Substance Use Disorders

RC Rounds Dr. A Jewett

MCQ

- Which of the following is not a name for cannabis?
  - Dagga
  - Weed
  - Skunk
  - Boom
  - Gangster
  - None of the above

MCQ

- Which of the following does NOT have a withdrawal syndrome in the DSM V associated with use?
  - Cannabis
  - Cocaine
  - Ketamine
  - Amphetamines

MCQ

- 16 year old boy with NFA presents with nystagmus, slurred speech, lethargy, and a perioral rash. Intoxication with which substance do you suspect is causing his symptoms?
  - PCP
  - Ketamine
  - Inhalant
  - Alcohol

MCQ

- Which one of the following factors is the strongest predictor of developing a substance use disorder in late adolescence and young adulthood?
  - Temperament
  - Delinquent Behavior
  - Genetic predisposition
  - Past use of substances
  - Education level

Substance Use Disorder

- Common risk factor = behavioral disinhibition – highly heritable general propensity to not constrain behavior in socially acceptable ways, take dangerous risks
- No w/d in PCP, hallucinogens, or inhalants
- When thinking any SUD →
  - Impaired control = take more, want to stop, spend lots of time on it, daily activity, craving
  - Social impairment = work, school, home, use even though its causing problems, give up activities, withdraw from family
  - Risky use = physically hazardous, use even when problems, can't abstain
  - Pharm = tolerance and withdrawal – don't need these to dx, and don't use if on for prescribed reason

"crsp"

- **No withdrawal symptoms in PCP, hallucinogen use disorder, or inhalant use disorder**
- **Impaired control**
  - Take it in larger amounts or over longer period than intended
  - Persistent desire to cut down or regulate it but unsuccessful
  - Great deal of time obtaining it, using it, recovering from it
  - Virtually all daily activities revolve around it
  - Intense desire or urge for it** (important – **current craving often used as treatment outcome measure because may be a signal of impending relapse**)
- **Social impairment**
  - Failure to fulfill obligations at work, school, home
  - May continue despite problems
  - Important social, occupational or recreational activities may be given up or reduced
  - May withdraw from family and activities
- **Risky use**
  - Using when physically hazardous
  - May continue using even when they have a physical or psychological problem created by the substance
  - Failure to abstain despite difficulty it is causing
- **Pharmacological criteria**
  - Tolerance – need more to get effect
  - Withdrawal – decline after heavy use
  - Neither tolerance nor withdrawal necessary for a diagnosis of use disorder, but associated with more severe clinical course
  - Not counted when diagnosing a use disorder with prescribed medications – erroneous diagnosis of addiction
- **Severity depends on number of symptoms**
- **Acute intoxication has different presentation than chronic** (ie. Moderate cocaine doses may initially produce gregariousness, but social withdrawal may develop if chronic)
- Routes with **rapid absorption into blood stream** – IV, smoking, snorting – tend to result in more intense intoxication and increased likelihood of escalating pattern of use leading to withdrawal, same w rapid acting substances
- **Short acting > long acting**
- **18-24 has high rates for virtually every substance – first intoxication and then use disorder**

Caffeine

- Intoxication:
  - Recent consumption of caffeine **(high dose well in excess of 250 mg)**
  - Five or more of the following: **restlessness, nervousness, excitement, insomnia, flushed face, diuresis, GI disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrythmia, periods of inexhaustibility, psychomotor agitation**
  - Significant distress or impairment, not another disorder or substance
- **Not just coffee** – tea, soda, energy drinks, OTC analgesics and cold remedies, chocolate, weight loss aids, additive to vitamins and food products
- 85% of children and adults consume caffeine regularly
- **Data is not available at this time to demonstrate significance of a caffeine use disorder;** intoxication and withdrawal are relevant
- The above can occur at lower doses (200 mg) in elderly, children, unexposed
- > 1 g per day – muscle twitching, rambling speech, cardiac arrythmia, psychomotor agitation
- Mild sensory disturbances → ringing in the ears, flashes of light
- **Smaller doses can lower heart rate (high doses elevate)**
- Increased bowel motility
- **Half life caffeine 4-6 hours,** usually remit in first day without lasting consequences
- Doses 5-10 g can be lethal, grand mal seizures and respiratory failure
- **OCPs significantly decrease the elimination of caffeine and consequently may increase the risk of intoxication**
- Can cause **anxiety disorders, sleep disorders**
- Comorbid in depressive disorders, bipolar disorders, eating disorders, psychotic disorders, sleep disorders, and SUDs (anxiety disorders may avoid it)
- Withdrawal:
  - Prolonged daily use, abrupt cessation followed within **24 hrs by three or more of the following: headache, fatigue or drowsiness, dysphoric mood/irritability, difficulty concentrating, flu like sx (N, V, muscle pain)**
  - **Headache is hallmark** feature – may be diffuse, gradual, throbbing, severe, sensitive to movement
  - Impaired behavioral and cognitive performance, on EEG increases in theta power and decreases in beta 2 power
  - When stopping caffeine, more than **50%** will get headache, 70% have at least one symptom
  - Usually 12-24 hours after last caffeine dose, peak in 1-2 days; sx last 2-9 days with headaches up to 21 days; usually **remit rapidly w caffeine (30-60 min)**

Cannabis

- Cannabis acts of **CB1 and CB2 cannabinoid receptors in the CNS**; endogenous ligands behave like neurotransmitters
- Steady **increase in potency of cannabis has been observed (increased THC from 1% in some strains to 15%)**
- Do see tolerance and withdrawal; tolerance often lost when cannabis discontinued for at least several mo
- **Withdrawal syndrome new to DSM V → irritability, anger, aggression, anxiety, depressed mood, restlessness, sleep difficulty, decreased appetite or weight loss**
- Signs of use → red eyes, cannabis odor, yellowing of fingertips, chronic cough, burning of incense, exaggerated craving and impulse for specific foods, sometimes at unusual times of the day and night
- Cannabinoids are the most widely used illicit psychoactive substance in the US
- 3.4% in 12-17 year olds, 1.5% in 18 or older
- **More in males than females**
- Rates highest in 18-29 year olds at 4.4%, decreases with age (0.01% at over 65)
- Cannabis, along with alcohol and tobacco, is traditionally the first substance that adolescents try
- Many perceive it as less harmful than ETOH or tobacco, and **perception contributes to increased use**
- Also results in **less behavioral and cognitive dysfunction than ETOH** → used in more diverse situations, can use throughout day, more likely to cause cannabis use disorder
- **Early onset of cannabis use (prior to age 15) is a robust predictor of the development of cannabis use disorder and other types of SUD and mental disorders of young adulthood → related to conduct disorder, psychosis**
- Risk factors → conduct disorder, high behavioral disinhibition, externalizing or internalizing disorders in childhood, academic failure, tobacco smoking, unstable family situation, use of cannabis among family members, fam hx SUD, low SES, ease of availability, 30-80% variance is genetic
- **Cannabinoids are fat soluble = persist in bodily fluids for a long time, excreted slowly**

Cannabis

- Do see cognitive dysfunction, amotivational syndrome (reduction in prosocial goal directed activity)
- **High levels of carcinogenic compounds**
- **Gateway → individuals who frequently use cannabis have a much greater lifetime probability than nonusers of using opioids or cocaine**
- Associated with poorer life satisfaction, increased mental health tx and hospitalization, higher rates of depression, anxiety disorders, suicide attempts, conduct disorder
- **Increased rates of alcohol use disorder (over 50%) and tobacco use disorder (53%)**
- Among those **seeking tx for cannabis use disorder – 74% report problematic use of another substance, alcohol most common**
- **MDD in 11%, anxiety 24% bipolar I in 13%, antisocial 30%, OCPD 19%, paranoid PD 18%**
- **Most significant medical effects in respiratory system – bronchitis, sputum, SOB, wheezing**
- Intoxication = recent use of cannabis, **impaired motor coordination**, euphoria, anxiety, **sensation of slowed time**, impaired judgment, social withdrawal, signs = conjunctival injection, increased appetite, **dry mouth**, tachycardia; specify with perceptual disturbances – **hallucinations with INTACT reality testing** (if not intact, consider cannabis induced psychotic disorder)
- Develop within **2 hrs of cannabis use, last 3-4 hours**, duration longer when oral, **may persist or recur for 12-24 hrs because of slow release from fatty tissue**
- Withdrawal = previous heavy and prolonged use (daily over a period of months), irritability, anger, aggression, nervousness, anxiety, sleep difficulty, insomnia, disturbing dreams, decreased appetite, weight loss, restlessness, depressed mood, abdo pain, shakiness, sweating, fever, chills, headache
- Occurs in 50-95% of heavy users
- Onset in 24-72 hours, peak within first week, last 1-2 weeks; **sleep difficulties x 30 days**
- **More common and severe among adults**
- **Cannabis induced psychotic disorder, anxiety disorder, sleep disorder, delirium**

