Continued cannabis use in situations or activities where it is dangerous.
- (i) Continued use despite knowledge of cannabis-related physical or psychological problems.
- (j) Tolerance (need to use more cannabis to achieve the same effect, or diminished effects with continued use of the same amount of cannabis).
- (k) Withdrawal (e.g., irritability, anxiety, sleep difficulty, decreased appetite, abdominal pain, sweating, headache, relieved by drinking).

Patients who meet two or three of these criteria have a **mild** CUD, four to five criteria indicate a **moderate** CUD, and six or more indicate a **severe** CUD.

### **Clinical features of CUD**

- Baseline risk factors: younger, current psychiatric disorder, current or past problematic use of alcohol or other substances
- Smokes cannabis daily in large doses (e.g., 2–3+ grams)
- Spends a significant amount of time smoking every day
- Poor psychosocial function (family, work, school)
- Strong resistance to discontinuing cannabis
- Believes that cannabis is essential to relieve anxiety
- Concern expressed by family members

## Patient intervention

- Tell patient that you believe that their cannabis use is harmful to them.
- Explain that, while cannabis intoxication may temporarily relieve anxiety, in the long term it makes mood worse, and mood, function, and relationships will improve if cannabis use is reduced or stopped.
- Use a motivational interviewing approach with patients who are ambivalent about treatment (62):
  - Explore patient's own reasons for change with the goal of encouraging **change talk**.
  - Ask: "What are some of the good things about using cannabis? What are some of the not-so-good things? How does using cannabis fit in with your goals? What are some of the good things about **not** using cannabis? What are some of the not-so-good things? How would you like your life to be different? Where do you go from here?"
  - Reflect back patient's motivations in order to strengthen commitment to change.
  - Non-confrontational, patient-centred approach that elicits higher levels of change talk and lower levels of resistance in patients than other approaches.
- Ask if patient is willing to commit to a goal (abstinence or reduced use).
- If patient is not ready to commit, ask about cannabis use and readiness to change at each visit.
- If ready to commit, negotiate a goal:
  - If reduced use is chosen, offer advice on reducing use and harms (see page 68).
- Treat concurrent mood or anxiety disorders.

- Encourage healthy lifestyle choices:
  - Work with your doctor to quit tobacco (if applicable).
  - Avoid friends who use cannabis regularly.
  - Avoid social situations involving cannabis use.
  - Find alternative activities, such as exercise and spending time with friends.
  - Find someone you can talk to about your cannabis use.
- Offer pharmacotherapy to treat withdrawal symptoms and cravings:
  - Some preliminary evidence for nabilone, gabapentin, and over-the-counter N-acetylcysteine (NAC) (63).
  - Nabilone: Starting dose **1 mg tid**; titrate to effect
  - Gabapentin: **1200 mg daily**
  - NAC: **1200 mg daily**
- Refer to psychosocial treatment if available.
- Arrange regular follow-up to discuss progress.
- Perform urine drug screens in follow-up visits to encourage patient accountability and monitor cannabis use (64).
  - A single use can produce a positive urine drug screen up to 1 week after use.
  - Long-term users can have positive urine drug screens up to 46 days after last use.

## Cannabis withdrawal

- Onset: Several days after daily heavy use
- Symptoms: Anxiety, irritability, depression, insomnia, abdominal discomfort, sweating, headache

# Cannabis therapy

Health Canada allows physicians to authorize the use of cannabis for medical purposes for their patients; however, cannabis is **not** an approved therapeutic product in Canada, nor has any medical regulator endorsed or approved cannabis as a safe and effective therapy. This means that, in the event that a patient experiences harm from medical cannabis, the physician cannot claim that they were prescribing according to approved medical standards.

Family physicians receiving requests for cannabis authorization should keep the following guidelines in mind:

- Physicians are **not obligated** to authorize cannabis.
- Physicians should **monitor** all patients on cannabis therapy for indications of harm, including misuse.
- Physicians should **stop** authorizing cannabis to patients when there is evidence of harm.

## Evidence for cannabis therapy for pain

- Evidence very weak (65):
  - Five placebo-controlled RCTs on subjects with neuropathic pain.
  - Trial durations ranged from 1–5 days, total of 226 subjects.
  - Functional outcomes not assessed.
  - Subjects in cannabis group experienced dose-dependent cognitive impairment and intoxication.
- Nabilone (oral pharmaceutical cannabinoid) and nabiximols (buccal THC/cannabidiol spray) both have greater evidence of safety and effectiveness for pain than dried cannabis (66).

