

Conflict of Interest

Medical Director of Bellwood Health Services

Advisory Board for Sublocade (Indivior)



Outline

- Approach to treatment of different substances
- Learn about medications used for long term management of substance use
- Understand how medications can be effective in managing cravings



Spectrum of Psychoactive Substance Use

Non-problematic

 recreational, causal or other use that has negligible health or social impact

Beneficial

 use that has positive health, spiritual or social impact e.g. pharmaceuticals, coffee/tea to increase alertness,

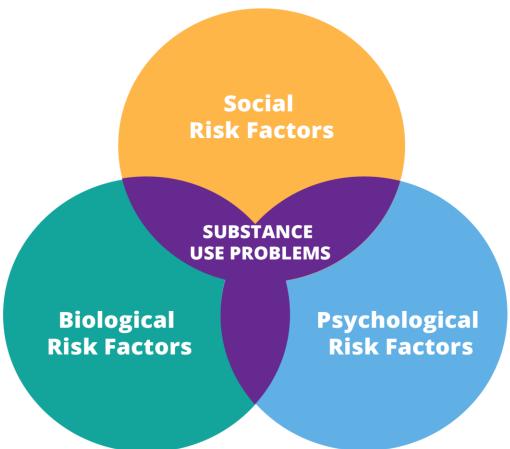
Problematic

Potentially harmful

 use that begins to have negative consequences for individual, friends/family or society e.g. impaired driving, binge consumption, routes of administration that increase harm

Substance Use Disorders

 Clinical disorders as per DSMV/ICD10 criteria **Biopsychosocial Model**





Substance Use Disorder (DSM V)

Very similar to those outlined in DSM-IV for abuse and dependence combined

- meeting 2-3 of the criteria indicates Mild substance use disorder
- meeting 4-5 of the criteria indicates Moderate
- meeting 6-7 of the criteria indicates Severe



DSM V Criteria

Criterion	DSM-IV substance dependence	DSM-5 substance use disorder
Tolerance	✓	✓
Withdrawal	\checkmark	\checkmark
Taken more/longer than intended	\checkmark	\checkmark
Desire/unsuccessful efforts to quit use	\checkmark	\checkmark
Great deal of time taken by activities involved in use	✓	✓
Use despite knowledge of problems associated with use	✓	✓
Important activities given up because of use	✓	✓
Recurrent use resulting in a failure to fulfill important role obligations		✓
Recurrent use resulting in physically hazardous behavior (e.g., driving)		✓
Continued use despite recurrent social problems associated with use		✓
Craving for the substance		\checkmark

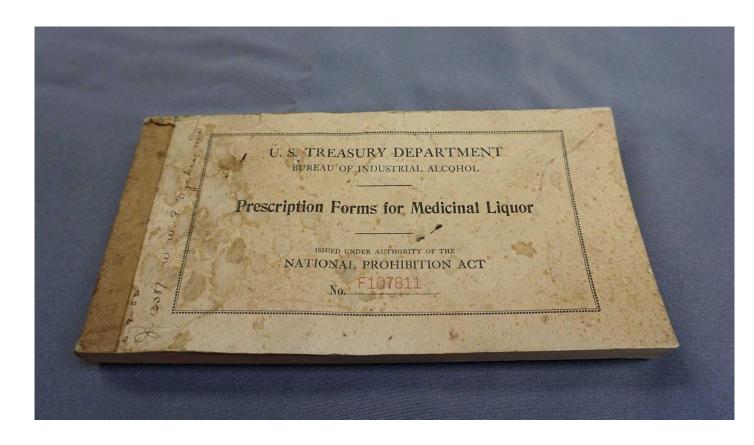


DSM-V Substances

- Alcohol
- Phencyclidine
- Inhalant
- Stimulant (amphetamine, cocaine)
- Cannabis
- Hallucinogen
- Opioid
- Sedative, hypnotic, or anxiolytic
- Tobacco