Hallucinogens

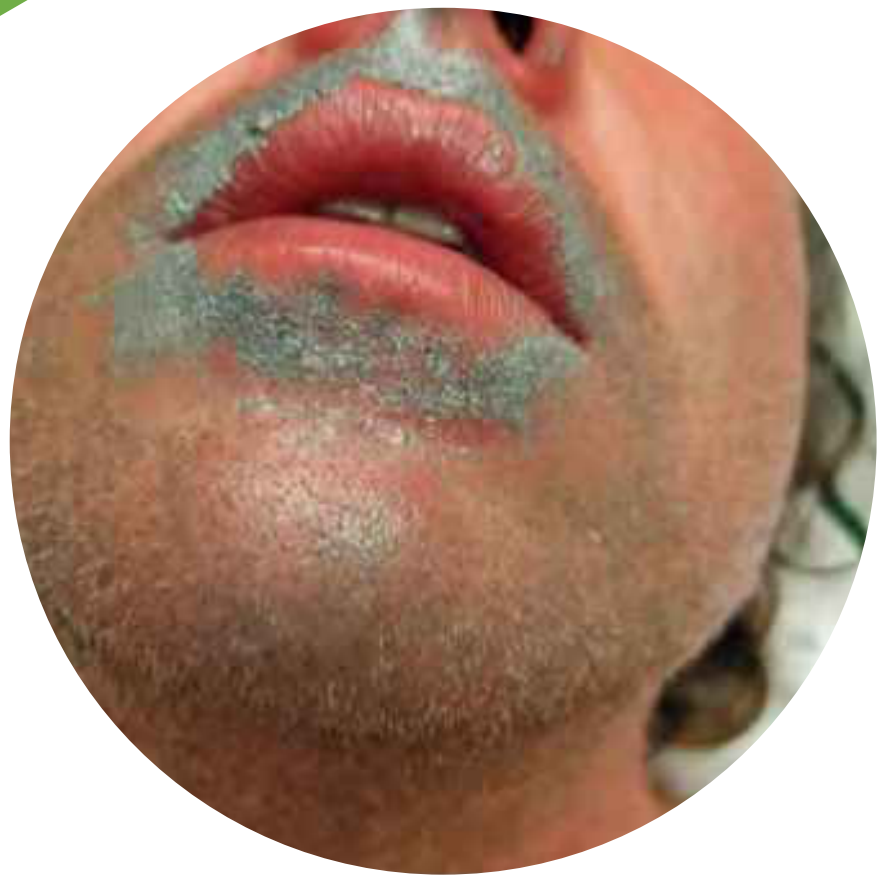
- PCP, ketamine, LSD, mescaline, MDMA, ecstasy, psilocybin, DMT, morning glory, salvia, jimsonweed
- Hallucinogen related disorders = PCP use disorder, other hallucinogen use disorder, PCP intoxication, other hallucinogen intoxication, hallucinogen persisting perception disorder, other PCP or hallucinogen induced disorders, unspecified **NOTE – no withdrawal**
- PCP = angel dust, similar compounds like ketamine, cyclohexamine, dizocilpine
- **Dissociative anesthetics to street drugs**
- Feelings of separation from mind and body (dissociation) at low doses; at high doses stupor and coma
- Usually smoked or oral, but can be snorted or injected
- **Primary psychoactive effects of PCP last a few hours, but total elimination rate is 8 days or longer – hallucinogenic effects may last for weeks and precipitate a persistent psychotic episode resembling scz**
- PCP can be detected in urine for up to **8 days or longer**
- Produces **dissociative symptoms, analgesia, nystagmus, HTN, violent behavior, can get hypotension and shock**
- 2.5% of the population has used phencyclidine, **ketamine more in whites, PCP predominantly black or Hispanic**
- **Males more than F**
- Chronic use of phencyclidine may lead to deficits in memory, speech, cognition that may las for mo; can get seizures, dystonias, dyskinesias, catalepsy, hypothermia, hyperthermia, ICH, rhabdomyolysis, resp problems, and cardiac arrest
- Hallucinogens usually orally but sometimes smoke, rarely taken intranasally or by injection
- Tolerance develops with repeated use and has autonomic and psychological effects; **some cross tolerance between LSD and other hallucinogens**
- **MDMA unique → hallucinogen and stimulant**, is evidence of **withdrawal in MDMA alone (depression, lethargy)**
- Other hallucinogen use disorder is one of the rarest 0.6% in 18-29 years, decreasing to 0 in over 45
- Unclear if association with early age at onset with elevation for use disorder, ecstasy most risky
- **Other hallucinogen use disorder – low incidence, low persistence, high rates of recovery**
- Evidence for **long term neurotoxic effects of MDMA/ecstasy use** → impairments in memory, psychological function, neuroendocrine function, serotonin system dysfunction, sleep disturbance, adverse effects on **brain microvasculature**, white matter maturation, damage to axons, diminished functional connectivity
- **Increased rates of mental disorders, particularly with use of ecstasy and salvia**

Hallucinogens

- **PCP Intoxication** high yield for exam
  - **Within 1 hr**
  - **Vertical or horizontal nystagmus**
  - **HTN or tachycardia**
  - **Numbness of diminished responsiveness to pain**
  - **Ataxia**
  - **Dysarthria**
  - **Muscle rigidity**
  - **Seizures or coma**
  - **Hyperacusis**
- **Can get catatonic like syndrome, lasts for several hours, but may last several days or longer, detected for up to 8 days in urine**
- **Note – not diaphoresis, in fact more likely flushed, red skin as in anticholinergic syndrome**
- **REDDANES: rage, erythema (of skin), dilated pupils, delusions, amnesia, nystagmus, excitation, skin dryness**
- Other hallucinogen intoxication:
  - Marked anxiety or depression, IOR, fear of losing ones mind, paranoid ideation, impaired judgment, depersonalization, intensification of perceptions, derealization, illusions, hallucinations, synesthesia
  - **Pupillary dilation, tachycardia, SWEATING, palpitations, blurring of vision, tremors, incoordination**
- **Hallucinogen persisting perception disorder**
  - Following cessation of use of a hallucinogen, the re-experiencing of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (ie. Geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia and micropsia) → cause distress and impairment, not from medical issues (epilepsies, brain lesion, NCD, scz)
  - **Re-experiencing while sober**
  - Can be episodic or continuous
  - **May last weeks, months, years, primarily after LSD, not related to number of occasions of use – can occur with minimal exposure**
  - **May be triggered by other substances (ie. Cannabis or alcohol) or in adaptation to dark environments**
  - Reality testing remains intact, prevalence **4.2%** in hallucinogen users
  - Associated with **panic disorder, alcohol use disorder, MDD**
- Other Phencyclidine induced disorders – **psychotic disorder, bipolar disorder, depressive disorder, anxiety disorder, delirium**
- Other hallucinogen induced disorders – psychotic disorder, bipolar disorder, depressive disorder, anxiety disorder, delirium