## **Evidence for cannabis therapy for anxiety**

- Observational studies have shown that cannabis use worsens anxiety and PTSD symptoms; stopping cannabis use improves anxiety and PTSD symptoms (67, 68).
- Pure cannabidiol (with no THC) may have some therapeutic benefit in treating anxiety (69).

## **Indications**

- Severe neuropathic pain condition (e.g., HIV, diabetes) that has failed to respond to an adequate trial of all standard analgesics (opioids, anticonvulsants, antidepressants, pharmaceutical cannabinoids).
- Not indicated for fibromyalgia, low back pain, or other common pain conditions seen in primary care.
- Not indicated for anxiety, PTSD, insomnia, or depression.

## **Contraindications and precautions**

- Age under 25
- Current, past, or strong family history of psychosis (48)
- Cardiovascular or respiratory disease
- Current, past, or strong family history of problematic substance use (alcohol, opioids, benzodiazepines, stimulants)
- Current, active mental illness (anxiety, depression, PTSD)
- Pregnant or planning to get pregnant

# Authorizing cannabis therapy

## Dosing

- Physicians must complete a medical document specifying the daily amount of dried cannabis and the period of use (maximum one year).
- No legal restriction on the amount of cannabis authorized.
- Possession limit: the lesser of the equivalent of 150 g or 30 times the daily amount authorized.
- While not legally required, physicians should also specify the THC and cannabidiol concentrations.
- Maximum recommended daily dose of dried cannabis:  
**400 mg with maximum 9% THC**
  - Maximum dose used in controlled trials (70)
  - Recommended by College of Family Physicians of Canada guidance document (71)
- Acute and long-term adverse effects are related to the dose of THC:
  - Cannabidiol may mitigate against the harmful psychoactive effects of THC.
  - Prescriptions should specify a cannabidiol concentration at least as great as THC.

## Management of requests for dried cannabis

- If dried cannabis is not indicated or contraindicated:
  - Explain that standard treatments are safer and more effective.
  - Explain that dried cannabis carries serious risk of harm, especially in higher doses, when it is contraindicated.
  - Assess patient for a cannabis use disorder, especially if patient is persistent or aggressive.

## Medical cannabis clinics

- Use **caution** when referring patients to medical cannabis clinics.
- Some clinics authorize excessive amounts of cannabis (e.g., 2–3 g per day) for non-indicated conditions for patients at high risk for cannabis-related harms.
- Do not refer to medical cannabis clinics unless they have released a **detailed clinical summary** of their authorizing practices (assessment, indications, contraindications, dosing, and monitoring).

# Part IV: Benzodiazepines

## Introduction

Benzodiazepines are effective anxiolytics, but they are associated with serious harms. Physicians find it difficult to mitigate against these harms because they tend to be unpredictable, vague and hard to detect, and multifactorial (e.g., falls, fatigue, depression). Therefore, as with opioids, safe benzodiazepine prescribing requires careful patient selection, close monitoring, and tapering when indicated. This section provides guidelines on safely prescribing benzodiazepines and managing adverse effects, including benzodiazepine use disorder.

## Benzodiazepine therapy

### Indications

- Severe acute anxiety
- Generalized anxiety disorder that is unresponsive to other treatments (e.g., SSRIs, SNRIs)
- Panic disorder that is unresponsive to other treatments (SSRIs are first-line agents)
- Depression, bipolar disorder, or schizophrenia (adjunct therapy)
- Insomnia
- Alcohol withdrawal
- Seizures, spasms
- Pre-procedure sedation

