

**Management of substance
use disorders in primary
care**

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Introduction

Mentoring, Education, and Clinical Tools for Addiction: Primary Care–Hospital Integration (META:PHI) is an implementation project aiming to bridge the gap between research and practice in the medical treatment of addiction. The purpose of this project is to set up and implement care pathways for addiction at seven sites in Ontario, foster mentoring relationships between addiction physicians at these sites and other health care providers, and create and disseminate educational materials for addiction care.

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Part I: Alcohol use disorders

Introduction

Alcohol misuse is common in Canadian society. Approximately 15% of the population are “at-risk drinkers,” i.e., they consume alcohol in excess of the Canadian low-risk drinking guidelines (1). Additionally, about 3% of the population meets the criteria for an alcohol use disorder (AUD). Alcohol misuse is a leading preventable cause of mortality and morbidity. In 2004, there were an estimated 4,700 deaths and 274,700 disability-adjusted life years lost (DALYs) attributable to alcohol in Canada, representing 7.1% of all deaths and 9.3% of all DALYs (2). The costs to the health care system are enormous. In 2002, alcohol problems accounted for 1,246,945 days in general hospitals, 54,114 days in psychiatric hospitals, and 3,018,688 days in inpatient and outpatient alcohol treatment centres. Total direct health care costs that year were \$2.29 billion (3).

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 (4); there is evidence that the length of treatment has a greater impact on outcome than the intensity of treatment (5). Surveys suggest that patients would

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much prefer to receive treatment in a primary care setting than in a formal addiction setting. For example, in a population survey of Ontario residents (n=1084), only 36% of those with a history of alcohol dependence had sought help for their condition. The physician was the most common source for those seeking help (29.7%), followed by attendance at Alcoholics Anonymous (12.3%). Only 7% attended a formal program (6).

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 (7-10). Yet 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 (11). A strong and growing body of evidence indicates that these interventions are effective, easily learned, and practical in a primary care setting.

The diagnostic continuum of alcohol problems

Alcohol use occurs along a spectrum of severity: abstinence, low-risk drinking, at-risk drinking, and alcohol dependence (which the DSM-V terms an *alcohol use disorder*, or *AUD*). Milder alcohol problems are much more common than severe alcohol problems. This is similar to other conditions (such as hypertension) that occur along a continuum of severity.

The distinction between at-risk drinking and AUD is important for treatment planning. While at-risk drinkers and people with mild AUDs often respond to brief advice and reduced drinking strategies, patients with moderate to severe AUDs often require pharmacotherapy, abstinence, self-help groups, and formal treatment programs.

At-risk drinking

At-risk drinkers have the following properties:

- (a) Patient drinks above recommended guidelines.
- (b) Patient may have alcohol-related psychological, social, or physical problems.
- (c) Patient does not meet the criteria for an AUD.

(a) Canadian low-risk drinking guidelines

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

Table 1: Guidelines for low-risk drinking (12)

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.

These guidelines allow for moderate drinking because numerous case-control and cohort studies have demonstrated that moderate drinkers have a lower mortality from coronary artery disease than either abstainers or heavy drinkers (13). Alcohol exerts its cardioprotective effect by increasing HDL and by inhibiting platelet aggregation. However, there are several caveats to these recommendations:

- Patients who choose to abstain from alcohol should not be encouraged to drink for its cardiovascular benefits. Most of the cardioprotective effects of alcohol can be obtained by consuming less than one drink a day. Other lifestyle habits are of equal or greater benefit to cardiovascular health, including exercise and diet.
- Lower consumption is recommended for women because they have a smaller volume of distribution and therefore higher blood alcohol concentrations for a given rate of alcohol consumption, putting them at greater risk of harm for any amount of consumption.
- The health benefits of moderate drinking are restricted to older patients. A 34-year cohort study of 50,000 Swedish male conscripts, followed from age 1-20 up to age 55, found that mortality linearly increased beyond consumption of 30 g alcohol (slightly less than two drinks) per day. There was a decrease in non-fatal MI but no

increase in fatal MI, and 420 deaths from alcohol-related causes (14).

- Moderate alcohol consumption has adverse effects as well as cardiovascular benefits. Alcohol consumption slightly increases the risk of breast cancer in women. A cohort study of 1.2 million British women estimated that the incidence of breast cancer increases by about 1% per additional drink consumed per day (15).

Separate guidelines have been developed for short-term risks (i.e., acute alcohol intoxication) and long-term risks. The risks of acute alcohol intoxication include accidents, violence, and suicide. The guideline outlines strategies for avoiding acute intoxication:

- Do not drink more than three drinks per occasion for women or four drinks per occasion for men.
- Do not drink more than three drinks in a four-hour period. Since alcohol is metabolized at a steady rate of slightly less than one drink per hour, this will prevent a rapid rise in blood alcohol level.
- Do not drink prior to activities that require complete alertness, such as operating a motor vehicle or caring for small children.

Long-term risks, such as alcoholic liver disease, can be minimized by drinking no more than 10 drinks per

week with no more than two drinks per drinking day for women; or 15 drinks per week with no more than three drinks per drinking day for men. At least one or two days of abstinence is recommended per week, to reduce tolerance and to weaken the habit of daily drinking.

Abstinence or markedly reduced drinking is recommended in the following patient groups:

- Pregnant women, women planning to become pregnant, or women at high risk for becoming pregnant.
- Patients with health conditions that can be exacerbated by alcohol, such as gastritis or cirrhosis of the liver (from alcohol or hepatitis C).
- Patients on medications that interact dangerously with alcohol, such as high doses of opioids.
- Patients with psychiatric conditions that can be worsened by alcohol, such as an active mood disorder.
- Patients with a current or past history of addiction to alcohol or other drugs. Regular or heavy use of alcohol may precipitate a relapse in such patients.

(b) Alcohol-related problems

Psychological problems related to alcohol consumption include insomnia, anxiety and depression. Social problems include spending inadequate time with one's family, reduced work performance due to fatigue or hangover, or impaired driving charges. Physical problems include gastritis, hypertension, fatty liver, recurrent trauma, insomnia, and sexual dysfunction.

Common presentations of at-risk drinking:

- Trauma
- GI symptoms (gastritis, nonspecific dyspepsia, recurrent diarrhea)
- Hypertension
- Depression, anxiety
- Insomnia
- Social and family dysfunction
- Sexual problems

Alcohol use disorders

The DSM-V gives the following criteria for an AUD (16):

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

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.

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Table 2: At-risk drinking vs. AUD

	At-risk drinking	AUD
Withdrawal symptoms	No	Often*
Standard drinks consumed	14+ per week	40-60+ per week
Drinking pattern	Variable; depends on situation	Tends to drink a set amount
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

* The presence of withdrawal symptoms (tremor, morning relief drinking, seizures) generally indicates a diagnosis of alcohol use disorder.

Problem drinkers often drink moderately when the occasion warrants it, and they usually consume less than 40-60 drinks per week. In contrast, alcohol-dependent individuals tend to drink in a stereotypical fashion, consuming large amounts daily or almost daily for extended periods of time.

Problem drinkers tend to be socially stable, and alcohol does not have a profound impact on their lives. The alcohol-related problems they experience are less severe than with the alcohol-dependent patient. For example, the problem drinker may have alcohol-induced insomnia or arguments with his or her spouse, whereas the alcohol-dependent patient may experience GI bleeds, job loss, or family break-up. (However, at-risk drinkers sometimes suffer severe consequences, such as motor vehicle accidents.)

Screening and detection of alcohol problems

Studies have consistently shown that physicians have low rates of identification of alcohol problems. For example, in a cross-sectional study, 1,700 patients from 94 primary care physicians' offices completed the Alcohol Use Disorders Identification Test (AUDIT) after their office visit, and their physicians were asked if they suspected that the patient had an alcohol problem. Physicians suspected an alcohol problem in only 27% of the patients who scored positive on the AUDIT (17). This indicates that primary care clinics should routinely screen for alcohol problems rather than relying solely on clinical suspicion.

Screening surveys

The three simplest and most useful screening surveys are the CAGE, the single alcohol screening question, and the AUDIT.

(a) CAGE questionnaire (18-20)

The sensitivity of the CAGE questionnaire for identifying lifetime alcohol problems in patients in various clinical settings is estimated to be about 70%, with a specificity of 90% (21). Two out of four positive responses suggest a current or past alcohol problem, although even one positive response

warrants further assessment. The CAGE questionnaire is less sensitive with women (21), and some have suggested that a cutoff score of one rather than two be used for women (22).

Since the CAGE questions are retrospective, a positive response may indicate a past rather than a current problem. The physician needs to interpret the CAGE in light of information on the amount and frequency of alcohol consumption since the CAGE does not inquire about this.

Table 3: 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.

(b) Binge-drinking question (23)

This screening test consists of a single question: “How many times in the past year have you had five or more drinks on one occasion (for men), or four or more drinks on one occasion (for women)?” An

answer of one or more indicates unhealthy drinking. The test has a sensitivity of over 80% in a primary care population, but it has a low specificity (65%) for detecting an AUD (23). The test is recommended by the National Institute for Alcoholism and Alcohol Abuse in the US. Its advantages are that it is even briefer than the CAGE, and the question is concrete and not awkward.

(c) Alcohol use disorders identification test (AUDIT) (24)

The alcohol use disorders identification test (AUDIT) is a ten-item self-report questionnaire. It asks questions about past-year quantity and frequency of drinking, consequences of drinking (e.g., blackouts), and questions similar to the CAGE. It may be more accurate than the CAGE in identifying alcohol use disorders (25). Also, unlike the CAGE, it can help distinguish alcohol dependence from hazardous or at-risk drinking. A score of 7–12 indicates hazardous drinking, whereas score of 13 or more suggests alcohol dependence (25).

Table 4: AUDIT

<i>1. How often do you have a drink containing alcohol?</i>				
0 Never	1 Monthly or less	2 2-4 times per month	3 2-3 times per week	4 4+ times per week
<i>2. How many drinks containing alcohol do you have on a typical day when you are drinking?</i>				
0 1-2	1 3-4	2 5-6	3 7-9	4 10+
<i>3. How often do you have 6 or more drinks on one occasion?</i>				
0 Never	1 Less than monthly	2 Monthly	3 Weekly	4 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>				
0 Never	1 Less than monthly	2 Monthly	3 Weekly	4 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>				
0 Never	1 Less than monthly	2 Monthly	3 Weekly	4 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>				
0 Never	1 Less than monthly	2 Monthly	3 Weekly	4 Daily or almost daily
<i>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</i>				
0 Never	1 Less than monthly	2 Monthly	3 Weekly	4 Daily or almost daily

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<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>				
0 Never	1 Less than monthly	2 Monthly	3 Weekly	4 Daily or almost daily
<i>9. Have you or someone else been injured because of your drinking?</i>				
0 No		2 Yes, but not in the past year	4 Yes, 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>				
0 No		2 Yes, but not in the past year	4 Yes, within the past year	

* Scored out of 40 points. A score of 8+ suggests at-risk drinking or alcohol dependence.

* The higher the score, the greater the likelihood of alcohol dependence. A score of 20 or more indicates a strong chance of alcohol dependence.