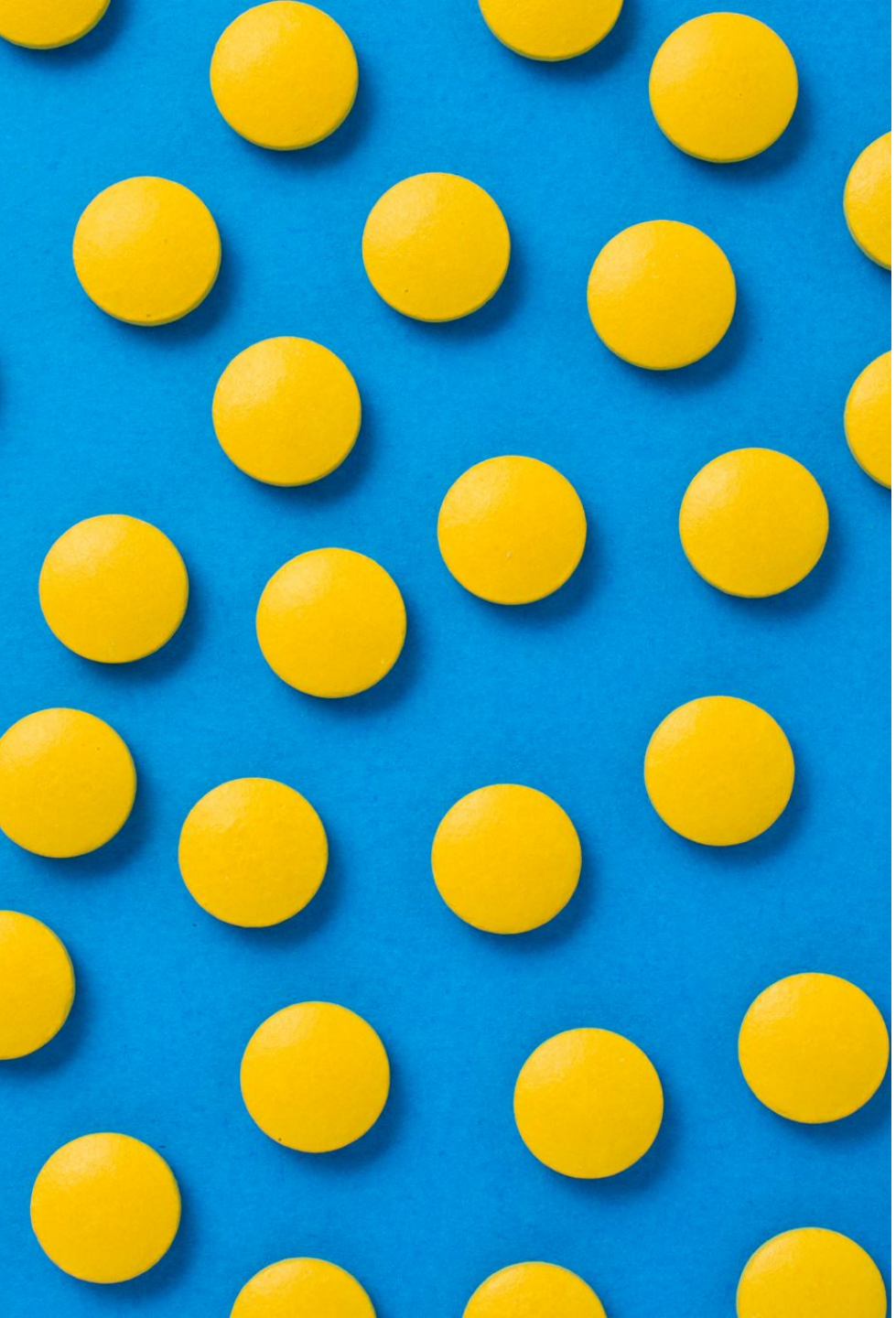
Inhalants

- Problematic pattern of use of a hydrocarbon based inhalant substance
- Volatile hydrocarbons = toxic gases from **glues, fuels, paints, toluene**
- NO, amyl-, butyl-, isobutl-nitrite other substance use disorder
- **No withdrawal syndrome, mild; tolerance in 10%**
- Supported by recurring episodes of intoxication with **negative results in standard drug screens** which do not detect inhalants, possession or lingering odors of inhalant substances, **peri-oral or peri-nasal glue sniffers rash**, paraphernalia, homeless children, medical complications (**white matter pathology**, rhabdomyolysis)
- Associated with **past suicide attempts**, especially if prev episodes of low mood or anhedonia
- 0.4% of **12-17 year olds**, but used in 10% of 13 year old children at least once
- Can be deaths – sudden sniffing deaths – **cardiac arrhythmia,** not dose related and can occur on first exposure
- Typically remits after adolescence – if persists, associated with severe problems, SUDs, ASPD, **suicide attempts**
- **Prevalence in M=F in adolescence**, very rare in adult females
- Long term users at risk for TB, HIV/AIDS, STIs, depression, anxiety, bronchitis, asthma, sinusitis
- Deaths from respiratory depression, arrythmias, asphyxiation, aspiration of vomit, or accident and injury
- Intoxication = **belligerence, assaultiveness, apathy, impaired judgment, dizziness, nystagmus, incoordination, slurred speech, unsteady gait, lethargy, depressed reflexes, psychomotor retardation, tremor, generalized muscle weakness, blurred vision or diplopia, stupor or coma, euphoria**
- Intoxication lasts **minutes to hours**
- Inhalant induced psychotic disorder, depressive disorder, anxiety disorder, **NCD,** delirium



Sedative, Hypnotic, or Anxiolytic

- Include benzos, benzo-like drugs (zolpidem, zaleplon), carbamates, barbiturates
- **Not nonbenzo antianxiety agents like buspar – not associated with misuse**
- Very significant levels of tolerance and withdrawal can develop
- Often associated with alcohol, cannabis, opioid, and stimulant use disorders
- **Tolerance to brainstem depressant effects develops much more slowly**, and as the individual takes more substance to achieve euphoria or other desired effects, there may be a sudden onset of respiratory depression or hypotension, which may result in death
- Can also be associated with **severe depression that can lead to suicide**
- Greatest in 18-29 year olds (0.5%), lowest in 65 and up (0.04%), males>F in adults, F>M in 12-17 year olds (0.4%)
- **As increase in age – cognitive impairment increases, metabolism decreases, both acute and chronic toxic effects increases (cognition, memory, motor coordination), can look like a progressive dementia in elderly**
- **If neurocognitive disorder present – more likely to have intoxication and impaired function at low doses**
- Can be seen in 40s and older with people who escalate dose of prescribed medications; in youth, more to get a high
- **Females at higher risk for prescription drug misuse**
- On exam – disinhibition, confusion, slower pulse, decreased respiratory rate, slight drop in BP
- High doses can be lethal especially if mixed with alcohol
- Intoxication = inappropriate sexual or aggressive behavior, mood lability, impaired judgment, slurred speech, incoordination, unsteady gait, nystagmus, impairment in cognition (attention, memory), stupor or coma
- Anterograde amnesia – like blackouts
- Withdrawal within hrs to days → autonomic hyperactivity (sweating, pulse over 100 bpm), hand tremor, insomnia, nausea and vomiting, transient visual, tactile or auditory hallucinations or illusions, psychomotor agitation, anxiety, grand mal seizures; with perceptual disturbances if reality testing intact
- If shorter acting, rapidly absorbed substances like triazolam – can begin within hrs; long acting like diazepam may be 1-2 days later
- Delirium can be life-threatening
- **LOT (10 hrs or less) – withdrawal symptoms in 6-8 hours, peak on second day, improve by 4-5th day**
- If diazepam, symptoms may not develop for 1 week, peak at second week, and decrease during 3-4th week
- May be additional longer term symptoms at a much lower level of intensity that persist for several months
- Usually higher doses, long term use; but reported even at 15 mg diazepam daily for several mo
- Can cause psychotic disorder, bipolar disorder, depressive disorder, anxiety disorder, **sleep disorder, sexual dysfunction**, neurocognitive disorder, delirium