## Adverse effects

Effect	Factors that increase risk
Depression Suicidal ideation	<ul style="list-style-type: none"> <li>• High doses</li> <li>• Concurrent use of alcohol/opioids</li> <li>• Underlying mood disorder</li> </ul>
Falls Hip fractures	<ul style="list-style-type: none"> <li>• Older adults</li> <li>• Neurological/cognitive impairment</li> <li>• Long-acting agents (e.g., diazepam)</li> </ul>
Confusion Worsening dementia	<ul style="list-style-type: none"> <li>• Older adults</li> <li>• Dementing condition</li> </ul>
Motor vehicle accidents	<ul style="list-style-type: none"> <li>• Early in therapy before tolerance develops</li> <li>• Concurrent use of other sedating agents</li> </ul>
Decreased respiratory drive	<ul style="list-style-type: none"> <li>• Early in therapy</li> <li>• Respiratory illness/dysfunction</li> <li>• Concurrent use of other sedating agents</li> </ul>
Sleep apnea	<ul style="list-style-type: none"> <li>• Underlying risk (e.g., obesity)</li> <li>• Concurrent use of other sedating agents</li> </ul>
Blackouts Parasomnias	<ul style="list-style-type: none"> <li>• Triazolam or alprazolam</li> <li>• Higher doses</li> </ul>

## Prescribing benzodiazepines

- Consider alternative therapies before prescribing benzodiazepines.
  - For anxiety: SSRIs, SNRIs, mood stabilizers, psychotherapy
  - For insomnia: trazadone, tryptophan, low-dose TCA, sedating SSRIs, zopiclone
- Initial prescriptions should be for a maximum of **3 weeks**.
- Prescribing for anxiety:
  - Titrate patient to **lowest effective dose**.
  - Long-term therapy should be prescribed only to patients with severe anxiety interfering with daily function who have failed an adequate trial of psychotherapy and of other anxiolytics (e.g., SSRIs, mood stabilizers).
  - Taper dose when indicated (see below).
- Prescribing for insomnia:
  - Patients should avoid daily use for prolonged periods, as tolerance for sedation develops quickly, and abruptly stopping after several weeks of daily use will result in rebound insomnia.
  - Patients should be advised on sleep hygiene:

Go to bed and get up at a reasonable time; don't sleep late, even if you're tired.

Eat only small amounts before bed.

Avoid caffeine and alcohol at night.

Only use the bed for sleeping and sex; don't read, watch TV, use your phone, etc.

If you can't sleep, get up and do something else for 15 minutes (but don't turn on a screen).

Exercise most days of the week.

If you get up frequently to urinate, avoid drinking too much at night.

## Benzodiazepine equivalent table (72)

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

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

\*\* Equivalency uncertain.

## Benzodiazepine withdrawal

<b>Clinical features</b>	Abrupt discontinuation of benzodiazepines after daily use for 2+ months Can occur even at therapeutic doses, though more severe with high doses, long duration of use, or underlying anxiety disorder
<b>Time course</b>	Onset 2–4 days after abrupt cessation May take weeks or months to resolve
<b>Symptoms and signs</b>	Anxiety-related symptoms (panic, irritability, poor concentration) Neurological symptoms (dysperceptions, tinnitus, déjà vu) Sweating, tremor usually not seen except with sudden cessation of high doses
<b>Complications</b>	Abrupt cessation of high doses (50 mg of diazepam/day or equivalent) can cause acute hypertension, seizures, delirium Can trigger suicidal ideation in patients with mixed anxiety and mood disorder
<b>Effect on sleep</b>	Rebound insomnia (vivid dreams, fitful sleep) Takes several weeks to resolve

# Benzodiazepine tapering

## Rationale

- Recommended over abrupt cessation unless patient has only been taking the medication intermittently or for a few weeks.
- Periodic tapering attempts are warranted even for patients taking therapeutic doses with no apparent adverse effects:
  - Patients sometimes feel more alert and energetic at lower doses, and are better able to engage in psychotherapy.
- Controlled trials have shown that many adults are able to successfully reduce their benzodiazepine dose with appropriate support (73, 74) and that tapering can be performed in primary care (75).

## Indications

- At higher risk for sedation, falls, and sleep apnea (e.g., elderly, heavy drinkers, on opioids or other sedating medications)
  - Benzodiazepines markedly increase opioid toxicity and the lethality of an opioid overdose (76).
- Daily responsibilities requiring alertness and clear thinking (e.g., students, drivers, looking after small children)
- Cognitive impairment, fatigue, depression
- At risk for unsafe medication use

## Approach to tapering

- Explain benefits of tapering (improved energy, mood, and function; reduced risk of falls; etc.).
- Work with patient to determine rate of taper.
  - Slow, flexible tapers work better than rapid tapers.
- Halt or reverse taper if patient experiences clinically significant increase in anxiety.
- Follow patient regularly (every 1–4 weeks).
- At each visit, ask not just about withdrawal symptoms but benefits of tapering: more alert, less fatigued, improved mood.
- Involve family members if possible; they often notice improvement before patient does.
- Ideal time to introduce comprehensive management strategies for underlying anxiety disorder, including psychotherapeutic techniques (mindfulness, CBT), lifestyle modification (exercise, sleep, reduce coffee and alcohol) and pharmacotherapy (antidepressants).