Alcohol





Alcohol Use Categories

- Abstinence: Patient does not drink alcohol
- Low-risk drinking: Patient drinks within low-risk guidelines
- At-risk drinking: Patient drinks in excess of the low-risk guidelines but experiences minimal adverse effects
- Alcohol use disorder (AUD): Patient meets DSM-V criteria
 - 2-3 = mild AUD
 - 4–5 = moderate AUD
 - 6+ = severe AUD



Canadian Low-risk Drinking Guidelines





Audit

AUDIT ALCOHOL SCREENING TOOL

1 unit is typically:	JNIT GUIDE					
Half-pint of regular beer, lager or cider; 1 small glass low ABV wine (9%); 1 single measure of spirits (25m		\bigcirc		₹	\overline{Y}	
The following drinks have more than one unit:					_	
A pint of regular beer, lager or cider, a pint of strong /premium beer, lager or cider, 440ml regular can cider/lager, 440ml "super" lager, 175ml glass of wine	(12%)	13	2	1	T	

Questions		Sco	ring syst	em	20	Your
Questions	0	1	2	3	4	score
How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times per month	2 - 3 times per week	4+ times per week	
How many units of alcohol do you drink on a typical day when you are drinking?	1 -2	3 - 4	5 - 6	7 - 9	10+	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Scoring: 0 - 7 Lower risk, 8 - 15 Increasing risk, 16 - 19 Higher risk, 20+ Possible dependence





Alcohol Use Disorder

- Present the diagnosis in a clear and sensitive way
- Offer help -> "treatable condition"
- Assess patient's state of change:
 - Abstinence is more likely to be successful
 - If reduced drinking goal is chosen, encourage a time-limited trial
- Treat withdrawal if necessary
- Treat concurrent conditions (anxiety, depression, hypertension, liver disease)
- Offer anti-craving medication



Alcohol Use Disorder - Treatment

- Encourage patient to make healthy lifestyle choices:
 - Stay away from people/places associated with drinking
 - Spend time with supportive family and friends
 - Take daily walks
 - Maintain regular sleeping/waking schedule
 - Plan regular activities outside the house as feasible
- Review options for formal treatment (residential, day, outpatient)
- Recommend AA or other community groups for support, practical advice, and a way to overcome loneliness and boredom
- Arrange follow-up; monitor drinking through self-report, GGT, MCV
- Acknowledge successes, even if partial or temporary
- If patient relapses, encourage contact and reconnection with treatment



PRESCRIBING ANTI-CRAVING MEDICATIONS

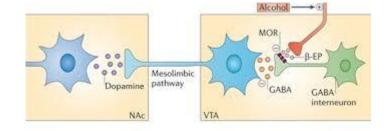


Role of Anti-craving Medications

- Should be routinely offered to patients with AUD
 - Shown to reduce alcohol use
 - Good safety profiles
 - Help retain patients in treatment
- Choice of medication depends on individual considerations (e.g., cost, side effects)
- Titrate dose until cravings are mild and patient is abstinent, or until troublesome side effects emerge
- Maintain until patient has been abstinent for at least several months, has minimal cravings, has social supports and new ways of coping with stress, and is confident that medication is no longer needed to prevent relapse
 - Usually at least 6 months



Naltrexone - 1st Line



Nature Reviews | Neuroscience

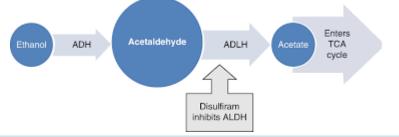
Action	Blocks opioid receptor, reduces euphoric effect
Side effects	Nausea, headache, dizziness, insomnia, anxiety, sedation Blocks analgesic action of opioids Can cause reversible elevations in AST and ALT; order at baseline and at 3–4 weeks
Contraindications/ precautions	Pregnancy Triggers severe withdrawal in patients on opioids Discontinue if AST/ALT rise more than 3x baseline at 3–4 weeks
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

Acamprosate - 1st Line

Action	Glutamate antagonist Relieves subacute withdrawal symptoms (insomnia, dysphoria, craving)
Side effects	Diarrhea
Contraindications/ precautions	Pregnancy Renal insufficiency
Dose	666 mg tid; 333 mg tid if renal impairment or BW < 60 kg Works best if patient is abstinent several days prior to initiation