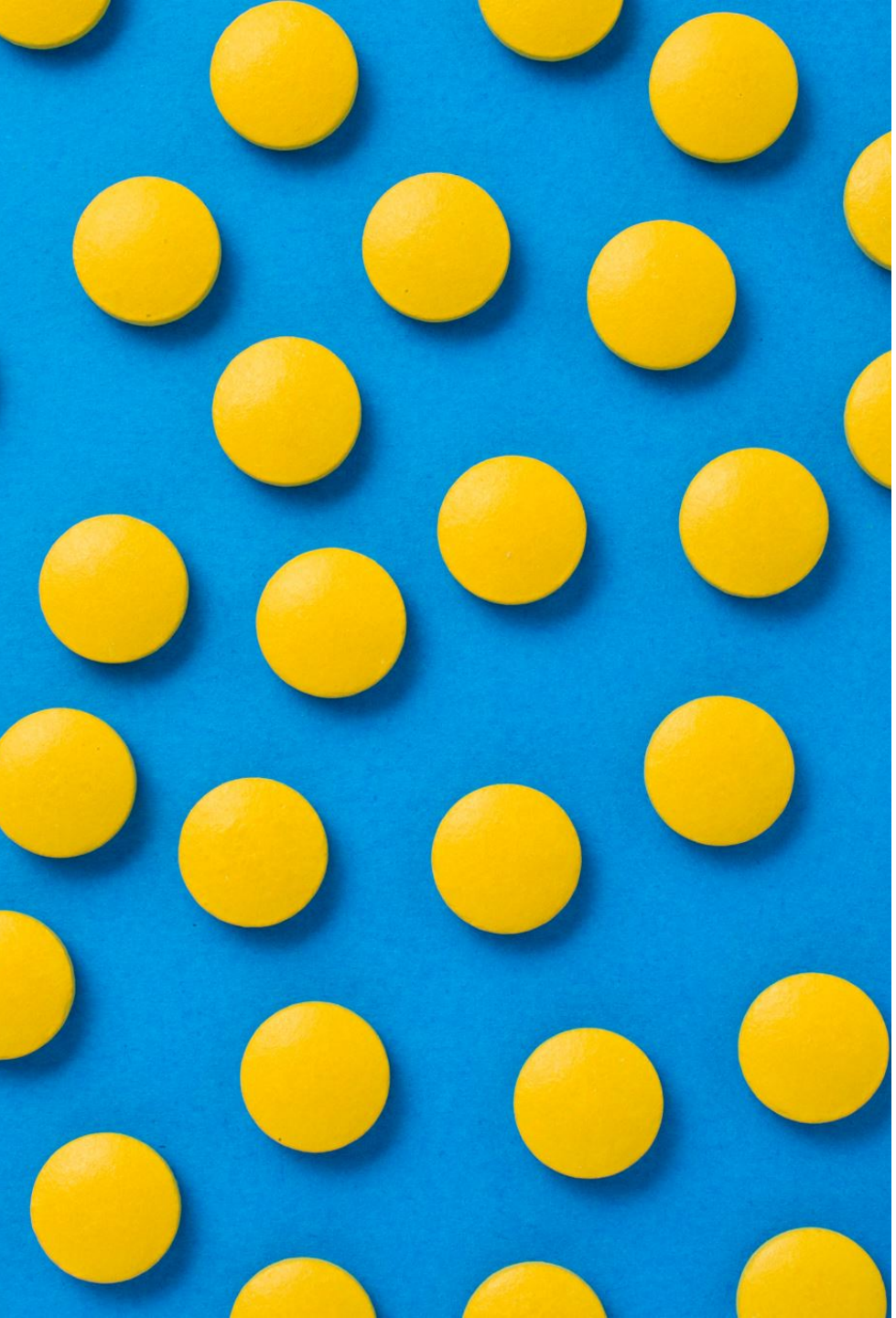


Stimulants

- Stimulants → amphetamine, dextroamphetamine, methamphetamine, methylphenidate, **khat** (plant derived)
- **Cocaine** – coca leaves, paste, freebase, crack, powder
- Oral, IV, or nasal
- **Stimulants can cause use disorder as rapidly as one week**
- Withdrawal = hypersomnia, **increased appetite**, dysphoria, intense depressive sx that resolve within 1 week, disturbances in attention and concentration, emotional lability, irritability, SI, bradycardia
- Psychoactive and sympathomimetic effects in intoxication
- **Amphetamine longer than cocaine, used less x per day**
- Can have chronic or episodic use
- Aggressive or violent behavior is common when high doses are smoked, ingested, or administered IV
- Can also see intense temporary anxiety and paranoid ideation and psychotic episodes
- Intoxication = rambling speech, headache, IOR, tinnitus, paranoia, AH in clear sensorium, tactile hallucinations, threats, aggression

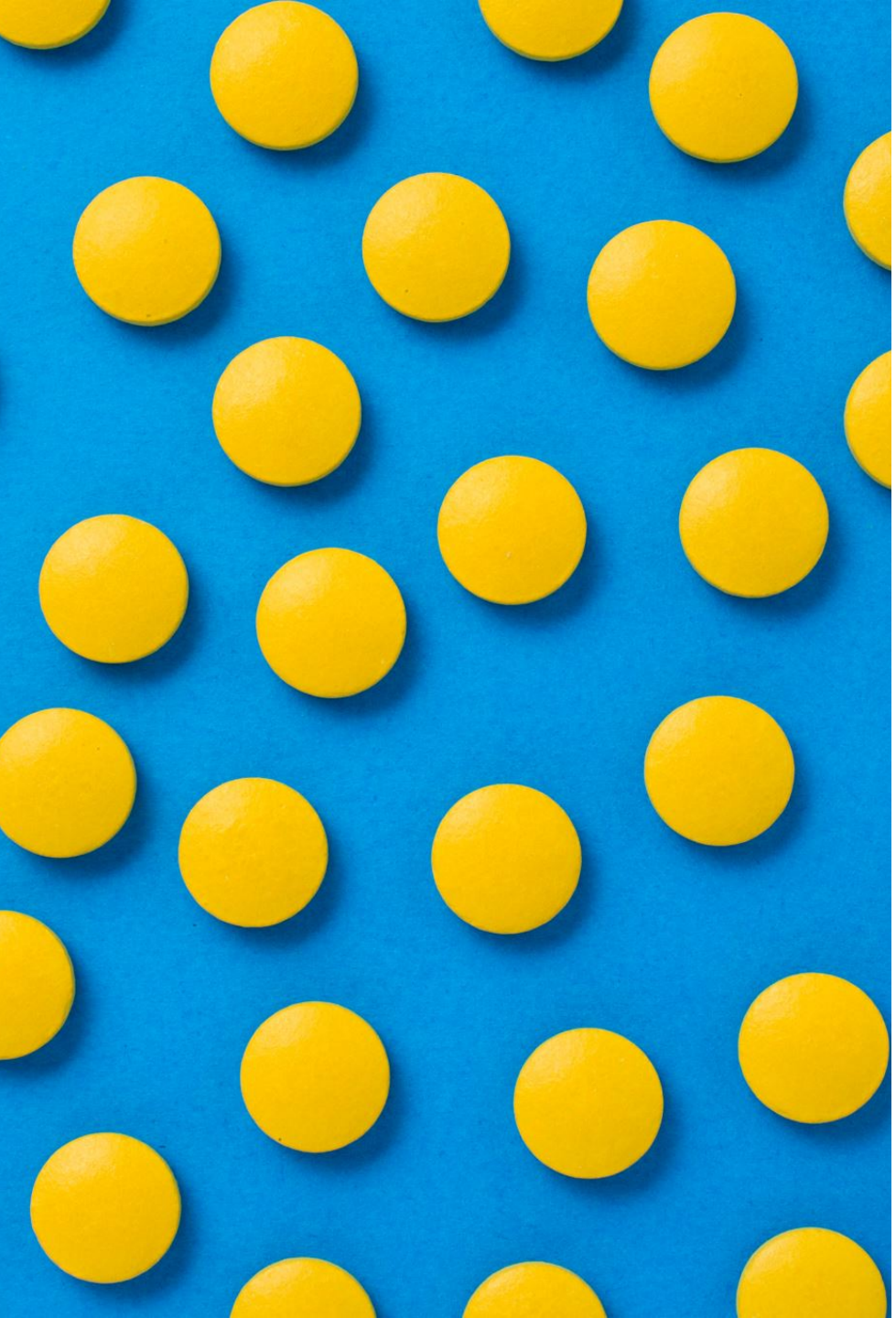
Stimulants

- **Amphetamine type = 0.2%, M=F (but adolescent F>M)**, IV M>F, non-prescribed use in 5-35% of college students
- **Cocaine type = 0.3%, more M than F**
- **First regular use usually around age 12**, meth tx admissions age 31
- Episodic use tends to be separated by 2 or more days of non use, binges (high dose use continually over hours to days)
- With continuing use, there is a **diminution of pleasurable effects due to tolerance and an increase in dysphoric effects**
- **Comorbid bipolar, scz, ASPD, other SUDs** are risk factors for development of stimulant use disorder
- Predictors of use in teens = **prenatal cocaine exposure**, postnatal cocaine use by parents, and exposure to community violence during childhood; for youths, living in an unstable home, having a psychiatric condition, associating with dealers and users
- Chronic use of cocaine impairs cardiac L ventricular function in African Americans
- **Benzoylecgonine – metabolite of cocaine – remains in urine for 1-3 days after a single dose, and may be present for 7-12 days for individuals w high doses**
- Mild elevation in LFTs if cocaine injectors or concomitant ETOH
- **Chronic cocaine – alterations in secretion patterns of prolactin**, **downregulation of dopamine receptors**
- Short half life amphetamine type stimulants (**MDMA, meth) – detected for 1-3 days,** up to 4; hair samples up to 90 d



Stimulants

- Intranasal users can get sinusitis, irritation, bleeding of nasal mucosa, perforated septum
- Smokers – respiratory problems
- Injectors – tracks and abscesses
- Risk of HIV with IV, hepatitis, TB,
- **Weight loss and malnutrition common**
- **Chest pain is common symptom in intoxication** → MI, palpitations, arrhythmias, sudden death from respiratory or cardiac arrest, stroke, seizures
- **Pneumothorax from performing Valsalva** to better absorb smoke
- **Cocaine use associated with irregularities in placental blood flow, abruption, premature labor and delivery, infants with very low birth weights**
- **Neurocognitive impairment common in meth users, meth mouth** (gum disease, tooth decay, mouth sores – toxic smoking and bruxism)
- **Cocaine users often use ETOH, amphetamine users often use cannabis**
- Cocaine users who ingest cocaine cut with l**evamisole – antimicrobial and vet medicine – may experience agranulocytosis and febrile neutropenia**