# Tapering protocol

<b>Formulation</b>	Safest to taper with patient's current benzodiazepine (but see below).
<b>Dosing interval</b>	Scheduled doses rather than PRN. Keep dosing interval the same for as long as possible (e.g., bid or tid). Advise patients not to skip or delay doses (in an attempt to speed up the taper), as this causes a sharp increase in anxiety.
<b>Rate of taper</b>	Taper slowly, no more than 5 mg diazepam equivalent/day at each office visit. Can taper as slowly as 1–2 mg diazepam equivalent/month. Can taper according to proportional dose remaining: taper by 10% of dose every visit until at 20% of original dose, then taper by 5% every visit. Let patient choose which dose is decreased (AM, PM, or HS). Adjust rate of taper according to patient response. Slow pace of taper once daily dose below 20 mg diazepam equivalent.
<b>Dispensing interval</b>	If patient runs out early, increase dispensing frequency to weekly, alternate days, or daily.
<b>Endpoint of taper</b>	Abstinence preferred. Reduced dose if patient experiences significant anxiety or insomnia with abstinence.

## Tapering with clonazepam

- If patient is emotionally attached to their benzodiazepine and resistant to tapering or repeatedly runs out early, consider switching patient to another agent for tapering.
- Little clear evidence for best agent for tapering; however, **clonazepam** is recommended over diazepam.
  - Although diazepam has a longer duration of action and therefore may result in a smoother withdrawal, clonazepam is less likely to cause prolonged sedation in the elderly and has a lower risk of euphoria and misuse.
- Protocol:
  - Initial dose should be lower than that of current agent, as patient may not be tolerant to new agent; convert to one half equivalent dose of original agent (see page 79).
  - Increase dose until patient is comfortable, but try not to go above fully equivalent dose.
  - Prescribe on bid or tid schedule.

## Benzodiazepine use disorders

As with opioid use disorders, a patient with a benzodiazepine use disorder is not using the medication for therapeutic purposes but to achieve sedation and euphoria. While tolerance for the anxiolytic effects of benzodiazepines develops very slowly, allowing patients to stay on a moderate dose for months or years, tolerance to the sedating and euphoric effects of benzodiazepines develops quickly, forcing patients to escalate the dose. The features of benzodiazepine **intoxication** are similar to those of alcohol intoxication: sedation, emotional lability, and impulsive or dangerous behaviour.

## **Risk factors**

- Male
- Younger
- Current or past history of problematic use of other substances
- Current active psychiatric disorder

## **Clinical features**

- Patient is taking a dose well above the usual therapeutic range.
- Patient frequently runs out early or accesses benzodiazepines from other sources.
- Patient has a pattern of binge use with recurrent intoxication and withdrawal.

# Management

<b>Treatment setting</b>	Outpatient taper recommended for patients on moderate doses who do not access benzodiazepines from non-medical sources. Residential treatment best for patients on very high doses (e.g., 100+ mg diazepam equivalent/day) or patients whose main source of benzodiazepines is the illicit market.
<b>Outpatient tapering</b>	Patients will have trouble tapering if they are given large amounts of benzodiazepines to take home. Dispense every 1–2 days with a strict agreement that prescriptions will not be refilled early. Patients experiencing significant sedation or intoxication should be tapered quickly (e.g., 5 mg diazepam equivalent every 3–7 days). Taper may be slowed when intoxication resolves.
<b>Psychosocial treatment</b>	Similar to treatment of other substance use disorders: formal treatment programs and self-help groups. Encourage patient to try different options to see what suits them best.
<b>Treatment of concurrent conditions</b>	Addiction to alcohol or opioids should be treated at the same time as the benzodiazepine addiction to reduce risk of dangerous drug interactions. Most patients with a benzodiazepine use disorder will also have a significant mental illness, which should be treated concurrently. Anticonvulsant medications (e.g., gabapentin, topiramate) may be helpful for both underlying mood disorder and alcohol/benzodiazepine withdrawal. Antidepressants and atypical antipsychotics may also be helpful. Shared care with psychiatrist is recommended.