Alcohol consumption history

A quantity frequency history of alcohol consumption is not as sensitive as screening tests in detecting alcohol use. However, combined screening and alcohol consumption history has higher detection rates than screening alone (26). Also, a consumption history is an essential for assessment and monitoring of alcohol problems.

Table 5: Alcohol history

- Ask **all** patients (women and the elderly are most likely to be missed).
- Ask **daily** or **weekly** amount.
 - A patient may have a negative response to a screening questionnaire and yet still be drinking problematically.
 - For patients who provide vague responses, ask about their previous week's drinking (this is the week that is most precisely remembered), and/or present the patient with a wide range of possible consumption (i.e., "Would you say your drinking is more on the order of 14 drinks or 30 drinks a week?").
- Ask about **maximum** consumption on any one day in the past month.
 - When patients are asked only about their average or typical weekly consumption, they often exclude sporadic heavy drinking days.
- Convert responses to standard drinks:
 - 12 oz. beer bottle, 5 oz. glass of wine, 1½ oz. liquor.
 - Doctors can be easily misled by patients who drink wine or spirits at home, because they often pour more than one standard drink into a glass. Patients should be asked how many bottles they consume weekly, and the size of the bottle (common bottle sizes - spirits: 13 oz. or 26 oz.; wine: 750 mL or 1 L).

Assessment of patients with a suspected drinking problem

The assessment may be conducted over several visits, and should comprise the following:

- Pattern of drinking.
- Withdrawal symptoms: Patients drinking 40 or more drinks per week are at risk for withdrawal. Ask about drinking in the morning and afternoon, tremor, or anxiety quickly relieved by a drink. Many patients attribute these symptoms to anxiety and do not realize that they are going through withdrawal.
- Consequences of alcohol/drug use: These also help distinguish at-risk drinking from alcohol dependence.
- Previous treatment attempts: This is important for treatment planning.
- Other drug use: Younger heavy drinkers often use other substances as well. Ask about tobacco, cannabis, benzodiazepines, opioids, over-the-counter drugs, and street drugs such as cocaine.
- Mood: In the U.S. Epidemiologic Catchment Area study, 37% of individuals with an alcohol disorder had a comorbid mental disorder (27). Therefore, the physician should inquire about symptoms of depression, anxiety, panic disorder, and psychosis. Alcohol use is strongly associated with adverse outcomes in depressed patients, including suicidality, poor social functioning, and increased health care utilization (28).

- **Social stability:** Factors such as current living arrangements, partners, and employment status have a bearing on treatment plans.
- **Safety:** Women with an alcohol use disorder are at high risk for recent intimate partner violence in relationships (29).
- **Current readiness to change:** Ask patients if they would like to change their drinking patterns within the next two months. Work on a treatment plan for patients in the “action phase” (i.e., patients who are ready to change).
- **Physical exam:** Measure the patient’s blood pressure and examine the liver. In older patients with a long drinking history, look for stigmata of chronic liver disease and conduct a neurological exam to rule out peripheral neuropathy, cerebellar disease, and dementia.

Laboratory detection of heavy drinking

The two most reliable serum markers are (a) gamma glutamyl transferase (GGT) and (b) mean cell volume (MCV). (c) Ethyl glucuronide, a metabolite of alcohol found in the urine, is also useful in certain clinical situations.

(a) GGT

Alcohol elevates GGT through enzyme induction; a high GGT does not necessary indicate alcoholic hepatitis. GGT is elevated by daily drinking of four or more standard drinks per day.

GGT testing can have several clinical roles:

- It can be used to corroborate a clinical suspicion of heavy drinking.
- It can be used to monitor treatment progress. In Ontario, drivers whose licenses have been suspended for alcohol use are required to submit monthly GGT to get their licenses reinstated.
- GGT reliably declines with abstinence (although it may remain somewhat elevated in patients with longstanding fatty liver or cirrhosis). The half-life of GGT is two to four weeks, so patients in early recovery will have marked declines in GGT with tests every one to two months. This can be very encouraging for patients and their families.

GGT testing has the following limitations:

- Cannot be used as a sole screening test because it has a sensitivity of only about 60%.
- Less sensitive in women than in men.
- Not as sensitive for detecting patients who have binges of only a few days' duration, or for detecting at-risk drinkers or patients with mild AUDs who drink less than four drinks daily.
- GGT is elevated by other medications (e.g., phenytoin), and other health conditions (e.g., any cause of fatty liver).

(b) MCV

Alcohol retards the maturation of red cells in the bone marrow, causing slight enlargement. It takes about three months for the red cells to regenerate. MCV is not as sensitive as GGT, but the combination of MCV and GGT is more sensitive than either test alone.

(c) Ethyl glucuronide

Ethyl glucuronide is detectable in the urine with even small amounts of alcohol for 24 hours or longer (30). Its sensitivity is about 0.67. Weekly or biweekly ethyl glucuronide tests are used in cases involving child protection, license suspension, and monitoring of professionals (e.g., physicians, pilots, etc).

Brief advice for at-risk drinkers

Randomized controlled trials have demonstrated that brief physician advice is effective in reducing alcohol consumption, morbidity and health care utilization in problem drinkers (31-35). The brief interventions are cost-effective, with a high ratio of health care savings to counselling costs (36).

Brief advice protocol for at-risk drinkers

- (a) Review low-risk drinking guidelines.
- (b) Link the patient's drinking with their health status, mood, sleep, and energy.
- (c) Review precautions and contraindications to alcohol consumption.
- (d) Have patient commit to a drinking goal: amount per occasion, frequency, and circumstances.
- (e) Review strategies to reduce consumption.
- (f) Ask patient to keep a daily drinking diary.
- (g) Order GGT and MCV.
- (h) Have regular follow-up.
- (i) Consider medication referral if problem persists.

(a) Review low-risk drinking guidelines.

Inform patients where their consumption fits within Canadian norms. Heavy drinkers are often related to and/or socialize with other heavy drinkers and are surprised to see that their alcohol consumption is quite high compared to the Canadian average.

(b) Link the patient's drinking with their current health status, mood, sleep, and energy level.

The physician should point out the association between the patient's alcohol consumption and his/her current health status. Even patients who do not have alcohol-related health problems sometimes feel better when they reduce their drinking, because the chronic sedative effects of alcohol can cause fatigue, low mood, and sleep disturbances.

(c) Review precautions and contraindications to alcohol consumption.

Contraindications and precautions include pregnancy, active peptic ulcer disease or gastritis, cirrhosis of the liver, alcoholic or viral hepatitis, or pancreatitis. Patients should be cautioned about potential adverse effects of alcohol use if they have medical conditions such as diabetes, bleeding disorders, or seizure disorders, or if they are taking medications such as antidepressants, ASA, NSAIDs, opioids, or sedatives.

(d) Have patient commit to a drinking goal.

The goal should be determined by the patient, with some guidance from the physician. Having the patient set the drinking goal leads to a greater sense of ownership and commitment. If the patient feels that this is not realistic, a goal above the low-risk guideline might be negotiated, aimed at minimizing intoxication and hazardous weekly consumption. The drinking goal should specify the maximum number of drinks

to be consumed on a single occasion, the frequency of drinking, and the circumstances in which drinking will take place. For example, a patient's goal might be to consume three drinks per day on Thursdays, Fridays, and Saturdays, and to avoid bars because the individual inevitably consumes large amounts of alcohol in that setting.

(e) Review strategies to reduce consumption.

Strategies to avoid intoxication will help the patient reduce overall alcohol consumption and prevent complications associated with acute intoxication, e.g., trauma:

- On a drinking day, drink no more than one standard drink per hour.
- Start drinking later in the evening.
- Sip drinks, don't gulp.
- Avoid drinking on an empty stomach.
- Dilute drinks with mixer.
- Alternate alcoholic with non-alcoholic drinks.
- Put a 20-minute “time-out” between the decision to drink and taking the drink.
- Avoid your favourite drink.

(f) Ask patient to keep a daily drinking diary.

Self-monitoring fosters behavioural change by making patients more conscious of their drinking patterns, providing positive feedback for reduced drinking, and allowing them to identify triggers for problem drinking.

(g) Order GGT and MCV.

GGT and MCV are useful in the identified problem drinker because an elevated test result often motivates the patient to change his or her drinking. Also, test results can be followed over time to monitor recovery and relapse.

(h) Have regular follow-up.

At each follow-up visit, ask about alcohol consumption, and note the patient's successes (e.g., comment on milestones such as three months of reduced drinking).

(i) Consider medication if problem persists.

If the patient continues to drink problematically, consider prescribing an anti-craving medication or referring the patient to an addiction physician for initiation.

Counselling a patient who is attempting to abstain from alcohol

Recognize that patients rarely stop drinking completely and permanently after treatment. Most patients struggle with slips and relapses for many months. Physicians should reflect back to patients on their progress and congratulate them if they are drinking less often, in smaller amounts, and have taken steps towards treatment and recovery.

Encourage patient to attend self-help groups (or aftercare groups for psychosocial programs).

Have regular follow-up. This demonstrates to patients that the physician considers their drinking as an important medical issue.

Suggest alternate activities for high-risk situations.

Physicians or counsellors should recommend alternative activities for situations that the patient identifies as high risk, such as bars, parties, or spending the evening alone.

Encourage social support. Patients who have a strong network of family and friends have a much better prognosis than socially isolated patients do. The patient should be encouraged to spend as much time as possible with family and friends who do not drink problematically.

Encourage daily exercise. Although evidence is sparse, exercise may be useful as an adjunct to formal psychosocial treatment (37).

Suggest simple strategies for coping with cravings:

- Have a 20-30 minute “time-out” between the decision to drink and actively seeking alcohol. For example, wait 20 minutes before driving to the liquor store or going to the bar. Cravings are temporary and often diminish after 20-30 minutes.
- Call or talk to someone. Patients can resist cravings if they acknowledge them to someone

else, and if they receive support and encouragement.

- Leave the situation. For example, if the craving occurs while the patient is home alone, he or she should leave the house to visit a friend, go to a shopping mall, etc.

Have a plan to interrupt a lapse. Patients need an emergency plan to follow if they slip, so that a full-blown relapse can be avoided; a common emergency plan is to call their AA sponsor for support.

Communicating with the alcohol-dependent patient

Presenting an AUD diagnosis

- Explain that patient is suffering from an illness, not from a moral weakness or lack of will power.
- Discuss your concerns about patient's health and social situation.
- Explain that the illness is treatable and you can help.
- Try to get patient to acknowledge that his/her troubles are caused by drinking, not the other way around (without arguing!).
- Identify where help is available (e.g., clinics, detox units, therapy groups, etc.).
- Explain about AA or other mutual-aid groups.
- Use principles of motivational interviewing.

Explaining a diagnosis of alcohol dependence is similar to explaining any other new chronic medical diagnosis, such as diabetes or a mood disorder.

Present the diagnosis in clear medical terms (*alcohol dependence*, or *alcohol use disorder*). Avoid the term *alcoholism*, unless the patient already self-identifies with that term.

Explain that alcohol dependence has genetic, social, and psychiatric causes. It is not the patient's "fault," any more than diabetes is. Many patients feel ashamed

and guilty that they are unable to stop drinking. Explain that alcohol dependence is characterized by a loss of control over drinking behaviour due to powerful, biological urges to drink. This does not indicate weakness or lack of concern.