Stimulants

- Intoxication:
  - Euphoria, affective blunting, changes in sociability, hypervigilance, interpersonal sensitivity, anxiety, tension, anger, stereotyped behaviors, impaired judgment
  - Tachycardia or bradycardia, pupillary dilation, elevated or lowered BP, perspiration or chills, N or V, evidence of weight loss, psychomotor agitation or retardation, muscular weakness, respiratory depression, chest pain, cardiac arrythmias, confusion, seizures, dyskinesias, dystonias, or coma
  - **Chronic use = sadness, bradycardia, decreased BP, decreased psychomotor activity**
- Withdrawal:
  - Within a few hrs to several days
  - **DYSPHORIC MOOD and fatigue, vivid, unpleasant dreams**, insomnia, hypersomnia, **increased appetite**, psychomotor retardation or agitation
  - **Bradycardia is often present and is a reliable measure of stimulant withdrawal**
  - Anhedonia and drug craving can often be present but are not part of the diagnostic criteria
  - Crash often seen after binges, eating and sleeping
- Induced Disorders
  - Psychotic disorder, bipolar disorder, depressive disorder, anxiety disorder, OCD, sleep disorder, sexual dysfunction, delirium

Tobacco

- On maintenance therapy = bupropion, varenicline, NRT
- **Tolerance = disappearance of nausea and dizziness after repeated intake and more intense effect of of tobacco the first time it is used in a day**
- Craving when they do not smoke for more than a few hours
- Smoking within 30 min of waking, daily, waking at night to smoke = use disorder
- **Serious medical conditions – lung and other cancers, cardiac and pulmonary disease, perinatal problems, cough, SOB, accelerated skin aging**
- 21% of US current smokers, 22% former smokers; use disorder 13% in adults, similar among males and females, decline from 17% to 4% with age
- **In developing nations, much greater smoking in males than females; females later on in life**
- More than 80% of users try to quit, 60% relapse in 1 week, 5% remain abstinent for life
- Most individuals try many times, so eventually ½ abstain, usually after age 30
- **Risks: externalizing personality traits, ADHD, conduct disorder, psychiatric disorders, low incomes, low education, 50% heritability**
- African American males tend to have higher nicotine blood levels for a given number of cigarettes – greater difficulty quitting
- **50% of smokers who do not quit will die from a tobacco related illness; smoking related morbidity in more than 1/2 of all users**
- Usually from exposure to CO, tars, non-nicotine content
- **Major predictor of reversibility is duration of smoking**
- **Second hand smoke increases risk of heart disease and cancer by 30%**
- Long term use of nicotine medications does not appear to cause medical harm
- Most common medical diseases are **CV illnesses, COPD, cancer**
- Also perinatal problems – low birth weight, miscarriage
- Nicotine dependent smokers are **2.7-8 x more likely to have psychiatric disorders** than non-dependent smokers or never smokers
- **Withdrawal within 24 hr**s = irritability, frustration, anger, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, **insomnia (50%),** peaks at 2– days, **lasts 2-3 weeks**
- Withdrawal much more intense from cigarettes or chew than nicotine meds (rapid onset and higher levels of nicotine with cigarette smoking)
- Heart rate decreases by 5-12 bpm in first few days and **weight increases 4-7 lbs in first year after stopping** smoking
- Withdrawal can **cause craving for sugary foods**, impaired vigilance, constipation, coughing, dizziness, dreaming, nightmares, nausea, sore throat
- Quitting can increase blood levels of medications (ie. Clozapine)

Other

- Includes anabolic steroids, NSAIDs, cortisol, anti-Parkinsonian drugs, antihistamines, NO, nitrites, betel nut (chewed – euphoria and floating sensation), kava (pepper plant - sedation, incoordination, weight loss, mild hepatics, lung abnormalities), cathinones (including khat plant agents that act like stimulants)
- **NO** used in medical and dental professionals, food service workers
- Whippet cartridges in whipped cream dispensers – up to 240 per day, adolescents
- Can cause **myeloneuropathy, spinal cord subacute combined degeneration, peripheral neuropathy and psychosis**
- Nitrite gases used in **homosexual men and adolescents with conduct disorder**
- **MPTP – contaminating by product in the synthesis of a certain opioid - kills dopaminergic cells and induces permanent parkinsonism in users who sough opioid intoxication**

Gambling

Persistent and recurrent problematic gambling behavior leading to clinically significant impairment or distress as indicated by the individual exhibiting four or more of the following in a 12 mo period:

- Needs to gamble with increasing amounts of money in order to achieve the desired excitement
- Is restless or irritable when attempting to cut down or stop gambling
- Has made repeated unsuccessful efforts to control, cut back, or stop gambling
- Is often preoccupied with gambling (persistent thoughts of reliving past experiences, handicapping or planning the next venture, thinking of ways to get money to gamble with)
- Often gambles when feeling distressed (helpless, guilty, anxious, and depressed)
- After losing money gambling, often returns another day to get even (chasing losses)
- Lies to conceal the extent of involvement with gambling
- Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling
- Relies on others to provide money to relieve desperate financial situations caused by gambling

Not in the context of a manic episode

Specify – episodic or persistent, early remission (3-12 mo), sustained remission (more than 12 mo)

Tidbits:

- Can see denial, superstitions, a sense of power and control over the outcome of chance events, overconfidence
- May be impulsive, competitive, energetic, restless, easily bored, overly concerned with approval of others, may be generous to extravagance when winning; others may be depressed and lonely
- **50% have SI, 17% have attempted**
- 0.2-0.3% in population in past year, lifetime **0.4-1%**
- **Progression of disorder is more rapid in females than in males**
- Does not depend on amount of money wagered or frequency but above criteria
- Early expression is more common in males – associated with impulsivity and substance abuse, most grow out of the disorder
- **Mid and later life onset of gambling disorder more in females, more slot machines and bingo gambling rather than sports betting, cards, horse races**
- **Females more likely to have depressive, bipolar, or anxiety disorders;** seek treatment sooner (but still tx seeking low – less than 10%)

APA SUD Guidelines

- **Nicotine use disorders – five NRTs (patch, gum, spray, lozenge, inhaler) and bupropion – all first line;** CBT, behavioral therapy, brief intervention, **not 12 step**
- MJ – no strong evidence
- Cocaine **– CBT, behavioral therapies, 12 step, no pharm have indications** (topiramate, disulfiram, modafinil may be promising), acutely can use **benzos**

Lower Risk Cannabis Use Guidelines 2017

- Most effective way to avoid risks is abstain from use
- Early initiation, especially before age 16, multiple subsequent adverse health and social effects in young adult life, especially if intensive and frequent, affects developing brain, the later its started the better
- **High THC containing products have more negative outcomes**, use low THC content product, high CBD:THD ratios
- **Synthetic cannabinoids have more acute and severe adverse health effects, avoid**
- Regular inhalation of combusted cannabis affects respiratory health; avoid, if use, **use vaporizers or edibles**
- **Avoid practices such as deep inhalation, breath holding, or Valsalva maneuver** to increase absorption while smoking – disproportionately increase the intake of toxic material into the pulmonary system
- Frequent or intensive (daily) cannabis use is strongly associated with higher risks of experiencing adverse health and social outcomes related to cannabis use; **keep it occasional – one day per week, on weekend at most**
- Driving while impaired has increased risk of MVA, **refrain from driving for at least 6 hrs after using, should be avoided**
- Populations at high risk – **first degree family history of psychosis or SUDs, pregnant women – should avoid completely**

CPS Statement on Implications of Cannabis Legalization on Youth 2017

- Human brain undergoes maturational process in adolescence that includes reorganization refinements, and functional improvements
- **Driven by changes in brain grey matter due to synaptic pruning and white matter due to myelination**
- **Continue til the mid 20s**, brain maturation at this time is vulnerable to stressors/insults
- Endocannnabinoid system plays role in maturation, **exogenous cannabinoids can affect this in a negative way**
- Regular cannabis use in youth can affect cognition – attention, memory, processing speed, visuospatial functioning, and overall intelligence; worse performance related to earlier onset of use; **abstinence improves some but not all**
- **Early and regular use increases risk of developing primary psychotic illness in those who are vulnerable – childhood trauma and genetics**
- **In people with psychosis – continued cannabis worsens long term symptom and functional outcomes**
- **May increase risk of depression and early regular use associated with younger age of onset of symptoms of psychosis and bipolar disorder**
- **High THC content can result in significantly worse outcomes**
- Early age of use of cannabis increases potential for adult dependence to cannabis
- May be associated with increased progression to other illicit drug use in context of particular factors – high frequency, early age of use
- **Prenatal cannabis exposure may have adverse effects on cognitive development, behavior, and academic achievement in offspring**
- **Age of access to cannabis should not be prior to age 21 with restrictions on quantity and THC potency for between 21-25**
- Significant support needed for public health education and resources targeting youth
- Significant support of more research needed
- Expand support for prevention, early ID, and cannabis cessation treatments
- **Prudent consideration or advertising and marketing guidelines, with clear markings of THC content, consistent public health warning esp during pregnancy**