Disulfiram





Action	Acetaldehyde accumulates when alcohol consumed Most effective when dispensed by family member
Side effects	With alcohol: Vomiting, flushed face, headache Without alcohol: Headache, anxiety, fatigue, garlic-like taste, acne, peripheral neuropathy (with prolonged use)
Contraindications/ precautions	Cirrhosis Pregnancy Unstable cardiovascular disease Alcohol reaction can cause severe hypotension and arrhythmias, especially in patients with heart disease or on antihypertensives May trigger psychosis at higher doses (500 mg) Can cause toxic hepatitis
Dose	125 mg PO OD; increase to 250 mg if patient reports no reaction to alcohol Wait at least 24–48 hours between last drink and first pill Wait at least 7–10 days between last pill and first drink

Gabapentin - 2nd Line

Action	Modulates dopamine
Side effects	Dizziness, sedation, ataxia, nervousness
Contraindications/ precautions	Can cause suicidal ideation (rare)
Dose	Initial dose 300 mg bid-tid; optimal dose 600 mg tid



Topiramate - 2nd Line

Action	Modulates GABA system May improve sleep/mood disturbance in early abstinence
Side effects	Sedation, dose-related neurological effects (dizziness, ataxia, speech disorder, etc.) resolve over time
Contraindications/ precautions	Can cause weigh loss (risk for underweight patients) Can clause glaucoma or renal stones Caution in patients of child-bearing age.
Dose	Initial dose 50 mg OD; titrate by 50 mg to a maximum dose of 200–300 mg daily Lower dose needed in renal insufficiency

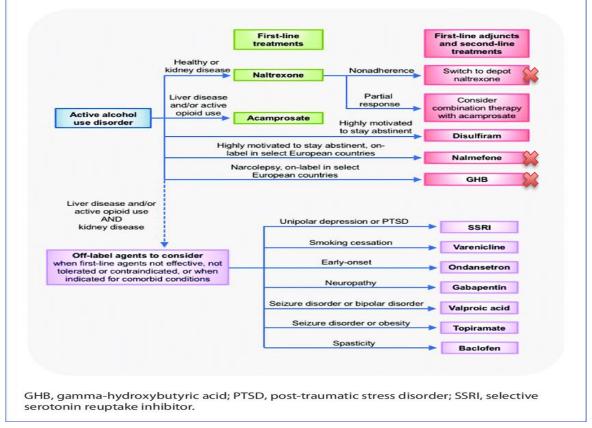


Baclofen - 2nd Line

Action	GABA agonist
Side effects	Drowsiness, weakness, can cause or worsen depression
Contraindications/ precautions	Use with caution in patients on tricyclic anti-depressants or MAO inhibitors
Dose	Initial dose 5 mg tid, increase to 10 mg tid; maximum daily dose 80 mg Lower dose needed with renal insufficiency



Suggested Approach to Alcohol Use Disorder





Varenicline

- Varenicline is a nicotine receptor partial agonist used for smoking cessation
- Some evidence that it reduces heavy drinking days in men who smoke
- Varenicline is covered by ODB with LU code 423; patients must take it as a smoking cessation aid, in conjunction with smoking-cessation counselling.
- The controlled trials started patients on 0.5 mg OD for three days, then 0.5 mg bid for four days, then 1 mg bid.



Ondansetron

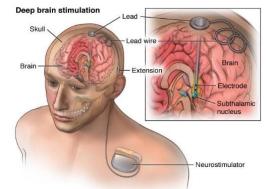
- Ondansetron, a serotonin 5-HT3 receptor antagonist
- Can be used as a second-line drug in patients with early-onset alcoholism (i.e., patients who developed AUD before the age of 25).
- Early-onset alcoholism has been associated with a genetic defect in the serotonin transporter system that increases dopamine and thus increases the euphoric effect of alcohol.
- Ondansetron modulates the serotonin system, reducing alcohol's reinforcing effects in patients with this genetic defect.
- ODB only funds ondansetron for chemotherapy-induced nausea. The controlled trial used a daily dose of 0.5 mg
- Ondansetron comes in 4 mg and 8 mg formulations, so compounding will be required.