Explain that a number of effective treatments exist for alcohol dependence, including AA, formal inpatient and outpatient treatment programs, and anti-alcohol medications. There is no one treatment program that works for everyone; patients have to figure out which combinations of treatments work best for them. Emphasize that the patient cannot stop drinking “on their own”; otherwise, they would have done so already. It is the patient’s responsibility to attend and follow through with treatment.

Review the link between the patient’s alcohol use and their current physical health, mood, and social relationships. Sometimes drinkers feel that their problems, such as marital discord, anxiety, or depression, must be solved first, because they are the root cause of their drinking. Explain that it is equally likely that their drinking is causing these problems, or that the problems and the drinking are making each other worse. Challenge the drinker to a trial of abstinence: if their drinking is causing their depression or marital conflict, the problem will become better within weeks.

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Review the patient's prognosis. Emphasize positive prognostic factors, such as a supportive family or a previous period of abstinence following treatment. Emphasize that treatment is often effective, and that there is a good chance the patient will experience major improvements in mood, functioning, well-being, sleep, and social relationships with treatment.

Alcohol withdrawal

Mechanism of withdrawal

Alcohol suppresses NMDA, the primary excitatory system in the CNS, and it enhances GABA, the primary inhibitory system. This accounts for the sedative effects of alcohol. Chronic use of alcohol causes up-regulation of the NMDA system and down-regulation of the GABA system, with an increase in the number and sensitivity of NMDA receptors and a decrease in GABA. This explains the phenomenon of *tolerance*, in which the heavy drinker can walk, talk, and function almost normally after ingesting alcohol in amounts that would cause coma or death on non-drinkers. On cessation of alcohol, the NMDA system requires several days to down-regulate. During this interval, the patient may experience withdrawal, which is essentially NMDA-induced autonomic hyperactivity.

The major risk factor for alcohol withdrawal is the amount consumed. Withdrawal is uncommon in patients drinking less than six standard drinks per day, but it becomes increasingly common and more severe with higher levels of consumption. The severity of withdrawal varies greatly between individuals, even if they drink equivalent amounts, but patients' individual withdrawal pattern is usually similar between drinking episodes. If they have experienced

withdrawal seizures in the past, they may do so again if their drinking pattern remains unchanged.

Clinical features of withdrawal

Uncomplicated withdrawal starts as early as 6-12 hours after the last drink and usually resolves in 2-3 days, although it can last up to 7 days. It consists of symptoms and signs of autonomic hyperactivity. Tremor (postural and intention, but not resting) and sweating are the most reliable physical signs. Other signs are tachycardia, reflexia, and ataxia. Symptoms include anxiety and nausea.

Complications: *Seizures* usually occur 12-48 hours after the last drink. They are typically grand mal, non-focal, one or two in number, and preceded by tremor. *Dysrhythmias* range in severity from occasional ectopic beats to atrial fibrillation and supraventricular or ventricular tachycardias. Hallucinations, usually tactile, can also occur.

Delirium tremens (DT) is a late complication of severe, untreated withdrawal. DT typically occurs in medical or surgical patients whose alcohol withdrawal has gone unnoticed for several days. Serious medical illness such as pancreatitis may predispose patients to DT. It also occurs in patients who are socially isolated, immobile, and unable to call for help.

DT is characterized by global confusion and fluctuating level of consciousness. The patient often

has vivid hallucinations, and is disoriented and delusional. Symptoms are frequently worse after sunset. Patients in DT may have no physical signs, but sometimes they display profound autonomic hyperactivity, with severe diaphoresis and vomiting (leading to dehydration), tachycardia, hypertension, and fever. Death from arrhythmias can occur, due to QT prolongation and electrolyte imbalances.

Identification of alcohol withdrawal in primary care

Alcohol-dependent patients will often drink daily in order to relieve withdrawal symptoms, but they may not recognize that symptoms such as anxiety are caused by withdrawal-related. In such patients, effective treatment of withdrawal is an essential first step to abstinence and long-term treatment.

All alcohol-dependent patients should be asked about past and current withdrawal symptoms, including morning or afternoon tremor, sweating, and anxiety, relieved with drinking. They should also be asked about complications such as seizures.

Planned office management of alcohol withdrawal

Patients who experience daily or frequent withdrawal symptoms can have an elective treatment of withdrawal in the physician's office if they have social supports at home, do not have a history of severe

withdrawal, and are considered to be motivated and reliable.

Planned office withdrawal treatment should only be undertaken if the patient:

- Is committed to abstinence following withdrawal treatment, and agrees to a treatment plan and close follow-up.
- Is not on methadone or other opioids, multiple daily doses of benzodiazepines, or high doses of antipsychotics.
- Does not have liver dysfunction.
- Does not have respiratory impairment.
- Is less than 65-70 years old.
- Has a history of seizures or other withdrawal-related complications
- Has had previous hospital admission or prolonged ED stay for withdrawal treatment.

Symptom-triggered benzodiazepine treatment

Diazepam is the first-line medication for treating withdrawal on an outpatient basis. It is quickly absorbed orally and has a long duration of action. Lorazepam is safer in patients with liver dysfunction, patients on opioids, and elderly patients. However, patients with these characteristics are probably more safely treated in the ED or in a medical detoxification unit.

Diazepam is administered when the patient's symptoms are severe, rather than according to a fixed schedule. The severity of symptoms is measured using the Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) scale, a ten-point scale administered by the nurse or physician (38). The Sweating, Hallucinations, Orientation, Tremor (SHOT) scale, a simpler scale validated in the emergency department, can also be used (see Appendix A) (39).

The scales should be administered every one to two hours. A score of ten or more on the CIWA-A or two or more on the SHOT indicates the need for benzodiazepine treatment. Diazepam is administered in a dose of 20 mg, but 10 mg may also be used for mild symptoms. This dose is high, but it is safe in withdrawal because heavy drinkers are cross-tolerant to benzodiazepines. Many patients respond to just one or two doses of diazepam, although some patients require several hundred milligrams. Additional doses are usually not needed once symptoms have resolved. Diazepam is effective for the full duration of alcohol withdrawal; its active metabolites have a duration of action of up to five days.

Table 6: Protocol for office management of withdrawal

- Advise patient to have their last drink the night before their scheduled morning appointment. If the patient shows up intoxicated, reschedule or admit to a local withdrawal management centre.
- Upon arrival, patient should be shown to a quiet clinic office.
- Nurse or physician should administer the CIWA-Ar scale or SHOT scale every 1–2 hours (see Appendix A).
- Give diazepam 10–20 mg for CIWA score of 10+, or SHOT score of 2+.
- Continue administering diazepam until patient has minimal tremor and CIWA-Ar is below 8, or SHOT is 1 or less, on two consecutive occasions.
- If uncertain about whether withdrawal has fully resolved, prescribe 3–5 tablets of 10 mg diazepam, 1 tablet q-4 H for tremor. Patient must agree to discontinue diazepam if he/she resumes drinking. Diazepam should be dispensed by spouse/partner if possible.
- Prior to discharge, initiate a treatment plan:
 - Prescribe anti-craving medications.
 - Advise patient to attend AA and arrange formal psychosocial treatment.
 - Arrange follow-up in a few days (1–2 days if lorazepam used).
- Patient should be driven home or accompanied by a friend or relative.

Referral to ED: Patients should be referred to the ED if their withdrawal is still moderate or severe despite 80 to 100 mg of diazepam, or if they experience complications (e.g., confusion, tactile hallucinations, tachycardia or severe hypertension, recurrent vomiting).

Referral to withdrawal management: Withdrawal management services are usually not staffed by nurses or physicians, but their workers are experienced in monitoring patients who are intoxicated or in withdrawal, and the services will refer patients to a nearby ED if they display any concerning symptoms. Furthermore, they know a great deal about community resources and will facilitate patients' entry into treatment. A brief stay in a withdrawal management centre can be helpful for patients who:

- Are in crisis and need rapid access to psychosocial treatment, e.g., spouse is about to leave them.
- Are homeless or transiently housed.
- Have few or no social supports.
- Have in the past immediately relapsed following ED or outpatient withdrawal treatment.

Home treatment of withdrawal

The common practice of prescribing take-home doses of benzodiazepines (e.g., "lorazepam 1 mg tid for tremor") is not recommended. Many patients continue to drink while taking benzodiazepines,

increasing their risk of toxicity and addiction. Also, withdrawal treatment should be viewed as the first step towards abstinence and recovery, rather than mere symptom relief.

On occasion, however, it is unavoidable, for example, if the patient is in withdrawal at the time of the visit and is unwilling to remain in your office, or to attend an ED or withdrawal management. Home treatment should be reserved for patients who are in mild withdrawal and are unlikely to require hospitalization or emergency treatment; for moderate to severe withdrawal, the physician should insist that the patient attend the ED. The patient should agree to not drink alcohol while taking the benzodiazepine.

The physician should prescribe diazepam 10 mg q-4 H PRN, no more than 6–10 tabs. The patient should be advised to go to emergency if symptoms are getting worse. If possible, a family member should dispense the diazepam. Follow-up should be arranged within the next two to three days.

Pharmacotherapy for alcohol dependence

Anti-craving medications such as naltrexone, acamprosate, and disulfiram have been shown to have modest but significant effects on drinking outcomes (40). Naltrexone, the most commonly used anti-craving medication, is equally effective whether prescribed in a primary care or specialty setting (41). Naltrexone, acamprosate, and disulfiram are associated with reductions in inpatient days, emergency department visits and overall health care costs (42, 43). The number need to treat (NNT) is around 12.

Physicians prescribe anti-alcohol medications for only a small minority of alcohol-dependent patients (44). The evidence suggests that physicians should offer routinely to all alcohol-dependent patients, just as they do for patients attempting to quit smoking. In one trial, primary care physician management of alcohol dependence with naltrexone had better drinking outcomes than specialized outpatient addiction treatment by non-medical therapists (45).

Choice of anti-alcohol medication

There have been few studies directly comparing the effectiveness of different anti-alcohol medications. Naltrexone and acamprosate have the strongest evidence of benefit. Naltrexone is useful for patients

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with mild to severe alcohol use disorder. Acamprosate is most useful for recently abstinent patients with moderate to severe alcohol use disorder who are experiencing subacute withdrawal symptoms (anxiety, insomnia, craving). Note that for patients on Ontario Drug Benefits, the physician must apply to the Exceptional Access Program (EAP) to obtain coverage for naltrexone and acamprosate. Disulfiram should be considered as a first choice in patients whose partners are willing to dispense it daily. Baclofen is the safest option for patients with cirrhosis of the liver. Topiramate and gabapentin should be considered in patients who have anxiety or emotional lability, or who are also using cocaine. Baclofen, topiramate, and gabapentin are covered as a general benefit for patients on social assistance, so they can be prescribed while waiting for EAP approval of naltrexone or acamprosate. Several combinations (gabapentin and naltrexone, disulfiram and naltrexone) have been shown to be effective.