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- **1/5 Canadians meet criteria for SUDs in lifetime, most ETOH**
- **Comorbidities - MDD 32-54%, anxiety 36%, bipolar 56.1%, psychotic disorders 50%**
- War on drugs more enforcement, with **dramatic increases in incarceration rates but little change in drug tx**
- DSM IV → V – **added craving and removed legal requirement**, no longer abuse or dependence but rather use disorder
- Earlier you use a substance, the more likely to have a use disorder; **past use most predictive**
- Addiction → initially psychosocial factors most important – formative environment (parents, peers), self medication (abuse, anxiety), lower SES, early exposure to substance, male, younger age but when exposed to a substance, neurobiology takes over
- **Cocaine and amphetamine the best for activating dopamine in the brain (10% of initial users get persistent SUD compared to cannabis and alcohol where 10% of regular users develop persistent SUD)**
- Increased dose – increased addiction liability, mode of use – IV or smoked the highest reinforcing effect
- **What brain structure is responsible for identifying the salience of a substance? Nucleus Accumbens**
- Dopamine → mood, **reward experience and expectation (especially D3),** motivation and attention, memory salience (links SUD with cues, classic and operant conditioning)
- **Hallucinogens like LSD are primarily serotonergic – minimal persistence**
- Dopamine has a primary role in the development of SUD, **but less so in relapse and persistence of behavior**
- In rats, can make the pathway treacherous with electric shocks to get cocaine and they will happily do it because reward is so desirable to them
- **Dopamine receptors at least partially normalizes with sustained abstinence (14 mo) – why AA says to wait a year – wait for dopaminergic functioning to heal, dysphoria etc.**
- **Stress including anxiety and depression result in increased amygdala activity** (**CRF, NE**), cues activate glutamatergic pathways including prefrontal cortex leading to cascade effect (ie. Access to cash), **low dose or other substance use re-initiates use via D2/3 pathways** → paths to relapse

- **Alcohol 18.1% lifetime alcohol use disorder, 6.8% cannabis, 4% other, nicotine 13%**
- **Prior withdrawal severity best clue to what will happen in current withdrawal**
- Methadone long half life, very long withdrawal
- **Smoking is the primary preventable cause of premature death and disability**
- **Majority of patients with SUD die of tobacco related illness**
- High proportion of smokers have mental illness
- **Acts on nicotinic acetylcholine receptors widely distributed throughout the brain – alpha 4, alpha 5, beta 2**
- CYP 450 1A2 → clozapine and olanzapine → quit smoking and drug levels go up
- Half life of 2 hours therefore resolution of accumulation in 6-8 hrs
- Most smokers identify need to quit - need to address confidence and plans for quitting, rather than reasons to quit

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- **Withdrawal in 2-4 hrs, peaks at 24-48**
- Craving, restlessness, irritability, anxiety, depression, decreased concentration, increased appetite, vivid dreams
- **NRT doubles quit rate but still only 6%**
- **Bupropion 300 mg/d, varenicline 1 mg BID**
- **If high risk of depression, relapse – do bupropion or nortriptyline to stop smoking**
- **NRT has massive evidence base – avoid anything that changes pH in mouth (ie. Coffee) – oral absorption**
- **NRT subject to first pass metabolism – patch**
- **NRT is full agonist so requires complete cessation**
- NRT SE = localized skin reactions with patch, sleep disturbance, nausea, cardiovascular risk (no evidence), depression and suicide not reported as adverse effects
- **Bupropion**
  - Titrate to **150 mg po BID** in conjunction with counselling
  - Doubles the odds of quitting
  - MOA uncertain – weak inhibition of dopamine and noradrenaline reuptake augmenting NA neurotransmission
  - Non-competitive antagonism of nicotinic Ach receptors with the **alpha 3 beta 2** subtype being the most sensitive
  - Patients report varying subjective effects leading to smoking cessation – **loss of craving, cigarettes taste bad**
  - **May be preferred in depressed smokers** (nortriptyline and bupropion SR found to be effective in increasing long term cessation rates in those with a past hx of depression)
  - Side effects = sleep initiation and maintenance, especially with increased dose and afternoon dosing, dry mouth, nausea, seizures, psychosis and agitation, suicidality
  - **Contraindicated in patients with eating disorders and seizure history**
  - **Has been used safely and effectively in patients with schizophrenia**
- **Varenicline**
  - Dosing 0.5 mg po daily, then BID, then 1 mg po BID
  - **Highly selective and potent partial agonist of the NAchR alpha 4 beta 2 subtype** with weaker effect at other subtypes
  - Does have **increased cessation rates compared to bupropion**
  - Flexible self dosing beyond 12 weeks
  - Side effects = nausea, **depression and suicidality, - health Canada and FDA warning need to document**

- Peak use during late adolescence/early adulthood (15-25)
- 1/11 users develops SUD
- **Use dependent on perception of risk*,** tobacco use, parental and peer group factors, socioeconomic status, presence of mental disorder
- THC content much higher
- Few present for tx
- **Doubles rate of psychosis**
- Legalization – **bump in older age groups, youth rates tend not to change,** increases in unintentional overdoses in children, decreases in opioid overdose fatalities reported initially but then disappeared
- Acts via **CB1 (brain) and CB2 (immune system) G protein linked receptors** inhibiting adenyl cyclase
- **CB1 receptors mediate neuropsychiatric effects** = **basal ganglia and cerebellum (molecular layer) – movement**, hippocampus and cortex – memory, ventromedial striatum and nucleus accumbens – addiction liability
- Neurotransmitter effects = Ach – decreases activity esp in hippocampus, NMDA – inhibits, GAB – increases, dopamine – increases activity in striatum and mesolimbic tissues and stimulates release in NA via disinhibition of GABA tonic inhibition
- Acute/subacute from 48-72 hrs to 1 week – **impairment in verbal and visual memory, executive functioning, psychomotor speed, manual dexterity; severity of use correlates to deficits**
- **Evidence of persistent deficits in adolescent onset users even with abstinence**, but may be confounded; no evidence of long term deficits in adult onset users
- Intoxication = **slowed reaction time and info processing**, impaired perceptual-motor coordination (driving), impaired short term memory, slowed time perception, hallucinations at high doses, bloodshot eyes, munchies, giddiness, sedation, amotivational syndrome (lacks evidence), supportive management only
- **Possible role for NAC – current research in works**
- Withdrawal = primarily anxiety, decreased appetite, decreased sleep, generally mild, cognitive effects resolve with abstinence in 72 hours, supportive, no indicated/effective pharmacotherapies (ie. Nefazodone, mirtazapine, bupropion, nabilone) – helps with sleep and nabilone, maybe olanzapine in psychosis

Ottawa Review Course - **Cannabis** - Crockford

Ottawa Review Course – Sedatives - Crockford

- Benzos and barbs
- Potentiate GABA
- 10% of users become dependent
- Risks: history of addiction, PRN use, positive effect of substance, shorter half life
- Physiologic dependence develops **rapidly (2-4 weeks)**
- Taper off early if started to treat anxiety with an antidepressant
- Avoid regular use of sleeping pills – sleep hygiene best
- **2nd most common prescription drug dependence**
- **GHB** does not show up in drug screens – get it through gyms, ?physical enhancement, appear drunk
- **Intoxication – looks like ETOH, but you can give charcoal/lavage**
- Flumazenil IV → in textbooks but not often used as can cause seizures and arrythmias
- Similar sx in withdrawal – some protracted symptoms, rebound of prior symptoms
- **Last half of taper the hardest (10% per week as outpt, 10% per day as inpt), can add something else like gabapentin that modifies anxiety to finish taper**
- High risk of OD after detox
- **Weeks of anxiety and insomnia after stopping**
- Strategy like opioids except no clonidine – last ¼ consider anticonvulsants, SSRIs, trazodone

Cocaine:

Catecholamine **reuptake inhibitor**

More expensive than meth

Effect for 2-3 hrs

Crack = cocaine HCl and Na bicarbonate – able to be smoked

Free base IV

Cocaine powder v expensive, snorted

Amphetamines

Promote catecholamine release from the vesicle at VMAT2 receptor

Meth – approx. 5$ per point, smoked or IV

Effect for 6-8 hrs

Prescription amphetamines – oral, snorted

Designer ones – MDMA, mix of hallucinogen (serotonin) and amphetamine

Direct effect on DA pathway = **highest dependence liability**

Meth

More psychosis – more dopamine

Promotes release, and partially blocks reuptake of newly synthesized catecholamines in CNS

Bug hallucinations

Due to structural similarity – substitutes for dopamine transporter, noradrenaline transporter, serotonin transporter, vesicular monoamine transporter 2