Novel Approaches

- Novel therapeutic options currently under investigation for AUD include neuromodulation, and psychedelics
- Neuromodulation, such as deep brain stimulation, is thought to work on the nucleus accumbens to target centers of reward behavior and reduce cravings

Phase I trial at Sunnybrook: (https://sunnybrook.ca/media/item.asp?c=1&i=2028&f=deep-brain-stimulation-alcohol-use-disorder-frank-plummer)





Psychedelics

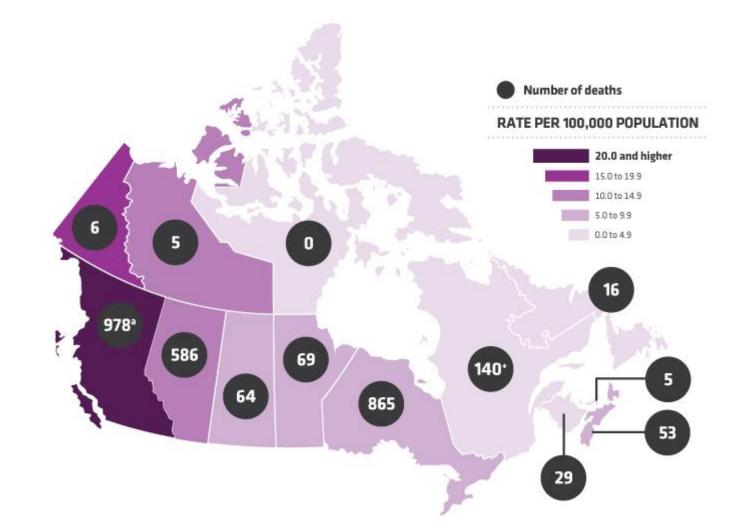
- Psilocybin, LSD, Ketamine
 - Currently being investigated for use in the treatment of PTSD, AUD
 - Only Ketamine is currently legally available for use in Canada.
 - Likely 2 to 5 year timeframe. Caution urged





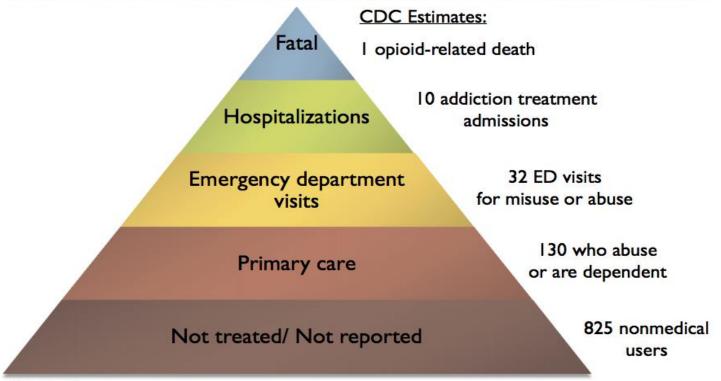
OPIOIDS







Injury Pyramid



Adapted from:

http://apps.who.int/iris/bitstream/10665/149798/1/9789241508018_eng.pdf?ua=1&ua=1&ua=1

http://www.cdc.gov/drugoverdose/pdf/policyimpact-prescriptionpainkillerod-a.pdf



Opioids

Table 1. Common generic, trade and street names for opioids

Generic name	Trade name (examples)	Street names
Buprenorphine	BuTrans®	Bupe, bute
Buprenorphine-naloxone	Suboxone®	Subby, bupe, sobos
Codeine	Tylenol®2,3,4 (codeine + acetaminophen)	Cody, captain cody, T1, T2, T3, T4
Fentanyl	Abstral®, Duragesic®, Onsolis®	Patch, sticky, sticker
Hydrocodone	Tussionex®, Vicoprofen®	Hydro, vike
Hydromorphone	Dilaudid®	Juice, dillies, dust
Meperidine	Demerol®	Demmies
Methadone	Methadose®, Metadol®	Meth, drink, done
Morphine	Doloral®, Statex®, M.O.S.®	M, morph, red rockets
Oxycodone	OxyNEO®, Percocet®, Oxycocet® Percodan®	Oxy, hillbilly heroin, percs
Pentazocine	Talwin©	Ts
Tapentadol	Nucynta®	Unknown
Tramadol	Ultram® Tramacet® Tridural® Durela®	Chill pills, ultras