## References

1. Saitz R, Horton NJ, Larson MJ, Winter M, Samet JH. Primary medical care and reductions in addiction severity: a prospective cohort study. *Addiction* (Abingdon, England). 2005;100(1):70-8.
2. Moos RH, Moos BS. Long-term influence of duration and intensity of treatment on previously untreated individuals with alcohol use disorders. *Addiction* (Abingdon, England). 2003;98(3):325-37.
3. Parthasarathy S, Mertens J, Moore C, Weisner C. Utilization and cost impact of integrating substance abuse treatment and primary care. *Medical care*. 2003;41(3):357-67.
4. Willenbring ML, Olson DH. A randomized trial of integrated outpatient treatment for medically ill alcoholic men. *Archives of internal medicine*. 1999;159(16):1946-52.
5. Druss BG, von Esenwein SA. Improving general medical care for persons with mental and addictive disorders: systematic review. *General hospital psychiatry*. 2006;28(2):145-53.
6. Friedmann PD, Hendrickson JC, Gerstein DR, Zhang Z, Stein MD. Do mechanisms that link addiction treatment patients to primary care influence subsequent utilization of emergency and hospital care? *Medical care*. 2006;44(1):8-15.
7. Solbergdottir E, Bjornsson G, Gudmundsson LS, Tyrfinngsson T, Kristinsson J. Validity of self-reports and drug use among young people seeking treatment for substance abuse or dependence. *Journal of addictive diseases*. 2004;23(1):29-38.
8. Butt P, Beirness D, Cesa F, Gliksman L, Paradis C, Stockwell T. *Alcohol and health in Canada: A summary of evidence and guidelines for low risk drinking*. Ottawa: Canadian Centre for Substance Abuse; 2010.
9. American Psychiatric A, American Psychiatric A, Force DSMI. *Diagnostic and statistical manual of mental disorders : DSM-5*. 2013.
10. Bradley KA, Boyd-Wickizer J, Powell SH, Burman ML. Alcohol screening questionnaires in women: a critical review. *Jama*. 1998;280(2):166-71.

11. Ewing JA. Detecting alcoholism: The CAGE questionnaire. *Journal of the American Medical Association*. 1984;252(14):1905-7.
12. King M. At risk drinking among general practice attenders: Validation of the CAGE questionnaire. *Psychological medicine*. 1986;16(1):213-7.
13. Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. Primary care validation of a single-question alcohol screening test. *Journal of general internal medicine*. 2009;24(7):783-8.
14. Babor T, Higgins-Biddle JC, Saunders J, Monteiro MG. *AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care*. 2 ed. Geneva, Switzerland: World Health Organization; 2001.
15. Rosman AS. Utility and evaluation of biochemical markers of alcohol consumption. *Journal of substance abuse*. 1992;4(3):277-97.
16. Sharpe P. Utility and evaluation of biochemical markers of alcohol consumption. *Annals of Clinical Biochemistry*. 2001;38(part 6):652-64.
17. Fleming MF, Barry KL, Manwell LB, Johnson K, London R. Brief physician advice for problem alcohol drinkers. A randomized controlled trial in community-based primary care practices [see comments]. *JAMA*. 1997;277(13):1039-45.
18. Kahan M, Wilson L, Becker L. Effectiveness of physician-based interventions with problem drinkers: a review. *CMAJ*. 1995;152(6):851-9.
19. Gossop M, Harris J, Best D, Man LH, Manning V, Marshall J, et al. Is attendance at Alcoholics Anonymous meetings after inpatient treatment related to improved outcomes? A 6-month follow-up study. *Alcohol and alcoholism (Oxford, Oxfordshire)*. 2003;38(5):421-6.
20. Burkitt MJ, Raafat A. Nitric oxide generation from hydroxyurea: significance and implications for leukemogenesis in the management of myeloproliferative disorders. *Blood*. 2006;107(6):2219-22.
21. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British journal of addiction*. 1989;84(11):1353-7.