Attenuate monoamine metabolism by inhibiting monoamine oxidase

Dopamine effects underlie the reinforcing properties and potential neurotoxicity

Glutamate damaging GABAergic interneurons in the cerebral cortex

Give benzo unless opiate use too – then olanzapine or risk resp depression

Intoxication = energy, alertness, euphoria, agitation, irritability, CV events, thought disorder

Different than scz which has more auditory hallucinations, clear sensorium, persistent symptoms, negative symptoms, bizarre delusions

ART = acceptance, reassurance, talk down (if not psychotic)

Beware antipsychotics – rhabdomyolysis

Withdrawal = rarely need hospitalization, see depression, inattention, **increased appetite, fatigue**, hypersomnolence, craving – supportive

Treatment – **residential superior to outpatient**, relapse prevention skills early, no current pharm options

Impulsivity significant

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- Hallucinogens – LSD, psilocybin, DMT, mescaline, bind to 5HT2 receptors acting as agonists or promote 5HT release, limited addiction potential, can get persisting flashbacks
- NMDA antagonists – PCP, Ketamine – dissociative, more E than W, agitation, delirium, **nystagmus** (vertical and horizontal), ataxia, delusions, hallucinations, muscle rigidity/posturing, seizures, coma, death → **do not try to talk down, use benzos over antipsychotics (rhabdo)**
- Inhalants – younger age group, poverty, paint thinner, anoxia plus direct effects of the volatile binding to cell membrane or associated compounds – rapid effect with amnesia, incoordination, euphoria, sedation, respiratory suppression, ataxia, coma, death, potential long term liver and brain toxicity
- Pramipexole can cause gambling disorder
- For screening – drug abuse screening test (DAST), ask about drugs, current use, amts, duration, routes, last use, consequences, previous treatment
- Urine tests
    - Amphetamines – **fast out of urine**, 48 hrs, lots of false positives
    - Cannabis – up to 1 mo if regular use, one week if one use
    - Hallucinogens typically not identified
    - Cocaine – parent drug 24-48 hrs, metabolites 72-96 hrs
    - Opioids and barbs depends on half-life of drug

Ottawa Review Course – Concurrent Disorders

Signs of a primary psychiatric disorder

- Psychiatric symptoms **predate substance use**
- Limited quantity of substance use
- Prominent **family history** of psychiatric disorders
- Persistent psychiatric symptoms with abstinence
- **Female**
- Full psychiatric disorder criteria met with typical features
- History of **good response to psychiatric treatments**
- History of **substance use treatment failures**

Consequences of comorbidity

- Decreased treatment adherence
- Decreased response and remission rates
- Increased risk of relapse to and decreased recovery
- Increased suicide risk
- Increased risky drug practices – IV
- **Worse overall social fxn**
- **Increased health care utilization**
- Problematic diagnosis
- Exclusion from tx

Concurrent Disorders

- **Current recommendations emphasize that concurrent substance use is not a barrier to depression tx**
- **Ideally period of 2 weeks should be sought to aid dx for best outcome**
- Efficacy of antidepressants for depressive sx similar for depressed outpatients with or without ETOH dependence, worse in drug dependence
- **Substance use minimally changed with depression tx → NEED SUD tx too**
- Depression tends to improve with abstinence alone in 2-4 weeks, if persists, likely underlying MDD – add antidepressant
- Psychoeducation – link sx and low mood to SUD, behavioral activation
- **Anxiety tends to persist and takes up to 1 yr to improve with abstinence**
- Emphasize panic monitoring, relaxation training, exposure therapy
- **Avoid benzos – trazodone, gabapentin, atypical antipsychotics, mirtazapine**
- Type A late onset alcoholics may benefit more
- SSRIs reduce depression and anxiety but minimal reduction in SUD unless robust response
- TCAs less safety, but greater responses in trials – SSRI studies typically added relapse prevention and CBT
- Venlafaxine has lack of controlled trials, similar to TCAs
- Bupropion – negative RCTs for SUD alone, agitating in patients with anxiety
- Benzos – rapidly effective, potential for abuse, do not cause depression, can cause psychomotor cognitive impairment

Concurrent Disorders

- In Bipolar disorder – manic like episodes due to stimulants or sedative withdrawal typically resolve within days without tx
  - Avoid antidepressants without mood stabilizer
  - VPA and Li first line (VPA may be better in SUDs)
  - Depression should be ongoing focus
  - **?citicoline for stimulant and bipolar use disorder**
  - Li is gold standard for Bipolar I with or without SUDs especially if family history of Bipolar, typical mania depression euthymia, lack of kidney, thyroid, heart disease – not effective alone for SUD, decreased suicide, tx both mania and depression
  - VPA may decrease relapse to heavy drinking, added benefit for bipolar patients when added to Li, good for mania, not so good for depression – rapid cycling, mixed presentations, no fam hx
  - Carbamazepine – some utility in ETOH withdrawal, liver toxicity problematic, 3rd line for bipolar
  - LTG – no benefit for SUD or concurrent bipolar and SUD
- **ADHD – atomoxetine likely preferred**
- **Stimulants treating ADHD do not increase future substance use but prob don't decrease it either**
- SCZ
  - SUD can trigger onset
  - **Best data for clozapine in SUDs**
  - If substance induced psychosis typically resolves within **10 days of detox alone – don't dose too high if not sure**
  - **Preliminary data for ziprasidone, quetiapine, abilify in SUDs**, mixed in olanzapine and risperidone, none for lurasidone or asenapine

Concurrent Disorders

- **Best outcomes occur when both disorders are treated simultaneously by the primary treating physician – sequential or parallel tx less effective**
- Treat psychiatric sx to full remission
- Tailor pharmacotherapy to target sx (sleep, anxiety, cravings, physical complaints)
- **Inquire about SUD and utilize brief interventions at each visit**
- Consider agents for sleep during withdrawal (ie. Trazodone, zopiclone)
- **Avoid confrontation and be empathetic**
- **Aim to help them shift one stage of change with each interaction**
- Psychoeducation – link symptoms to use
- CBT
- Avoid benzos
- Increase follow up care
- Involve family
- Follow UDS
- Goals of Tx:
  - Full remission of psychiatric disorder if present
  - Progressive reduction of SUD aiming for abstinence
  - Functional improvement
  - Retention in Tx – active intervention, relapse prevention
- Harm reduction
  - **Suboxone and methadone, differential taxation of ETOH, needle exchange, safe consumption sites**
  - Proven means to reduce societal harm
  - Provision of adequate care meeting a patients stage of change as part of a progressive and ongoing Tx strategy
  - **Recognize relapse as part of recovery – why OAT preferred over abstinence for opioid use disorders**
- Stepped care – least intrusive treatment modality of known effectiveness, match to severity of addiction and severity of co-morbidity
- SBIRT = screen, brief interventions, referral for treatment, pharmacotherapy
- Best data for **minimum involvement of 90 days**, behavior change takes 3 mo to be stably incorporated; **duration in treatment is best predictor of treatment outcome**
- **Concurrent disorders will require longer treatment times**
- **All patients completing residential tx require outpatient follow up care**
- **Patients with greatest substance use or co-morbidity severity benefit most inpatient/residential, stimulant users, prior suicide attempts, or current SI, requires removal from current environment, needs to be able to tolerate groups, unstable home environment or limited supports**
- Consider withdrawal potential, medical problems, psychiatric problems, motivation for change, relapse potential, recovery environment
- Detox alone does not alter addiction outcomes
- Self help groups (ie. AA, NA) – minimally intrusive, effective for those who attend; needs high motivation, good for stable living situation, part of recovery network, sometimes get told not to take meds
- Family very important to involve – address lost trust, perception of consequences, problematic dialogue, red flags for relapse, disease model, discuss role of enabling

Change

- **Pre-contemplation → contemplation → preparation → action → maintenance**
- Fit intervention to stage of change – ie identify pros and cons → highlight benefits of change and build confidence → develop a plan with dates → enact plan and follow up → relapse as a learning opportunity
- Brief interventions – **1-4 short counselling sessions as brief as a few minutes aimed to moderate substance abuse or encourage dependent patients to enter treatment**, more advice driven than MI – found to be **equally effective** as more extensive treatment
- Brief interventions best delivered by those viewed as **being significant to the patient**
- Say are you ready to try and quit using at this time?
    - If no – restate your concern, encourage consideration, state continued willingness to help
    - Yes – help set a quit date, develop a plan, provide education
- FRAMES – feedback, responsibility (only they can change), advice (to abstain), menu of options for tx, empathy, self efficacy (state belief they can change)
- MI views ambivalence as a normal process of change
- Project MATCH with alcohol – random assignment to CBT, MET, twelve step – no differences in efficacy between groups but more severe dependence may suggest TSF over CBT, motivational interventions best is higher levels of anger, TSF better for those whose social networks supported drinking
- Relapse prevention – recognize high risk factors and develop coping skills to manage them, identify and manage relapse warning signs, manage negative emotional states, manage social pressures, cravings, patterns of thinking, balanced lifestyle, recovery network, interrupt lapses and relapses to minimize damage
- Step 4 and 5 high relapse – moral inventory, making amends