Note: OxyContin® is no longer marketed in Canada and was replaced with OxyNEO®. Generic controlled-release oxycodone was approved by Health Canada. Oxymorphone (Opana®) has been approved by Health Canada, but is currently not marketed in Canada.

https://www.drugfreekidscanada.org/wp-content/uploads/2012/11/Opioid-table2.jpg



What is fentanyl?

Synthetic

Opioid analgesic

•Several fentanyls, salts, derivatives, analogues

Fast

•Rapid onset, short duration

Potent

•50-100x more potent than morphine

Controlled

 Controlled Drugs and Substances Act, Schedule I

Therapeutic

 Cancer pain, severe/continuous pain (opioid tolerant patients), anesthesia

Health Canada Drug Product Database: http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp Controlled Drugs and Substances Act: http://laws-lois.justice.gc.ca/eng/acts/c-38.8/



Opiate Withdrawal Timeline

Start

Take your last dose



72 Hours

Physical symptoms at peak

Chills, fever, body aches, diarrhea, insomnia, muscle pain, nausea, dilated pupils



1 Week

Physical symptoms start to lessen

Tiredness, sweating, body aches, anxiety, irritability, nausea



2 Week

Psychological and emotional symptoms

Depression, anxiety, irritability, restlessness, trouble sleeping



1 Month

Cravings and depression

Symptoms can linger for weeks or months



Risks of Untreated Withdrawal

- Suicide, if patient cannot access opioids
- Relapse, with heightened risk of overdose
 - Tolerance to opioids markedly declines within a few days of abstinence
 - Illicit opioids are often laced with fentanyl



Treatment Options: Abstinence-based Psychosocial Treatment

- Often preferred by patients to long-term opioid agonist treatment
- Increased risk of relapse and opioid overdose due to prolonged withdrawal and cravings
- Patients should be given harm reduction advice



Harm Reduction Advice

- Never use opioids alone
- Make sure you and your friends know the signs of overdose (pinpoint pupils, falling asleep, slowed/stopped breathing, bluish skin around lips or under nails)
- Always carry naloxone (available from pharmacies free of charge to anyone)
- If a friend has overdosed:
 - Shake them and call their name
 - Call 911
 - Administer naloxone and start chest compressions
- If you are taking opioids after a period of abstinence (even a few days), take a much smaller dose than you used to



Harm Reduction Advice

- Only medications obtained from a prescription and purchased at a pharmacy are guaranteed to be what they are supposed to be
 - Many opioids (and other drugs, such as cocaine) are laced with fentanyl
 - Fentanyl is very potent and can be lethal even in tiny amounts
- Do not inject opioids
- Do not mix opioids with other substances, especially alcohol or benzodiazepines



Treatment Options: Structured Opioid Therapy

- Opioid prescribing under conditions that limit misuse.
- Usually for someone for chronic pain at high risk or has OUD
- Only uses opioids supplied by one prescriber, does not use alcohol or other substances
- Approach: Slow, controlled tapering over months
- Switch to opioid maintenance therapy if structured opioid therapy fails (i.e., patient continues to use more than prescribed)



Treatment Options: Opioid Agonist Therapy

- Substitution of illegal and/or euphoria-inducing opioid with longer-acting, less euphoric opioid
- Relieves withdrawal symptoms/cravings for 24 hours



Opioid Maintenance Therapy

- Maintenance therapy has historically used **methadone**
 - Full, potent opioid agonist
- Risk of sedation/overdose
- Requires a federal exemption to prescribe (Not since May 19, 2018).
- Many CPSO requirements for physicians
- NPs are expected to complete courses on controlled prescribing meet the accountabilities from their college
- Another option is buprenorphine
- Partial opioid agonist with a ceiling effect
- Even very high doses rarely cause respiratory depression (unless combined with alcohol/sedatives)
- Binds tightly to receptors, displacing other opioids
- Usually combined 4:1 with **naloxone** as abuse deterrent
- Can be prescribed by any doctor in Ontario