Table 7: Comparison of anti-alcohol medications

Medication	Advantages	Disadvantages	Clinical role
Naltrexone	Strong evidence of effectiveness. Well tolerated.	EAP application required for patients on social assistance.	For mild to severe AUD. Probably most effective in patients with strong family history of AUD.

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Medication	Advantages	Disadvantages	Clinical role
Acamprosate	Strong evidence of effectiveness. Well tolerated.	EAP application required for patients on social assistance.	Most effective in patients with severe AUD who have been abstinent for at least a few days but are experiencing subacute withdrawal symptoms: anxiety, insomnia, craving.
Disulfiram	More effective than naltrexone or acamprosate when dispensed daily by third party, e.g., spouse or pharmacist.	Not covered (but available at low cost from certain pharmacies). Has more cautions and contraindications than other anti-alcohol meds.	Patients who are committed to abstinence and have someone who could dispense the medication daily.
Baclofen	Well tolerated. Safe in patients with liver cirrhosis. General benefit.	Only a few small controlled trials have been conducted.	Use while waiting for approval from EAP. In patients with liver cirrhosis.

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Medication	Advantages	Disadvantages	Clinical role
Topiramate	Large controlled trial showed benefit. May have mood stabilizing effects in patients with anxiety.	Sedation is a common side effect.	While waiting for approval from EAP. In patients with anxiety or labile mood. May reduce cravings in cocaine users.
Gabapentin	May have mood-stabilizing effects in anxious patients.	Sedation is a common side effect.	While waiting for approval from EAP. In patients with anxiety or labile mood.
Combinations: Gabapentin + naltrexone, disulfiram + naltrexone	May be more effective than either medication alone, although research is preliminary.	No known increased risks over either medication alone.	In patients who have not responded to naltrexone, consider adding gabapentin or topiramate (for patients with anxiety, insomnia or depression) or disulfiram (if dispensed by third party).

Clinical information for anti-alcohol medications (see Appendix B)

(a) Disulfiram

Mechanism of action: Disulfiram inactivates acetaldehyde dehydrogenase. This causes a buildup of acetaldehyde when alcohol is consumed, resulting in flushed face, headache, chest pain, and vomiting.

Effectiveness: Several open-label controlled trials have shown that when administered daily under supervision, disulfiram is more effective than anti-craving medications, including naltrexone, acamprosate, and topiramate (46-48). Therefore, disulfiram should be considered in alcohol-dependent patients who endorse abstinence as a treatment goal and who agree to take the medication under supervision from a spouse or pharmacist. Patients should be maintained on the drug for at least four to six months, the length of time most patients need to establish a stable alcohol-free lifestyle.

Precautions, contraindications, and side effects: Most reactions are self-limited, but severe hypotension and vagally-induced arrhythmias can result in myocardial infarction, congestive heart failure, and other life-threatening complications. Convulsions and respiratory distress can also occur. The reaction is dose-dependent, but fatalities have occurred with a single drink. Patients with underlying coronary artery

disease, cerebrovascular disease, severe pulmonary disease, seizure disorders, or those on anti-hypertensive medication are at greater risk of a severe reaction. Disulfiram can cause a toxic hepatitis, and is contraindicated in patients with severe cirrhosis or alcoholic hepatitis. It has also been linked with birth defects. Side effects include fatigue, impotence, peripheral neuropathy, and depression.

Dosing: The usual dose is 125 mg at night. Disulfiram has a long duration of action, for seven days (range two to ten). Patients should be warned to wait one or two days after drinking before resuming disulfiram, and to avoid alcohol-containing medicines or food.

(b) Naltrexone

Mechanism of action: Alcohol consumption causes a release of endorphins, which partly explains the euphoria that people experience when they drink. Individuals genetically predisposed to alcohol dependence experience a greater endorphin release than other people, making alcohol more pleasurable and reinforcing for them. Naltrexone, a competitive opioid antagonist, blocks the binding of endorphins at the receptor site. Thus, some patients who drink while taking naltrexone will experience less pleasure than they did previously. This decreases the reinforcing effects of alcohol and the cravings or urges to drink.

Effectiveness: Controlled trials and systematic reviews have demonstrated that naltrexone reduces the duration, intensity, and frequency of binges in alcohol-dependent patients (40, 49). Patients do not have to be abstinent when starting naltrexone, and it is effective even with limited psychosocial treatment (50).

Precautions: In general, naltrexone is safe and well tolerated (51). The safety of naltrexone in patients with severe hepatitis or cirrhosis has not been established. As a competitive opioid antagonist, naltrexone will trigger a potentially severe opioid withdrawal syndrome in patients who use opioids regularly.

Dosing: The standard dose is 50 mg per day.

Length of treatment: If, after six months, the patient is abstinent, is no longer craving alcohol, and feels confident that he or she no longer needs naltrexone, it may be discontinued. If the patient is experiencing cravings or occasional “slips,” naltrexone may be maintained for a longer period of time.

(c) Acamprosate

Mechanism of action: Chronic alcohol consumption suppresses the excitatory NMDA system (which uses glutamate as a neurotransmitter) and activates the inhibitory GABA system. The CNS compensates by increasing the number and sensitivity of NMDA

receptors, while inhibiting the GABA system. With abrupt cessation of alcohol, the NMDA system is still in overdrive and it takes weeks or months for it to normalize. This results in subacute withdrawal symptoms, including anxiety, insomnia and irritability. Acamprosate acts to restore the balance between glutamate and GABA, thus relieving subacute withdrawal symptoms and making it easier for patients to abstain (52).

Effectiveness: Controlled trials have shown that acamprosate is effective in the treatment of alcohol dependence (53). Naltrexone may be more effective than acamprosate, although the relative effectiveness of the two drugs depends in part on the desired outcome (49). Acamprosate may be somewhat more effective than naltrexone at maintaining abstinence, whereas naltrexone may be more effective at reducing cravings and the intensity and duration of binges. Thus, acamprosate may be a better choice for patients who are committed to abstinence but who suffer from subacute withdrawal symptoms such as anxiety and insomnia. Naltrexone may be appropriate for patients who suffer from strong cravings and have recurrent binges. Of course, these two patient groups can be very difficult to distinguish, so in many cases the physician should try naltrexone or acamprosate first, and switch to the other medication if the first one fails.

Side effects and precautions: The medication is well tolerated. The most common side effect is diarrhea. The dose should be reduced in renal insufficiency.

Dosing: Acamprosate is more effective when started after detoxification from alcohol, rather than while the patient is still drinking (54). Its standard dose is 666 mg three times per day.

(d) Topiramate

Mechanism of action: Topiramate appears to reduce cravings by normalizing the dopamine reward system that has been dysregulated by alcohol.

Effectiveness: A recent systematic review of seven placebo-controlled trials involving 1100 subjects concluded that topiramate improved drinking outcomes, and may even be somewhat more effective than naltrexone and acamprosate (55). The trials used doses ranging from 75 mg to 300 mg per day. An older systematic review had similar results (56). In one trial, 200 mg of topiramate was more effective than 50 mg of naltrexone at reducing drinking and cravings (57). However, a recent placebo-controlled trial found no benefit (58). Therefore, topiramate should be considered in patients in patients who have failed naltrexone or acamprosate, or who are waiting for EAP coverage. It should also considered, alone or in combination with naltrexone, in alcohol-dependent patients who have an anxiety or mood

disorder (59), and in patients who have a concurrent cocaine use disorder (60).

Side effects: Topiramate can cause blurry vision, insomnia, paresthesias, dizziness, fatigue, anxiety, and weight loss.

Dosing: The usual dose range is 100 to 300 mg, titrated to reduce alcohol use without causing unacceptable side effects.

(e) Baclofen

Baclofen has been shown in several small trials and a systematic review to increase abstinence rates in alcohol-dependent patients. Its minimally effective dose is probably 20 mg tid; considerably higher doses have been used. It is well tolerated and safe, even in patients with severe liver disease (61, 62).

(f) Gabapentin

Several controlled trials have demonstrated effectiveness of gabapentin in treating alcohol dependence. In the most recent trial, 150 alcohol-dependent patients were randomized to receive placebo, gabapentin 900 mg per day, or gabapentin 1800 mg per day. After 12 weeks, the 1800 mg per day group had an abstinence rate of 17%, compared to 11% for the 900 mg group and 4% for the placebo group. Insomnia, dysphoria, and cravings also declined in the gabapentin groups relative to placebo

(63). In another 16-week controlled trial with 150 subjects, the group receiving naltrexone 50 mg plus gabapentin 1200 mg had improved drinking outcomes relative to placebo, or naltrexone alone (64). The indications for gabapentin are similar to those of topiramate: alcohol-dependent patients with anxiety, depression, or insomnia, who have failed at naltrexone treatment or who are awaiting approval for naltrexone.

(g) Combinations

Several combinations have been shown to be more effective than single agents or placebo. One controlled trial showed that gabapentin and naltrexone was more effective than naltrexone alone in improving alcohol outcomes (64). In another trial, disulfiram and naltrexone was more effective than placebo in improving outcomes in patients with concurrent alcohol and cocaine addiction (65). In a third trial, naltrexone and disulfiram, alone or in combination, were effective in improving alcohol outcomes in patients with AUD and post-traumatic stress disorder (66).

Psychosocial treatment programs

Inpatient and outpatient treatment programs

Inpatient treatment programs are indicated if the patient has a dangerous or highly unstable home environment (e.g., an abusive or addicted spouse at home), severe medical or psychiatric problems, addiction to a drug that may require inpatient detoxification (e.g., large doses of benzodiazepines), or if outpatient management has failed. Programs generally last 21 to 28 days. Components include didactic seminars, group psychotherapy, orientation to Alcoholics Anonymous (AA), and, sometimes, family services, including involvement in Al-Anon. Similar treatment is offered in intensive outpatient programs (day treatment), often lasting 3 to 6 weeks. Both inpatient and day programs have aftercare groups that meet every one or two weeks for up to two years. In general, outpatient treatment programs are almost as effective as and less costly than inpatient programs.

Alcoholics Anonymous (AA)

Patients should be encouraged to participate in mutual aid groups such as Alcoholics Anonymous or Women for Sobriety. The AA program consists of studying and following the Twelve Steps, e.g., Step 1: “We admitted we were powerless over alcohol and

that our lives had become unmanageable.” For many patients, AA provides a source of hope, practical assistance and advice, and a means to overcome social isolation and shame.

Meetings may be open or closed, with the latter being for members only. Closed meetings enable members to discuss difficult personal issues in confidence, whereas open meetings are for the general public as well. In speaker meetings, AA members recount their experiences with alcohol and their recovery. In discussion meetings, an AA member describes some of his or her experiences and then leads a discussion on a topic related to recovery. Step meetings are usually closed meetings and consist of a discussion of one of the Twelve Steps.

Each person who joins AA is encouraged to obtain a sponsor (a more senior AA member willing to offer individual guidance in following the AA program). The sponsor often plays a crucial role in the patient’s recovery.

AA provides practical advice and support for its members. AA helps overcome social isolation for members whose main social contacts have been with other drinkers. Members may need to attend more than one group in order to find a group of individuals with whom they feel most comfortable.

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Some patients feel that AA is only for individuals who are religious. The spirituality of the AA program is distinct from religious dogma, and has been described as a series of themes: release (freedom from the compulsion to drink), gratitude (including an awareness of what he/she has), humility and tolerance.