22. De Sousa A. A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. *Alcohol and alcoholism* (Oxford, Oxfordshire). 2004;39(6):528-31.
23. de Sousa A, de Sousa A. An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. *Alcohol and alcoholism* (Oxford, Oxfordshire). 2005;40(6):545-8.
24. Laaksonen E, Koski-Jannes A, Salaspuro M, Ahtinen H, Alho H. A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. *Alcohol and alcoholism* (Oxford, Oxfordshire). 2008;43(1):53-61.
25. Mueser KT, Noordsy DL, Fox L, Wolfe R. Disulfiram treatment for alcoholism in severe mental illness. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions*. 2003;12(3):242-52.
26. Petrakis IL, Nich C, Ralevski E. Psychotic spectrum disorders and alcohol abuse: a review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. *Schizophrenia bulletin*. 2006;32(4):644-54.
27. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Jama*. 2006;295(17):2003-17.
28. Snyder JL, Bowers T. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence: A relative benefits analysis of randomized controlled trials. *The American journal of drug and alcohol abuse*. 2008;34(4):449-61.
29. Rosner S, Leucht S, Leher P, Soyka M. Acamprosate supports abstinence, naltrexone prevents excessive drinking: Evidence from a meta-analysis with unreported outcomes. *Journal of psychopharmacology* (Oxford, England). 2008;22(1):11-23.
30. Baltieri DA, Daro FR, Ribeiro PL, de Andrade AG. Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction* (Abingdon, England). 2008;103(12):2035-44.

31. Johnson B, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K. Topiramate for treating alcohol dependence: A randomized controlled trial. *Jama*. 2007;298(14):1641-51.
32. Ma J, Ait-Daoud N, Johnson B. Topiramate reduces the harm of excessive drinking: Implications for public health and primary care. *Addiction (Abingdon, England)*. 2006;101(11):1561-8.
33. Furieri FA, Nakamura-Palacios EM. Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. *The Journal of clinical psychiatry*. 2007;68(11):1691-700.
34. Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcoholism, clinical and experimental research*. 2008;32(8):1429-38.
35. Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR, et al. Gabapentin combined with naltrexone for the treatment of alcohol dependence. *The American journal of psychiatry*. 2011;168(7):709-17.
36. Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, et al. Baclofen efficacy in reducing alcohol craving and intake: A preliminary double-blind randomized controlled study. *Alcohol and Alcoholism*. 2002;37(5):504-8.
37. Addolorato G, Leggio L, Ferrulli A, Cardone S, L. V, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet*. 2007;370(9603):1915-22.
38. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA*. 2004;291(15):1887-96.
39. Lucey MR, Connor JT, Boyer TD, Henderson JM, Rikkens LF. Alcohol consumption by cirrhotic subjects: patterns of use and effects on liver function. *The American journal of gastroenterology*. 2008;103(7):1698-706.
40. Brunette MF, Noordsy DL, Xie H, Drake RE. Benzodiazepine use and abuse among patients with severe mental

illness and co-occurring substance use disorders. *Psychiatric services* (Washington, DC. 2003;54(10):1395-401.

41. Dasgupta N, Kramer ED, Zalman MA, Carino S, Jr., Smith MY, Haddox JD, et al. Association between non-medical and prescriptive usage of opioids. *Drug and alcohol dependence*. 2006;82(2):135-42.
42. *Avoiding abuse, achieving a balance: tackling the opioid public health crisis* Toronto: College of Physicians and Surgeons of Ontario; 2010.
43. *Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain*. National Opioid Use Guideline Group, 2010. Canada: National Opioid Use Guideline Group; 2010.
44. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *Journal of psychoactive drugs*. 2003;35(2):253-9.
45. Lopez Quintero C, Perez de Los Cobos J, Hasin D, Okuda M, Wang S, Grant B, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug & Alcohol Dependence*. 2011;115(1-2):120-30.
46. Halah MP, Zochniak MP, Barr MS, George TP. Cannabis Use and Psychiatric Disorders: Implications for Mental Health and Addiction Treatment. *Curr Addict Rep*. 2016;3(4):450-62.
47. Batalla A, Bhattacharyya S, Yücel M, Fusar-Poli P, Crippa JA, Nogué S, et al. Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings. *PloS one*. 2013;8(2):e55821.
48. Schoeler T, Petros N, Di Forti M, Pingault JB, Klamerus E, Foglia E, et al. Association Between Continued Cannabis Use and Risk of Relapse in First-Episode Psychosis: A Quasi-Experimental Investigation Within an Observational Study. *JAMA psychiatry* (Chicago, Ill. 2016;73(11):1173-9.
49. Kalant H. Adverse effects of cannabis on health: an update of the literature since 1996. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28(5):849-63.
50. McInnis OA, Porath-Waller A. Chronic use and cognitive functioning and mental health: An update. *Canadian Centre on Substance Abuse*; 2016.