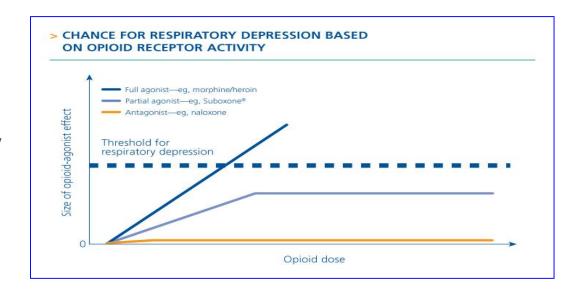
Buprenorphine versus Methadone

	Methadone	Bup/nx	
Effectiveness as maintenance treatment	Very effective Effective but less than m		
Overdose risk	Very high	Low	
Who can prescribe	Any MD (Must inform CPSO) and NP	Any MD or NP	
Rx of acute withdrawal	Not safe or practical (takes weeks to reach optimal dose)	Very effective Optimal dose reached within 1-3 days	



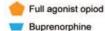
BUPRENORPHINE: A "SAFE CEILING"

- Doses beyond 24 mg-32 mg don't have any additional opioid effects
 - Less likely to cause respiratory depression in overdose
 - Ceiling can be compromised by concomitant alcohol or other central nervous system depressants, or when buprenorphine is misused





Precipitated Withdrawal Mechanism 20 minutes later min Net effect Net effect Net effect **Bridging at Molecular Level** Day 2-3 Day 4 Day 1 Net effect Net effect Net effect



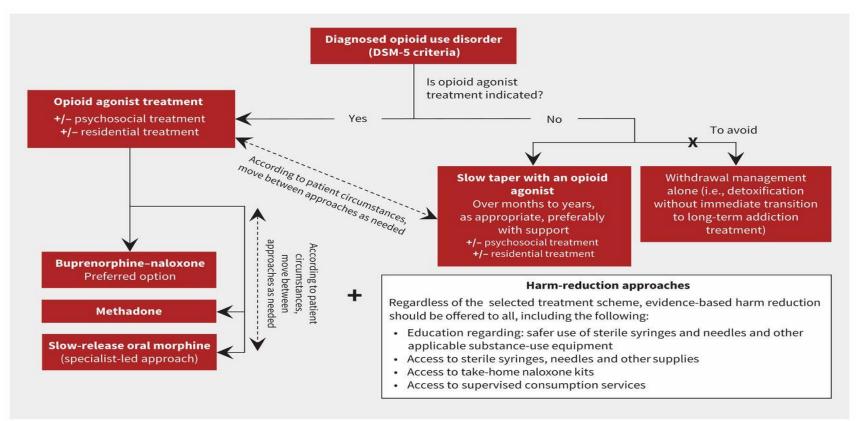
Methods of transitioning from opioid agonists to buprenorphine

Ghosh, Canadian Journal of Addiction 10(4):41-50, December 2019.

Variable	Classic induction method	Microinduction bernese method	Buprenorphine transdermal patch method	Rapid microin- duction method	Fentanyl patch method	SROM conversion strategy	Microdosing with buprenorphine and SROM
Setting of treatment	Outpatient for methadone less than 70 mg. Inpatient setting for methadone doses greater than 70 mg	Outpatient	Outpatient	Inpatient	Inpatient	Outpatient	Outpatient
Dose of methadone most effective for <50 mg = low, 50-100 mg = moderate, >100 mg = high	Low	Low to moderate	Low to high	Low to moderate	Low to high	Low to high	Low to moderate
Risk of precipitated withdrawal	High	Low	Low	Moderate	Moderate	Low to moderate	Low to moderate
Time to induction	Typically 24-72 hours but sometimes as long as a week	A few days to a week	A few days to weeks	Hours	Hours to days	1 Week of SROM then 24 hours wait to start buprenorphine/ naloxone SL	Days
Ease of use	Difficult	Moderate	Easy	Moderate	Moderate	Moderate	Moderate
Need for withdrawal during induction	Yes	No	No	No	No	Yes	No
Cost	Inexpensive	Inexpensive	Expensive due to high cost of patches	Inexpensive	Expensive due to cost of fentanyl patches	Expensive due to high cost of SROM	Slightly expensive for 4 days of SROM
Additional concerns		Dividing tablets into small portions. Missed doses makes it difficult for titration of buprenorphine and tapering of methadone	Risk of diversion with buprenorphine patches		Risk of diversion of fentanyl patches if patient is not observed carefully	Risk of diversion if short-acting morphine is used during last leg of SROM transfer	Mostly used for illicit opioids