Physicians can facilitate attendance at AA by educating patients about the organization, by asking a patient from his/her practice who is an AA member to speak to alcohol-dependent patients who want to know more about the program and by providing lists of local meetings.

Physicians can best gain an understanding of AA by attending an open meeting, by discussing AA with experienced members, and by reading more about it.

Alcohol dependence and other medical and psychiatric conditions

Outpatient management of alcohol-induced cirrhosis

Many patients can function well even if large segments of their liver have been replaced by scar tissue. However, even moderate amounts of alcohol can accelerate liver damage. Therefore, the most important management strategy is abstinence.

Patients with decompensated hepatic cirrhosis (that is, patients who have had ascites, a variceal blood or other complication of cirrhosis) have a five-year survival rate of 60% if they abstain from drinking, but only 34% if they continue to drink. Their risk of variceal bleed is ten times higher if they drink heavily than if they abstain (67). Alcohol-dependent patients who continue to drink should be offered anti-craving medications; baclofen is the safest anti-craving medication for cirrhotic patients (68).

Other than abstinence, other important strategies to prevent complications are:

- Avoidance of benzodiazepines, as they can trigger hepatic encephalopathy.
- Avoidance of NSAIDs, and use of acetaminophen only in low doses.

- Prevention of hepatitis C through measures to reduce injection drug use.
- Immunization against hepatitis B.
- Measurement of portal blood pressure. Nadolol has been shown to reduce the risk of bleeding esophageal varices in patients with elevated portal pressures.
- Low-salt diet and diuretics in patients with ascites.
- Lactulose in patients at risk for hepatic encephalopathy, or who show early signs of encephalopathy: poor concentration, day-night reversal, inattention, slow responses.
- Urgent intervention for triggers to encephalopathy: electrolyte imbalance, blood loss, high protein meal, benzodiazepine use, or infection.

A liver transplant is by far the most effective treatment for cirrhosis. To get on a transplant list, the patient must be abstinent for between six months and two years, and must have participated in a treatment program.

Alcohol and hepatitis C

Patients with hepatitis C should be advised to drink moderately. A level of alcohol consumption that does not accelerate liver damage has not been established; one study found that patients who drank more than 70 grams of alcohol (five drinks) per day had a poor

response to anti-viral treatment, while patients who drank less than 30 grams (two drinks) per day had a sustained response (69). Therefore, patients should be advised to drink less than two drinks per day.

Alcohol and mood disorders

The relationship between mood disorders and alcohol dependence is complex. Heavy consumption of alcohol, like other sedating medications, can cause an organic mood disorder, while depressed patients are more likely to drink to self-medicate their symptoms. Mood disorders are more common in alcohol dependent patients than in the general population (28). Patients with a primary mood disorder are more likely to relapse post-treatment than patients without a mood disorder (70). As well, alcohol dependence is a major risk factor for suicidality (71).

It is difficult to distinguish alcohol-induced depression/ anxiety disorder from a primary disorder because the clinical features are similar. A primary disorder should be considered if the patient reports depressive symptoms even during prolonged periods of abstinence. In most cases, however, a trial of abstinence is indicated to determine if the patient has a primary or alcohol-induced mood disorder. Alcohol-induced disorders tend to resolve within weeks of abstinence or reduced drinking, whereas primary disorders remain the same or improve only marginally.

Antidepressant therapy should be initiated if the patient is unable to maintain abstinence or reduced drinking, if the depression persists despite abstinence, or if a primary mood disorder is strongly suspected (e.g., family history, history of depression even with abstinence). A meta-analysis found that antidepressant treatment had a modest effect on drinking outcomes in patients with both alcohol dependence and depression (28, 72).

Antidepressants should in most cases be combined with anti-craving medication. One trial found that sertraline and naltrexone improved both mood and drinking outcomes in depressed alcohol-dependent patients (73).

Insomnia

Alcohol dependence is associated with insomnia and non-restorative sleep. Night-time alcohol use causes rebound REM sleep and interferes with sleep architecture. Insomnia is a prominent feature of acute and subacute alcohol withdrawal. Patients should be reassured that insomnia will resolve after several weeks of abstinence. Subacute withdrawal may be treated with acamprosate. If hypnotic agents are needed, trazodone, gabapentin, and topiramate have the greatest evidence of benefit (74).

Benzodiazepines should be avoided if possible.

Reporting to the Ministry of Transportation

Canadian physicians are required to report to the Ministry of Transportation if they suspect a patient may be drinking and driving. Suggested criteria for reporting are listed below. Some provinces allow physicians to use their discretion in reporting; for example, they may defer reporting if the patient attends a treatment program and maintains abstinence. Other provinces oblige physicians to report in all cases.

Suggested criteria for reporting

Any of the following are reasonable grounds for reporting a patient to the Ministry:

- 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 a withdrawal seizure.
- Patient has other alcohol-related complications that impair driving ability (e.g., cerebellar ataxia).

Management of the patient with a suspended license

If the patient is angry, explain that Ontario physicians have a legal obligation to report; it is not discretionary. 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 patient visits are recommended. At each visit, the physician should enquire about alcohol consumption, and attendance at AA and treatment programs. GGT and MCV should be ordered regularly to confirm abstinence or reduced drinking. With the patient's permission, the physician should ask the patient's partner or a close family member to corroborate the patient's self-reported alcohol consumption.

Part II: Opioid use disorders

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 prescription opioid addiction (75, 76). 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 (77). However, these guidelines have had little appreciable effect: many Ontario family physicians continue to overprescribe opioids, while some are extremely uncomfortable prescribing opioids at all. This handbook 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.

Opioid prescribing

Acute vs. chronic pain

The severity of acute pain is largely determined by the severity and extent of tissue damage or inflammation. Acetaminophen, NSAIDs, opioids, local anesthetics, and other treatments are usually very effective for acute pain. In chronic non-cancer pain (CNCP), psychological and cognitive factors can influence pain perception through their effect on ascending and descending pain pathways. For this reason, opioids and other analgesics are only modestly effective for CNCP, and they rarely relieve the pain completely.

A variety of non-pharmacological approaches have been shown to be effective for CNCP, including cognitive behavioural therapy, mindfulness meditation, and physical modalities such as graded exercise programs. A number of non-opioid medications have also been shown to be effective and safe, including acetaminophen, NSAIDs, and (for neuropathic pain) anticonvulsants and antidepressants.

Short-term (i.e., up to three months in duration) placebo-controlled trials have found an average reduction in subjective pain ratings of 30% (around two points on a ten-point scale), with a wide variation in response (78). The impact on daily functioning is equivocal; it is possible that opioids improve function

in some patients by decreasing pain perception, but decrease functioning in others by causing sedation, fatigue and, constipation. The long-term effectiveness of opioids is uncertain.

Most patients on long-term opioids therapy do not experience any major side effects or harms.

However, evidence suggests that opioids can have several serious dose-related complications, including sexual dysfunction (79), overdose, hyperalgesia (80), falls (81), and sleep apnea (82, 83). For example, recent evidence has identified a strong relationship between prescribed dose and risk of overdose (84). In an observational study of elderly patients with osteoarthritis, the hazard ratio for fracture risk of opioids compared to NSAIDs or coxibs was 4.47 (85).

Several cohort studies have found an association between opioid use and lower mood and functioning, even after controlling for the type and severity of the underlying pain condition (86, 87). The causal link between disability and opioid use is not certain. It could be that patients at higher risk for disability are more likely to receive opioids; it is also possible that opioid-induced sedation, dysphoria, and hyperalgesia result in poor long-term outcomes.

Opioid prescribing should be viewed as a **therapeutic trial**; it can be continued if patients experience a meaningful benefit, defined as improved

function and a reduction in pain severity of two or more points on a ten-point scale without significant side effects. On the other hand, opioids should be tapered and discontinued if the patient has failed an adequate trial of two or more opioids. Continued opioid prescribing in this circumstance puts patients at risk for long-term side effects and complications.

Indications for opioid therapy

Opioids should be reserved for patients with a well-defined pain condition (nociceptive or neuropathic) that (a) has been shown to respond to opioids, and (b) causes both **pain and disability**, and for whom non-opioid treatments are ineffective, contraindicated, or have intolerable side effects. Not all pain conditions have evidence supporting the use of opioids; for example, there is very little evidence to support the use of potent opioids for common pain conditions such as fibromyalgia, muscle contraction headaches, or low back pain without a neuropathic component.

Before initiating opioid therapy, the physician should:

- Give a specific diagnosis for the cause of the pain, as neuropathic and somatic pain conditions require different treatment approaches.
- Ask the patient to rate the severity of the pain on a ten-point scale. The Brief Pain Inventory can be useful for this.

- Ask the patient about the impact of the pain on their daily lives. Have they given up activities because of pain?
- Ask the patient about aggravating and relieving factors. Is the pain constant throughout the day, or does it only occur with certain activities?
- Ask about previous non-opioid treatments and response to those treatments.
 - Nociceptive pain: acetaminophen, NSAIDs, SNRIs
 - Neuropathic pain: anticonvulsants, SNRIs, TCAs
 - All types of pain: Mindfulness programs, graded exercise
- Inquire about the quantity and frequency of current use of alcohol, opioids, benzodiazepines, cannabis, and other street drugs, and past and family history of addiction.
- Ask about anxiety and mood. Depressed patients tend to have a heightened perception of pain and are less responsive to opioid therapy.

Elderly patients with definite nociceptive or neuropathic pain conditions have a low risk of opioid addiction, and they often respond well to low opioid doses. However, they are at higher risk for opioid-induced sedation, confusion, falls, and fractures than younger patients. In a recent observational study, all opioids except tramadol (a weak opioid) were associated with a substantially elevated risk of falls in

the elderly (85). Therefore, weak opioids should always be tried first. The initial dose should be one-half that of younger adults, and subsequent doses should be titrated with smaller increments and at longer intervals. The patient and the family should be educated on early signs of opioid toxicity and should be warned not to drink alcohol. Patients taking benzodiazepines should have their dose tapered and discontinued if possible.

Some women rapidly convert codeine to morphine, which readily enters the breast milk and can cause neonatal toxicity. Therefore, pregnant or breastfeeding women who require analgesia should use non-opioid medication or opioids other than codeine. If codeine is used, it should be prescribed in moderate amounts and used for no more than four days. The patient should be advised to contact a physician immediately if she or her baby shows signs of toxicity. A large case-control study found an increased incidence of congenital heart defects in the neonates of pregnant women who had used opioids for CNCP in the first trimester (88). Further research is needed to confirm this association. In the meantime, pregnant patients or patients planning to become pregnant should have their opioids tapered and discontinued. The taper should be done slowly to avoid maternal withdrawal. The patient may be maintained on the lowest effective dose if she

experiences severe pain or pain-related disability during the taper.

Opioid prescribing protocol

In almost all cases, the “weak” opioids, i.e., codeine, transdermal buprenorphine, and tramadol, should be tried first for chronic pain. These agents are often effective for chronic pain, and evidence suggests they have a much lower risk of overdose, addiction, sedation, and falls than the potent opioids.