51. Sun S, Zimmermann AE. Cannabinoid hyperemesis syndrome. *Hospital pharmacy*. 2013;48(8):650-5.
52. Adamson P. Child Well-being in Rich Countries: A comparative overview. Florence, Italy: UNICEF Office of Research; 2013.
53. Le Strat Y, Ramoz N, Horwood J, Falissard B, Hassler C, Romo L, et al. First positive reactions to cannabis constitute a priority risk factor for cannabis dependence. *Addiction* (Abingdon, England). 2009;104(10):1710-7.
54. Fergusson DM, Horwood LJ, Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* (Abingdon, England). 2002;97(9):1123-35.
55. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America*. 2012;109(40):E2657-64.
56. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *Journal of addiction medicine*. 2011;5(1):1-8.
57. Dragt S, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, de Haan L, et al. Age of onset of cannabis use is associated with age of onset of high-risk symptoms for psychosis. *Canadian journal of psychiatry*. 2010;55(3):165-71.
58. Mann RE, Adlaf E, Zhao J, Stoduto G, Ialomiteanu A, Smart RG, et al. Cannabis use and self-reported collisions in a representative sample of adult drivers. *Journal of safety research*. 2007;38(6):669-74.
59. Li MC, Brady JE, DiMaggio CJ, Lusardi AR, Tzong KY, Li G. Marijuana Use and Motor Vehicle Crashes. *Epidemiol Rev*. 2012;34(1):65-72.
60. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ* (Clinical research ed). 2012;344.

61. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. *Wis Med J.* 1995;94(3):135-40.
62. Hettema J, Steele J, Miller WR. Motivational interviewing. *Annual review of clinical psychology.* 2005;1:91-111.
63. Balter RE, Cooper ZD, Haney M. Novel Pharmacologic Approaches to Treating Cannabis Use Disorder. *Curr Addict Rep.* 2014;1(2):137-43.
64. Moeller KE, Lee KC, Kissack JC. Urine Drug Screening: Practical Guide for Clinicians. *Mayo Clinic proceedings.* 2008;83(1):66-76.
65. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. *Canadian family physician Medecin de famille canadien.* 2015;61(8):e372-81.
66. Tsang CC, Giudice MG. Nabilone for the Management of Pain. *Pharmacotherapy.* 2016;36(3):273-86.
67. Wilkinson ST, Stefanovics E, Rosenheck RA. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. *The Journal of clinical psychiatry.* 2015;76(9):1174-80.
68. Moitra E, Anderson BJ, Stein MD. Reductions in cannabis use are associated with mood improvement in female emerging adults. *Depression and anxiety.* 2016;33(4):332-8.
69. Soares VP, Campos AC. Evidences for the anti-panic actions of Cannabidiol. *Curr Neuropharmacol.* 2016.
70. Kahan M, Srivastava A, Spithoff S, Bromley L. Prescribing smoked cannabis for chronic noncancer pain: preliminary recommendations. *Canadian family physician Medecin de famille canadien.* 2014;60(12):1083-90.
71. Authorizing Dried Cannabis for Chronic Pain or Anxiety: Preliminary Guidance from the College of Family Physicians of Canada. Mississauga, ON: College of Family Physicians of Canada; 2014.
72. Kalvik A, Isaac P, Janecek E. Benzodiazepine equivalents. *Pharmacy Connection.* 1995:20-32.

73. Paquin AM, Zimmerman K, Rudolph JL. Risk versus risk: a review of benzodiazepine reduction in older adults. *Expert Opin Drug Saf.* 2014;13(7):919-34.
74. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. *JAMA internal medicine.* 2014;174(6):890-8.
75. Vicens C, Fiol F, Llobera J, Campoamor F, Mateu C, Alegret S, et al. Withdrawal from long-term benzodiazepine use: randomised trial in family practice. *Br J Gen Pract.* 2006;56(533):958-63.
76. Jones CM, McAninch JK. Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines. *American journal of preventive medicine.* 2015;49(4):493-501.