SL = sublingual, SROM = slow release oral morphine.

Summary: Approach to Treatment for Opioid Use Disorder





New options for opioid management

- Microdosing induction of buprenorphine
- Rapid microdosing induction of buprenorphine
- Slow-release oral morphine
- Monthly injection of buprenorphine extended-release (for patients on 8 to 24 mg of sublingual buprenorphine)
- Buprenorphine implant (for patient on less than 8 mg of SL buprenorphine)
- Injectable opioid agonist therapy (iOAT)



THE ASSASSIN OF YOUTH

THE PLANT



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STAMP IT OUT

SERVICE TRANSPER 5. Continuous regulation and efficient law on frequency.

IT IS A CRIME for any person to plant, cultivate, possess, sell or give away Marihurna.

it is frequently used by crimina's to bolster up their courage. Most dangerous of all is the person under the influence of warshuaza at the wheel of an automobile. Their illusions as to time and space destroy their judgment as to speed and distance. When eighty miles an hour seem only twenty, they often leave a trail of fatal accideces in their wake. A user of maribuana is a degenerate.

THE NARCOTIC LEAGUE OF AMERICA

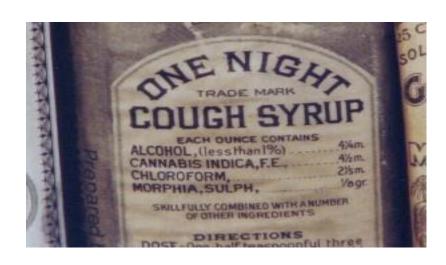
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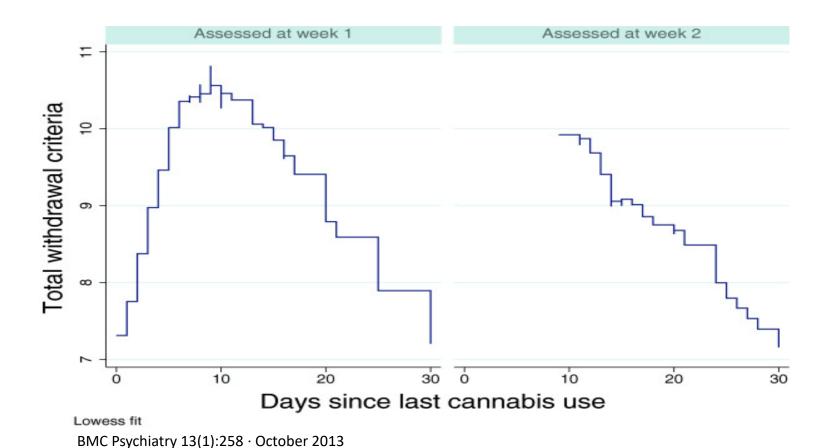
Cannabis Withdrawal

At least 3 of the following:

- Irritability, anger or aggression
- Nervousness or anxiety
- Sleep difficulty
- Decreased appetite or weight loss
- Restlessness
- Somatic symptoms causing significant discomfort
- Depressed mood



Cannabis Withdrawal Duration





Cannabis Treatment

- The cornerstone of treatment is behavioral (e.g MI, CBT, CM)
- Cannabinoid agonist (nabilone or nabiximols) can help reduce withdrawal, craving, and increase treatment retention.
- N-acetyl cysteine improves abstinence in youth but not adults