The choice of second-line opioid is based on individual clinical considerations, summarized in Table 8 below. Morphine is contraindicated in renal insufficiency, and some evidence suggests that hydromorphone and oxycodone have fewer cognitive effects than morphine in the elderly. Oxycodone and hydromorphone should be used with caution in patients at higher risk for opioid addiction, because evidence suggests they have a higher abuse liability than equianalgesic doses of morphine. The transdermal fentanyl patch is a third-line opioid, because even the 25 µg/hour patch is as potent as 60-100 mg of morphine/day. Transdermal fentanyl should only be used if the patient has taken at least 60-100 mg morphine equivalent daily for at least two weeks

Table 8: Safety issues to consider when selecting opioids

Agent	Safety issues
Codeine	Prescribe for no more than 4 days with breast-feeding women: some women rapidly convert codeine to morphine, causing neonatal toxicity. Overall lower risk of overdose and addiction than stronger opioids.
Tramadol	Associated with seizures in patients at high seizure risk, or when combined with medications that increase serotonin levels, e.g., SSRI antidepressants. Lower risk of overdose and addiction than stronger opioids.
Morphine	Greater risk of overdose than codeine and tramadol. A metabolite can accumulate to toxic levels in patients with renal impairment.
Oxycodone, hydromorphone	Greater risk of overdose than codeine and tramadol. Use with caution in patients at higher risk for opioid misuse and addiction.
Fentanyl	Before starting fentanyl, ask about opioid use within the last two weeks. Patient should be on a daily dose of a strong opioid, at least 60–100 mg MED, for at least two weeks. Do not switch from codeine to fentanyl regardless of the codeine dose. Maintain the initial dose for at least six days: use extra caution with patients at higher risk for overdose, e.g., elderly, patients taking benzodiazepines.

Agent	Safety issues
Meperidine (Demerol)	Not recommended for use in CNCP: oral meperidine has poor bioavailability and is less effective than codeine. Normeperidine, a toxic metabolite, can accumulate with frequent use of meperidine and in patients with renal insufficiency, leading to seizures.
Acetaminophen-opioid combinations	Use with caution to avoid acetaminophen toxicity. Generally, combination tablets contain acetaminophen 325 mg per tablet. The goal is for adults to take no more than 3.2 grams acetaminophen/day, which is therefore equivalent to 10 tablets/day for opioid/acetaminophen. The limit is 8 tablets/day for the combination of tramadol/acetaminophen. Do not prescribe acetaminophen or opioids to patients who are currently drinking heavily.
Controlled-release formulations	Contains higher opioid doses than intermittent release (IR); titrate with caution.
Parenteral opioids	Parenteral opioids not recommended (risk of overdose, addiction, infection).
Transdermal buprenorphine	Safe even in the elderly. Will cause precipitated withdrawal if given to a patient who is taking other opioids.

The dose should be increased in small increments, with at least one or two weeks between dose increases. For pain that lasts throughout the day, the dose is initially titrated with **immediate-release (IR)**

opioids, switching to scheduled, **controlled-release (CR)** opioids as the optimal dose is approached. In long-term therapy for constant pain throughout the day, IR preparations should not exceed 10-30% of total daily opioid dose. For pain that only occurs with activity, IR opioids may be used just prior to the activity.

Table 9: Opioid initiation and 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	-----

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

**CR: Start 50 mg bid in opioid-naïve, ≥50 mg bid if switching from other opioids. Maximum 250 mg bid. Exert caution when switching from pure mu-opioids.

At each office visit during titration, the physician should ask the patient to rate their pain before and after dosing, using a ten-point scale. Opioids show a graded analgesic response; each dose increase should provide greater and longer-lasting pain relief. The physician should also ask about side effects, changes in daily activity and mood, and adherence to the prescribed medication regimen. Patients who experience pain relief should become more active and show improvements in mood. The optimal opioid dose is one which causes clinically significant pain relief (at least 30%, or two points on the ten-point scale), and/or improved function, with no additional benefit from further dose increases (89, 90).

The Canadian guideline recommends a “watchful dose” of 200 mg morphine equivalent per day (MED) (77), although recent reviews suggest that a dose of 120 mg MED may be more prudent. This means that as this dose is approached, the prescribing physician should reassess the diagnosis and overall management plan, and reassess the effectiveness and side effects of opioid therapy. Controlled trials used mean doses less than half the 200 mg MED dose. Also, the analgesic effects of opioids likely plateau at higher doses because of hyperalgesia and analgesic tolerance. Finally, the serious complications of opioids, i.e., overdose, addiction, falls, and sleep apnea, are dose-related.

Table 10: 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

Minimizing adverse effects

Elderly patients may be at **increased risk of falling**. Do not prescribe opioids to cognitively impaired patients unless dispensed and overseen by a caregiver. Benzodiazepines should be tapered if possible. Opioid use should be avoided at night; if pain wakes the patient up, prescribe the smallest IR opioid dose and warn patients to take extra precautions when getting out of bed.

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 closely monitor a patient who experiences sedation during opioid initiation or dose

increase and contact the doctor or call emergency services at the first sign of an overdose.

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.

In order to prevent **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 switching

Patients who have significant side effects (e.g., constipation, sedation, falls) or inadequate analgesia with one opioid will sometimes have a better response to a different opioid. Thus, if a patient has not responded to an opioid at a dose of around 75 mg MED, it will usually be safer and more effective to switch to a different opioid rather than continue to increase the original opioid. Because the patient will not be fully tolerant to the new opioid, the initial dose of the new opioid should be **25-50% lower** than the equivalent dose of the original opioid, and should be titrated as described in Table 9.

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For 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 the patient on 6 mg/d in divided doses, ensuring the patient understands that taking extra doses is dangerous.

Opioid tapering

Indications for opioid tapering

Opioids should be tapered if the patient did not gain sufficient benefit despite an adequate trial of several opioid analgesics. There is evidence that patients who still have severe pain despite high opioid doses experience improved pain, mood, and functioning with opioid tapering (91-94). Opioids should also be tapered if the patient has significant adverse effects or medical complications that outweigh its analgesic benefits, such as constipation, fatigue, or sedation. Patients who are misusing or addicted to opioids should be tapered (structured opioid therapy) or placed on opioid substitution treatment.

Opioid tapering protocol

Opioids should be tapered slowly, over weeks or months, to minimize withdrawal symptoms. The doses should be scheduled rather than PRN, using CR opioids if possible. The tapering should be accompanied by close monitoring and supportive counselling. The endpoint of the taper is not necessarily abstinence; a partial taper is successful if the patient feels better and functions better at a lower dose, but tapering further causes increased pain.

When initiating a taper, explain to the patient that the high opioid dose is not helping their pain and is harming them in other ways, and that the taper will

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probably improve their mood, functioning and pain levels. The tapering schedule should be negotiated between patient and physician. The taper should be put on hold for a few weeks or months if the patient is going through a difficult time. The taper is completed when the patient is off opioids, or when the patient is on a lower dose and feeling and functioning better but reducing the dose even further causes increased pain.

Table 11: Protocol for opioid tapering

Formulation	CR preferred (until low dose reached).
Dosing interval	Scheduled doses rather than PRN Keep dosing interval the same for as long as possible (BID or TID). Advise patients not to skip doses.
Rate of taper	Taper slowly, no more than 10% of total daily dose every 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.
Dispensing interval	If patient runs out early, increase frequency to weekly, alternate day, or daily.
Endpoint of taper	≥ 60 mg MED (suggested watchful dose in elderly; controls pain with minimal side effects).
Frequency of visits	If possible, see patient prior to each dose decrease.
Approach at each visit	Ask not just about withdrawal symptoms but benefits of tapering: more alert, less fatigued, improved mood, improved pain, etc.

Managing opioid diversion

Diversion refers to the distribution of opioids or other abused medications to someone other than the patient for whom it was prescribed. Diversion is a lucrative activity; oxycodone sells for up to \$1/mg, so a prescription for a moderate amount, such as 20 percocet tablets, is worth \$100. The diverted opioids are a major source of drugs for addicted patients and patients who have had an overdose.

Physicians can reduce diversion in three ways: (1) reduce the supply of street opioids through careful patient selection and dose titration; (2) reduce the market for street opioids through identification and treatment of opioid dependence; and (3) make diversion more difficult through safe prescribing policies, such as creating treatment agreements with patients, adopting safe prescription writing practices, and ordering urine drug screens for patients.

Treatment agreement

A treatment agreement is a contract between the patient and the prescriber defining the terms of the patient's prescription. Agreements contain the following components:

- Maximum opioids to be dispensed per week.
- Prescriber will not dispense opioids early.
- Patient may acquire opioids from only one prescriber.
- Patient may not give opioids to friends or relatives.
- Patient may not acquire opioids from friends or relatives, from the street, or over the counter.
- Patient must keep regular appointments.
- Patient must provide urine samples for drug screening when requested.
- Consequences of breaking the contract.

Patients may run out of medication early during initial titration; however, if this continues beyond this period, the dispensing interval should be shortened to weekly or even daily. If the patient repeatedly breaks the agreement or has a serious violation, such as altering the prescription, the physician should in most cases cease prescribing opioids. Note, however, that physicians who discontinue opioids should in most cases continue to provide primary care, and certainly should arrange treatment if the patient is opioid addicted. Deception, such as making false claims about “losing” a medication, is a common clinical feature of addiction, and such behaviours cease when the patient is engaged in treatment.

Safe prescription writing

Patients who divert their medication sometimes attempt to alter their prescription in order to obtain a larger supply of the drug. The following precautions limit the risk of diversion:

- **Fax the prescription to the pharmacy** rather than giving it to the patient; keep the original for the patient's chart.
- Keep prescription pads in a safe location.
- Write the dose and number of pills in words and numerals.
- Write the name of the pharmacy on the prescription.
- Cross out blank parts of the prescription with double lines.
- Do not repeat over the telephone.
- Keep a flow sheet of opioids prescribed.

Urine drug screening (UDS)

Regular urine drug screening is indicated for patients at high risk for opioid misuse or addiction, and for patients showing aberrant drug-related behaviours such as running out of medication early. Physicians should specify on the requisition which drug or class of drugs they wish to detect, as this will help the lab choose the most appropriate testing technique. Prior to ordering the UDS, the physician should ask the

patient in detail about medication use in the previous two to three days.

Immunoassay and chromatography are the two main types of testing methods. Immunoassay, which most hospitals use, only detects opioids as a class without distinguishing the specific type of opioid (although dipsticks for specific opioids are now available through private companies). Immunoassay can detect opioids for up to seven days, but it often misses opioids that are chemically dissimilar to morphine, such as methadone, fentanyl, and oxycodone. Chromatography detects opioids for only one to two days after last use, but it has fewer false positives and negatives and can distinguish between different types of opioids.

There are two kinds of unexpected results: the absence of a prescribed opioid, and the presence of a non-authorized opioid. The former could indicate diversion, or that the patient was binging on the opioid, running out several days before the test. The latter could indicate double-doctoring (i.e., obtaining a prescription from more than one physician) or street use. Urine drug screens are not foolproof; a patient could, for example, take some of their opioid medication and divert the rest.

Preventing opioid overdose

In 2010, 550 people in Ontario died of an opioid overdose. One study found that most people who died of an opioid overdose in Ontario had received an opioid prescription within four weeks of death (95). This suggests that many overdose deaths can be prevented with improved opioid prescribing.

Symptoms of overdose

The early signs are emotional lability and “nodding off”. Patients are often able to appear relatively alert when engaged in social interactions, only to die of respiratory depression when they lie down for a “nap”. Therefore, any patient who may have taken an overdose urgently requires a medical assessment.

Risk factors

- **Lack of tolerance to opioids:** Tolerance to the sedating effects of opioids is gained and lost within days. Thus, patients can take a high dose without difficulty if it is titrated gradually over many weeks, but they can overdose if they stop opioids for one or two weeks and then resume the high dose.
- **Concurrent use of sedating drugs (e.g., alcohol, benzodiazepines):** While benzodiazepines rarely cause fatal overdoses by themselves, they greatly increase the risk of death in an opioid overdose.

- **Older age:** Older patients have slower clearance of opioid medication and greater sensitivity to its sedating effects.
- **Respiratory, hepatic, or renal impairment:** Morphine is contraindicated in patients with significant renal dysfunction, because an active metabolite of morphine can accumulate to toxic levels.
- **High risk for opioid misuse and addiction:** High-risk patients are more likely to engage in dangerous behaviours such as binging on the opioid, injecting or crushing oral tablets, or combining opioids with alcohol or benzodiazepines.

Prevention strategies

Physicians can help prevent overdoses by (a) engaging in patient education and (b) adopting careful prescribing practices.

(a) Patient education

Patients and family members should be given the following directions:

- Store medication in a secure and secret location, particularly if they have adolescent children living at home. A dose that is safe for one person could be fatal for others.
- Do not give or sell medication to anyone.

- Avoid drinking alcohol or using sedating drugs (including over-the counter drugs), especially during titration.
- Seek immediate medical attention at the first sign of overdose.

(b) Careful prescribing

Physicians should follow these guidelines when prescribing opioids:

- **Careful patient selection:** For patients at high risk for opioid toxicity or misuse, opioids should be reserved for patients who meet all three of these criteria: (a) have a well-documented organic pain condition; (b) have not responded to the standard non-opioid treatments; and (c) have a condition for which opioids are known to be effective.
- **Use codeine, transdermal buprenorphine or tramadol as first-line opioids:** Oxycodone has 1.5 to 2 times the analgesic potency of morphine, while hydromorphone is five times as potent. As a result, they carry a far greater overdose risk than codeine or tramadol (95).
 - Some physicians feel that potent opioids should be used as a first-line, because codeine is not always effective (at least partly because 10% of Caucasians lack the enzyme that converts codeine to morphine). However, it is

important to note that controlled trials have shown that both codeine and tramadol are effective for chronic pain (78). Furthermore, safety should be the paramount consideration when prescribing opioids chronically.

- **Avoid prescribing sedating drugs along with opioids:** Most opioid overdose deaths occur in combination with alcohol, benzodiazepines, atypical antipsychotics or other sedating drugs. When feasible, benzodiazepines should be tapered before or during opioid initiation.
- **Titrate slowly, keeping the dose well below 200 mg MED:** Among Ontario public drug plan recipients between 2003 and 2008, two-year opioid-related overdose mortality rates were 1.6, 7.9, and 9.9 per 1000 population for those prescribed < 200 mg MED, 200–400 mg MED, and > 400 mg MED respectively.(96)
- **Use caution when prescribing for the elderly:**
 - Always start with codeine, tramadol, or buprenorphine patch.
 - The initial dose should be no more than **one half** of that for younger patients.
 - Titrate more slowly and in smaller increments. Elderly patients often respond to small doses.
 - Call the patient or family one to three days after initiating opioid therapy to assess for sedation or falls.
 - Taper benzodiazepines.

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- Do not prescribe opioids to cognitively impaired patients unless dispensed by a caregiver.
- To prevent falls use caution when prescribing potent opioids and CR opioids, particularly at night.
- **Give high-risk patients naloxone if possible:**
Naloxone is not yet covered as a general benefit for patients on ODB, but some hospital pharmacies will distribute one or two vials to high-risk patients, and a number of public health units provide injection drug users with naloxone kits and overdose prevention training programs.

Recognizing opioid withdrawal

The physical symptoms of withdrawal start six hours after last use of IR opioid, peak after two to three days, and begin to resolve after five to seven days; psychological symptoms, though, can last for weeks. The physical symptoms are similar to the flu: myalgias, chills, nausea and vomiting, abdominal cramps, and diarrhea. The psychological symptoms are considerably more distressing to most patients than physical symptoms; they include insomnia, anxiety and irritability, dysphoria, and drug craving.

Complications include suicidal ideation, particularly if the patient is forced to remain abstinent (e.g., patients in prison). Overdose is the most common and serious complication. It occurs when the patient relapses to their usual dose after a period of abstinence, e.g., after discharge from a withdrawal management centre or a treatment program. Severe withdrawal in pregnant women can result in miscarriage or premature labour. There have been cases reports of bleeding gastric or duodenal ulcers in patients undergoing severe untreated withdrawal, probably due to hypersecretion of acid. Finally, withdrawal can exacerbate pre-existing psychiatric illnesses and cardiorespiratory illnesses such as asthma or angina.

The Clinical Opioid Withdrawal Scale (COWS) (97) can be used to monitor withdrawal (see Appendix C).

Managing opioid addiction

Marketing campaigns in the 1990s and early 2000s stated that the risk of addiction was less than 0.1%. In fact, the true risk of addiction is likely much higher than this. In a systematic review of opioid treatment for low-back pain, the prevalence of aberrant drug-related behaviours ranged from 5 to 24% (98). Family physicians should be aware of the signs of opioid addiction and routinely provide screening and management.

Risk factors

Patients are at higher risk for opioid misuse or addiction if they currently drink alcohol above the Canadian low-risk drinking guidelines, if they smoke cannabis heavily, or if they use street drugs or non-authorized prescription drugs. A past history of addiction to any substance is also a major risk factor, especially if the addiction was recent, prolonged, or severe. Other risk factors include a strong family history of addiction, being under 40 years old, and an active mental illness (such as anxiety, depression, or post-traumatic stress disorder).

For patients who are currently addicted to opioids, alcohol, or other drugs, opioid therapy should usually be withheld until the addiction is treated and is in remission. Prescribing opioids to a currently addicted patient increases the risk of diversion and overdose.

For patients who are at high risk but are not currently addicted to other drugs, opioids should be reserved for moderate to severe nociceptive or neuropathic pain conditions normally requiring opioid therapy that have failed to respond to non-opioid treatments.

Prescribers should observe the following guidelines:

- Codeine, buprenorphine, or tramadol should be used as first-line agents; evidence suggests that these agents, particularly tramadol, have a significantly lower risk of addiction than the potent opioids (99, 100).
- The dose should be titrated slowly using small increments, and the maintenance dose should be well below 200 mg MED.
- The physician should avoid opioids that the patient has misused in the past or that are commonly misused in the community.
- If a potent opioid is necessary, it is more appropriate in most cases to prescribe morphine than oxycodone, hydromorphone, or fentanyl, which appear to have a greater euphoric effect and therefore a greater addiction risk than equianalgesic doses of morphine (101-104).
 - Hydromorph Contin is a very potent opioid (an 18 mg tablet is equivalent to 90 mg MED) and can easily be injected; a 50 µg fentanyl patch is even more potent (equivalent to 120 mg MED or more) and it is easy to suck the patch or inject the fentanyl in the reservoir.

Symptoms, signs, and behaviours

Some patients experience a reinforcing psychological effect from opioids. A patient is said to be addicted if he or she repeatedly seeks this euphoric effect despite the social and psychological harms this causes.

Tolerance develops rapidly to opioid-induced euphoria, compelling the patient to seek higher doses of the drug. After a few weeks or months, the patient experiences withdrawal symptoms at the end of a dosing interval, characterized by insomnia, anxiety, drug craving, and flu-like symptoms such as myalgia.

The patient sometimes resorts to aberrant drug-related behaviours to maintain their supply of high drug doses, such as unsanctioned dose escalation, accessing opioids from other sources, or altering the route of delivery (crushing, snorting, or injecting oral tablets). Paradoxically, the patient often reports severe pain despite the high opioid dose, perhaps due to withdrawal-mediated pain, opioid-induced hyperalgesia, or opioid-induced dysphoria.

Opioid addiction is a difficult diagnosis to make, particularly in patients with chronic pain conditions; 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.

Addiction is diagnosed through the following sources:

- **History:** Addicted patients tend to give an inconsistent and confusing history of analgesic response; they report minimal analgesic benefit, yet fiercely resist any suggestion that the opioid be discontinued (e.g., “The opioid only takes the edge off – the pain is still 12 out of 10. But it’s the only thing that works, and if you stop it I’ll fall apart.”). They sometimes report an improved mood immediately after taking the opioids, followed by withdrawal symptoms at the end of a dosing interval. Typically they report depression, anxiety, and worsening social function over time.
- **Corroborating information:** Family members may report that the patient has become more withdrawn and irritable since being on the opioid. Previous doctors may report that the patient displayed aberrant behaviours such as running out of their opioid medication early.
- **Urine drug screens:** UDS may show unexpected negative results (the prescribed opioid is absent because the patient has run out early or diverted them), or unexpected positive results (non-prescribed opioids/benzodiazepines, street drugs).
- **Pattern of prescription opioid use:** Tolerance to the analgesic effects of opioids develops quite slowly, so patients with a stable pain condition are often able to remain on the same dose for months or years. In contrast, tolerance to the psychoactive effects of opioids develops very

quickly, forcing addicted patients to escalate the dose to achieve the same effect. With high daily doses, patients begin to use opioids not just for their euphoric effects but to ward off withdrawal symptoms.

Table 12: Diagnosing addiction in chronic pain patients

	Addicted pain patient	Pain patient
Profile	More likely to be younger and male, with personal or family history of addiction and mental illness	Typical of the physician's practice
Opioid dose	Very high for underlying pain condition	Moderate, typical for underlying condition
Analgesic response	Minimal response but high salience: "Opioids take edge off but I'll die if you stop them"	Graded analgesic response; willing to consider alternatives
Pattern of use	Binge; takes extra in morning and when stressed	Scheduled, and as directed
Withdrawal symptoms	Frequent, severe, accompanied by emotional distress	Minimal, because patients takes moderate dose and doesn't run out
Functioning	Often worsening	Improved because of better pain control
Aberrant behaviours	Runs out often, alters route of delivery, gets opioids from multiple sources	Sometimes runs out early on initiation of therapy

Options for management of opioid addiction

The three treatment options for suspected opioid addiction in pain patients are (a) structured opioid therapy, (b) abstinence-based treatment, and (c) opioid substitution treatment.

(a) Structured opioid therapy (SOT)

SOT consists of frequent dispensing of small amounts of opioids, close follow-up for mood and analgesic response, monitoring for aberrant drug-related behaviours through history and UDS, and tapering for patients on high doses. SOT should be reserved for patients at high risk for opioid addiction, and for opioid-addicted patients who do not acquire opioids from the street or other sources, do not alter the route of delivery, and are not currently addicted to other drugs. If a trial of SOT fails, the patient should be referred for opioid substitution treatment.