Cannabis Treatment

- Other agents such as gabapentin and quetiapine have some role in treatment
- Important to treat underlying psychiatric disorder (anxiety, depression)
- FAAH inhibitors and other endocannabinoid system modulator may hold great promise



Benzodiazepines and Hypnotics



How misuse of benzodiazepines, a common class of antianxiety medication, can lead to dependency

WENCY LEUNG > HEALTH REPORTER

TRENDING DAILY



Benzodiazepine

- Examples of benzodiazepine include: Xanax (alprazolam), Ativan (lorazepam), Valium (diazepam), and clonazepam.
- Long-term chronic benzodiazepine use is not indicated for anxiety disorder
- Indicated for short-term treatment of acute, severe episodes of anxiety (i.e flying)



Benzodiazepine

- Risks with long-term use include sedation, falls, sleep apnea, and dependence
- Withdrawal symptoms are similar to alcohol: anxiety, poor concentration, emotional lability, and sleep disturbance
- Abrupt cessation of high doses (>diazepam 50 mg or equivalent) can cause seizures, delirium, psychosis, and hypertension



Management of Benzodiazepine Withdrawal

- Substitution of long-acting benzodiaepine (e.g diazepam) followed by gradual taper
- Can take months to fully taper off
- Symptom relief may not be achieved until fully off benzodiazepines
- Gabapentinoids such as gabapentin or pregabalin are used to help with rebound anxiety.



Stimulants

MDMA (Ecstasy)

Methamphetamine (Crystal Meth)

Methylphenidate (Ritalin)

Cocaine

Methylphenidate (Ritalin)



Stimulants

- No currently first-line pharmacological approaches to stimulant use disorder
- Large body of evidence shows psychosocial interventions are effective in treating cocaine use disorder (De Giorgi 2018, Farronato 2012, Lussier 2006)
- Possible role for combining pharmacotherapy and psychotherapy
 - dopaminergic augmentation of contingency management (Pooling 2006)



Stimulants

Medications sometimes used include:

- Methylphenidate
- Modafinil
- Wellbutrin
- Topiramate
- Lisdexamfetamine
- Naltrexone
- Ketamine



ADHD and Stimulant Use Disorder

- Confirm ADHD diagnosis (and exclude withdrawal symptoms)
- Consider trial of methylphenidate ER or mixed amphetamine salts where benefits outweight harms
- Long-acting formulations probably have lower abuse potential than immediate-release



Tobacco

- Options: Nicotine replacement therapy (NRT), bupropion SR (Zyban), varenicline (Champix)
- NRT gum, lozenge, patch, inhaler, nasal spray. Relieves withdrawal symptoms and reduces harm caused by inhalation
- Bupropiron SR Increases dopamine amount, decreases cravings
- Varenicline- Nicotinic receptor partial agonist
- Combination of NRT with varenicline is the most effective but have greater adverse effects





Is Not Half So Soothing to

Mrs.
Winslow's
Soothing
Syrup

Baby as

OTHER'S

As Millions of Mothers
Will Tell You.

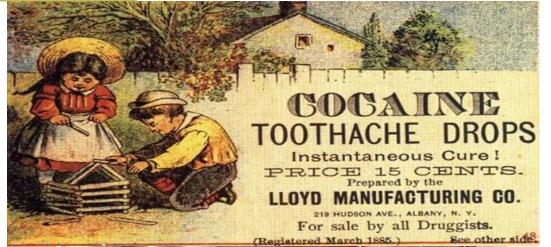
It Soothes the Child.
It Softens the Gums.
It Allays all Pain.
It Cures Wind Colic.
It is the Best Remedy for Diarrhoea.

It is absolutely harmless and for over sixty years has proved the best remedy for children while teething.

BE SURE YOU ASK FOR

Mrs. Winslow's Soothing Syrup







Thank You



"I'm finally learning how to relax. Unfortunately, relaxation makes me tense."



Resources

• Center for Effective practice:

https://cep.health/clinical-products/alcohol-use-disorder/

Meta:phi

https://www.metaphi.ca/assets/documents/provider%20tools/RAAM_BestPractices.pdf