Structured opioid therapy protocol

- Dispense opioids frequently (weekly or biweekly) in small quantities. If the patient regularly runs out early, dispense more frequently (as often as daily) and do not prescribe early refills.
- Taper the dose if above 200 mg MED.
- Taper benzodiazepines.
- Order periodic UDS.

(b) Abstinence-based treatment

Abstinence-based treatment is provided in withdrawal management centres and in residential psychosocial programs. Patients and their families often prefer abstinence-based treatment, but it is less effective than opioid substitution treatment; patients should be advised to try opioid substitution treatment if they relapse after abstinence-based treatment.

Patients are at high risk for overdose death if they relapse to opioids after completing an abstinence-based program because tolerance to opioids is lost within a few weeks of abstinence. Therefore, all patients should be educated about harm reduction strategies that will lower their risk of fatal overdose:

- Use only a small amount, much less than previous dose.
- Take the opioid orally rather than by injection.
- Never use alone.
- Do not combine opioids with alcohol or benzodiazepines.
- Have naloxone on hand to reverse an overdose (available through the local public health program).

(c) Opioid substitution treatment (OST)

Opioid substitution treatment, also called opioid agonist treatment, is the replacement of an illegal or

euphoria-inducing opioid with methadone or buprenorphine/naloxone (bup/nx), which are long-acting opioids that do not induce euphoria. This treatment consists of daily dispensing of methadone or bup/nx, regular urine drug screening, and ongoing counseling, and has the strongest evidence of effectiveness against opioid addiction.

OST is indicated for patients who:

- Have failed SOT.
- Are currently addicted to cocaine, alcohol, or other drugs.
- Inject or crush oral tablets or acquire opioids from other sources (i.e., family and friends, multiple doctors, or the street).

The physician should address common misconceptions about OST:

- *It's just replacing one drug with another:* Point out that while methadone and bup/nx are both opioids, they have an extremely slow onset and long duration of action, so they cause minimal or no cognitive impairment in opioid-dependent patients. In contrast, injection opioids cause profound intoxication because they reach the brain within seconds; the effects wear off quickly so patients can experience the early onset of withdrawal several times per day. The physician can illustrate this point with an analogy: The

measles vaccine contains a live virus, but it triggers an immune reaction that protects patients from measles infection.

- *If I have to go on OST, that means I failed:* Point out that powerful physiological forces, such as tolerance, withdrawal, and craving, make it extremely difficult to maintain long-term abstinence, even for the individuals with very strong willpower. Methadone and bup/nx control these forces, allowing the patient to engage in counseling and make the lifestyle changes they need for long-term recovery.
- *You're on these drugs for life:* Patients can successfully taper from methadone or bup/nx, especially if they are younger, have a brief history of opioid addiction (less than two years), are socially stable, and do not have severe, untreated psychiatric illnesses.

Prescribing buprenorphine/naloxone

Both methadone and bup/nx can be used in OST. An important difference between the two agents, however, is that while methadone can only be prescribed by physicians with an exemption from the College of Physicians and Surgeons of Ontario, **any family physician in Ontario can prescribe bup/nx.**

About buprenorphine

Buprenorphine is a 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, bup/nx relieves withdrawal symptoms and cravings for 24 hours without causing euphoria. Buprenorphine 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. It has a slow onset and long duration of action because it dissociates very slowly from the receptors. Its side effects similar to those of other opioids: nausea, constipation, and sedation.

Because buprenorphine is a partial opioid agonist, it is much less likely to cause an overdose than methadone, a full, potent opioid agonist. It also

causes fewer side effects, and patients maintained on bup/nx generally perform better on cognitive tasks than methadone-maintained patients. Methadone has a higher treatment retention rate, so patients that fail on bup/nx maintenance can be switched to methadone.

Initiating bup/nx treatment

Bup/nx is very safe, even in patients who have never taken it before, but it does displace opioids currently attached to the receptor, precipitating opioid withdrawal in patients who are physically dependent on those opioids. Therefore, the physician must ensure the patient has no opioid in their serum before taking the first dose. Precipitated withdrawal is rarely severe or dangerous, but patients who experience it are reluctant to try bup/nx again.

Bup/nx initiation protocol

- Give first dose in office setting, if feasible.
 - At least 12 hours since last IR dose, 24 hours since last CR dose.
 - Patient reports typical withdrawal symptoms, e.g., myalgias.
 - COWS score of 12+ (see Appendix C).
- 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. **8 mg** is the **maximum** first-day dose.
- Reassess in one to three 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/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, bup/nx 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 or other factors, then the physician should arrange supervised dispensing at home by a nurse or reliable relative.
 - Take-home doses may be prescribed once the patient is at an optimal dose and has stopped all unauthorized opioid use.
- The physician should arrange frequent office visits for counseling and UDS monitoring.

If you are not comfortable initiating bup/nx treatment with your patients, you should refer them to an addiction physician. Once patients have been titrated to an optimal dose of bup/nx by the addiction physician, they should be referred back to primary care for maintenance.

Prescriptions

All prescriptions for bup/nx (see Appendix D) 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 six tablets to take home)
- Limited use (LU) code for patients on ODB: 437 (for patients who have failed, have significant intolerance of, have a contraindication to, or are at high risk for toxicity with methadone) or 438 (when a methadone maintenance program is not available or accessible)

Managing stable patients on bup/nx

Office visits for prescription refills are usually brief and straightforward. The physician should check for adequacy of the dose; patients experiencing withdrawal symptoms or cravings may require minor dose adjustments of 2-4 mg per day. The physician should also ask about the patient's overall mood and functioning. Stable patients should leave at least one urine sample per month for screening. Unexpected results should be reviewed with the patient and, if necessary, with an addiction physician. Common unexpected results include the following:

- *Absence of norbuprenorphine:* Norbuprenorphine is a metabolite of buprenorphine. Its absence in a UDS indicates that the patient hasn't taken buprenorphine for several days, either because they are non-compliant with treatment or they are diverting their tablets.
- *Presence of unauthorized prescription drugs (e.g., opioids, benzodiazepines):* This could represent an innocent slip; for example, the patient took a medication from a family member for a headache. The patient should be informed that they should only take prescribed medication, or approved over-the-counter medications. It could also indicate that the patient is using these substances problematically. The frequency of urine drug testing might need to be increased.

- *Presence of illicit drugs (e.g., cocaine, methamphetamine):*
The presence of cocaine or crystal methamphetamine in a UDS usually signifies a serious problem and should not be dismissed as a one-off occurrence. The patient should be referred to an addiction physician.

Stable patients should also be asked about alcohol and cannabis use, as these substances are usually not tested on a UDS. Physicians can also provide their patients with ongoing comprehensive care:

- 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)
- Identify any new medical or psychiatric conditions.

Tapering bup/nx

Patients are often eager to taper off buprenorphine treatment because it is inconvenient, time-consuming, and a constant reminder of their addiction. Chances of successfully tapering are greater in patients who have a brief history of opioid addiction (less than two years), are socially stable and do not have severe, untreated psychiatric illnesses.

The ideal candidate for tapering:

- Wants to taper.
- Has not used drugs for at least six months.
- Is socially stable and has a supportive family or social network.
- Has a stable mood and good coping strategies.
- Has minimal contact with drug users.

Bup/nx 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 bup/nx for long periods when necessary.

Appendices

Appendix A: Alcohol withdrawal scales

1. Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar)

<p>NAUSEA AND VOMITING 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>AGITATION 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>TREMOR 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>TACTILE DISTURBANCES 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>

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<p>PAROXYSMAL SWEATS 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>AUDITORY DISTURBANCES 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>
<p>ANXIETY 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>VISUAL DISTURBANCES 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>HEADACHE, FULLNESS IN HEAD 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. Observation 0 not present 1 very mild 2 mild 3 moderate 4 moderately severe 5 severe 6 very severe 7 extremely severe</p>	<p>ORIENTATION AND CLOUDING OF SENSORIUM 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>

**2. Sweating, Hallucination, Orientation, Tremor
(SHOT) scale**

Sweating	0 – No visible sweating 1 – Palms moderately moist 2 – Visible beads of sweat on forehead
Hallucinations “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
Orientation “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
Tremor 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

Appendix B: Clinical information for anti-alcohol medications

1. Disulfiram (46, 48, 105-107)

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 (49)

Action

- Blocks opioid receptor and reduces euphoric effect of drinking.

Side effects

- Nausea, headache, dizziness, insomnia, anxiety, sedation.
- Blocks analgesic action of opioids.
- Can cause reversible elevations in AST and ALT; order at baseline and at 3–4 weeks.

Contraindications and precautions

- Pregnancy.
- Will trigger severe withdrawal in patients on opioid medications.
- Can cause reversible elevations in liver enzymes.
- May cause GI upset and elevated liver enzymes; check liver enzymes (baseline, 3 months) and discontinue if they 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 (108, 109)

Action

- Glutamate antagonist.
- Works best if abstinent at least 4 days prior to initiation.

Side effects

- Diarrhea, anxiety.

Contraindications and precautions

- Renal insufficiency.
- Pregnancy.

Dose

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

4. Topiramate (110-112)

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 (64, 113, 114)

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 (115, 116)

Action

- GABA agonist

Side effects

- Drowsiness, weakness, can cause or worsen depression.

Contraindications and precautions

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

Dose

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

Appendix C: Clinical Opioid Withdrawal Scale (COWS) (97)

	Interval	0	30m	2h	4h
Date	Time				
		Score	Score	Score	Score
Resting heart rate (measure after lying or sitting for one minute): 0 HR ≤ 80 2 HR 101–120 1 HR 81–100 4 HR > 120					
Sweating (preceding 30m and not related to room temp/activity): 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					
Restlessness (observe during assessment): 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					
Pupil size: 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible					
Bone or joint pain (not including existing joint pains): 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					

MANAGEMENT OF SUBSTANCE USE DISORDERS IN
PRIMARY CARE

	Interval	0	30m	2h	4h
Date	Time				
		Score	Score	Score	Score
Runny nose or tearing (not related to URTI or allergies): 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks					
GI upset (over last 30 minutes): 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhoea 5 multiple episodes of vomiting or diarrhoea					
Tremor (observe outstretched hands): 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching					
Yawning (observe during assessment): 0 no yawning 1 yawning once or twice during assessment 2 yawning 3+ times during assessment 4 yawning several times/minute					
Anxiety or irritability 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					
Gooseflesh skin 0 skin is smooth 3 piloerection (goosebumps) of skin can be felt or hairs standing up on arms 5 prominent piloerection					

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SCORE INTERPRETATION	Total	Total	Total	Total
5-12 MILD				
13-24 MODERATE				
25-36 MODERATELY SEVERE				
> 36 SEVERE				
	Initial	Initial	Initial	Initial

Appendix D: Sample bup/nx prescription

Clinic

Prescriber, MD

Hospital

Phone number

Fax number

Patient

Health card number

Date of birth

Pharmacy

Address

Fax number

Date

Buprenorphine/naloxone 8/2 mg SL OD

Start date – end date inclusive

Dispense daily observed

LU 437/438

Physician

CPSO number

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