Rates and predictors of conversion to Schizophrenia or Bipolar disorder following substance induced psychosis – April 2018, Am J Psychiatry

- **32% of patients with a substance induced psychosis converted to either bipolar or schizophrenia**
- Highest conversion with **cannabis induced psychosis with 47.4%** converting to either Scz or bipolar
- **Young age associated with higher risk of conversion**
- **Self-harm after a substance induced psychosis** was significantly linked to a higher risk of converting to both scz and bipolar disorder
- **Half the cases of conversion occurred within 3.1 years to scz, 4.4 years to bipolar**
- **Prev data 50% for cannabis, 30% for amphetamines, 24% for hallucinogens, 21% for opioids**
- **Most common form of substance induced psychosis was alcohol induced psychosis – conversion of 22.1%**

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- Pregnant opioid dependent woman → methadone
- Dancing girl with hyperthermia → MDMA
- **Patient with AUD, supportive wife/relative → disulfiram**
- Unstable/BPD, AUD → NO disulfiriam
- **Kidney stones → no topiramate**
- Opioids in AUD → no naltrexone
- Slurred speech, nystagmus → inhalants
- Belligerent, vertical nystagmus → PCP
- Cannabis – **moderate-strong evidence for spasticity in MS, pediatric epilepsy**; lower evidence in chemo induced N and V, HIV weight loss, chronic pain

K and S

- Caffeine half life 3-10 hrs – antagonist at adenosine receptors and increases concentration of cAMP, can affect dopamine and NE
- Causes global cerebral vasoconstriction
- Cannabinoid receptor = G protein linked, inhibitory G protein linked to adenylyl cyclase
- **Highest concentration in basal ganglia, hippocampus, cerebellum**
- **Not found in brainstem – minimal effects on respiratory and cardiac fxn**
- Long term use = respiratory disease, lung CA, seizure susceptibility, cerebral atrophy, chromosomal damage, birth defects, impaired immunity, decreased testosterone, irregular menses
- Motor skills impaired for 8-12 hrs post use
- **PCP has 3% deaths, most deadly hallucinogen**
- Can need 1-2 days to recover from PCP completely
- **Canthinones like khat plant, bath salts - cause massive release in dopamine, can see seizures, stroke, death**
- **Salvia binds to opioid k receptor**
- Inhalants increase concentration of ETOH – compete for liver metabolism
- Avoid benzos in inhalants – can increase respiratory depression and worsen toxicity
- For benzos – eventually GABA stimulation of receptor results in less Cl influx than even before benzo – sig tolerance
- **Seizures in 3-8% of cocaine ER visits - especially if epilepsy**
- **Cocaine can cause MI, HTN, CVD, nonhemorrhagic infarctions, ischemic colitis**
- Psychosis in 50% of stimulant use

Substances of abuse and movement disorders: complex interactions and comorbidities, Current Drug Abuse Rev, NIH, Deik et al.

Cocaine

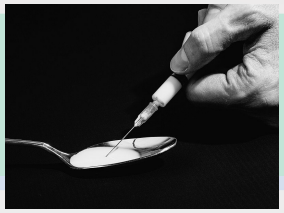
- Locomotor sensitization, de novo motor and vocal tics, exacerbation of existing Tic disorder
- Increases risk of acute dystonia with neuroleptics
- **If tics without any history, consider cocaine use**
- **Opsoclonus-myoclonus from intranasal use**
- Transient chorea and buccolingual dyskinesias (crack dancing) – self-limiting, choreoathetoid movements in orofacial and limb muscles associated with akathisia and can last for several days

Amphetamines

- **Binding at DAT dopamine transporter – reuptake inhibition and release of dopamine**
- Ecstasy, MDMA – release and inhibition of reuptake of serotonin, dopamine, norepi, MAO activity – causes inclusions in the substantia nigra and striatum – **can cause Parkinsonism,** also destroys serotonergic axon terminals selectively
- **Tremor in MDMA, trismus, bruxism, restless legs, acute dystonias**
- Vignette – **ecstasy tablets, cant open mouth, improves with IV diphenhydramine**
- Punding – non-goal directed repetitive activity, not exclusive to amphetamine abusers, also in cocaine and dopamine replacement

Methcathinone

- Levodopa resistant akinetic, rigid parkinsonism with myoclonus, speech dysfunction, bradyphrenia, gait and postural instability – like manganese poisoning, brain MRIs with hyperintensities



Opioids

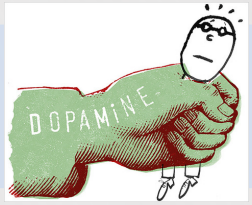
- Elevate forebrain dopamine levels by blocking the inhibitory GABA interneurons near the VTA which activates the mesocorticolimbic dopaminergic neurons
- **Myoclonus associated with opiate use – generalized, responds to naloxone or benzos**
- Higher risk if using antipsychotics, antiemetics, NSAIDs and antidepressants
- Meperidine can lead to full blown neurotoxic syndrome characterized by recurrent convulsions, myoclonus, asterixis
- **Chasing the dragon (heroin on foil) – spongiform leukoencephalopathy** – choreoathetoid movements, tremors, ataxia, obtundation, corticospinal tract signs
- Opioids do help restless legs

Cannabis

- Not typically associated with movement disorders other than jitteriness, restlessness, shakiness in withdrawal

Alcohol

- **Frequently associated with tremor – postural**
- **Cerebellar ataxia, legs more than arms – loss of Purkinje cells**
- During abstinence from ETOH – **essential like tremor responding to propranolol**
- Hepatic encephalopathy in liver disease – asterixis
- Essential tremor – very common movement disorder – **slowly progressive bilateral postural and action tremors of hands – alcohol ameliorates symptoms** – decreases amplitude rather than frequency of tremor, short-lived and may cause rebound



Dopaminergic agents

- Dopamine dysregulation syndrome – **4% of treated PD patients, usually young**
- Compulsive overuse of levodopa and other meds
- Can cause hypomania, psychosis, **violent dyskinesias – even causing weight loss**
- Altered appetites, hypersexuality, pathological gambling and shopping, aggression, euphoria
- Punding

Toxidromes

Toxidrome	Vital Signs	Mental Status	Pupils	Other Findings	Examples
Anticholinergic (ie a huge dose of atropine)	Hyperthermia (hot as hades), tachycardic, hypertensive, tachypnea	Hypervigilant, agitated (mad as a hatter), hallucinating	Mydriasis (blind as a bat)	Dry flushed skin (dry as a bone, red as a beet), urinary retention	Antihistamines, TCAs, atropine, scopolamine, antispasmodics
Cholinergic	Bradycardia (muscarinic), Tachycardia and hypertension (nicotinic)	Confused, coma	Miosis	SLUDGE (Salivation, lacrimation, urination, diarrhea, GI upset, emesis)	Organophosphate pesticides, nerve agents, physostigmine
Hallucinogen	Hyperthermia, tachycardia, hypertension	Hallucination, synesthesia, agitation	Mydriasis	Nystagmus	PCP, LSD, mescaline
Opioid	Hypothermia, bradycardia, hypotension, bradypnea	CNS depression, coma	Miosis	Hyporeflexia, pulmonary edema	Opioids (heroin, morphine, methadone, dilaudid, etc)
Sedative-Hypnotic	Hypothermia, bradycardia, hypotension, bradypnea	CNS depression, confusion, coma	Miosis	Hyporeflexia	Benzos, barbiturates, alcohols
Serotonin Syndrome	Hyperthermia, tachycardia, hypertension, tachypnea	Confused, agitated, coma	Mydriasis	Tremor, myoclonus, diaphoresis, hyperreflexia, trisumus, rigidity	MAOIs, SSRIs, meperidine, dextromethorphan
Sympathomimetic	Hyperthermia, tachycardia, tachypnea	Agitated, hyperalert, paranoia	Mydriasis	Diaphoresis, tremors, hyperreflexia, seizures	Cocaine, amphetamines, pseudoepherdine

Serotonin syndrome and neuroleptic malignant syndrome: Distinguishing features

	Serotonin syndrome (SS)	Neuroleptic malignant syndrome (NMS)
Onset	Within 24 hours	Days to weeks
Neuromuscular findings	Hyperreactivity (tremor, clonus, reflexes)	Bradyreflexia, severe muscular rigidity
Causative agents	Serotonin agonist	Dopamine antagonist
Treatment agents	Benzodiazepine, cyproheptadine	Bromocriptine
Resolution	Within 24 hours	Days to weeks

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Resources

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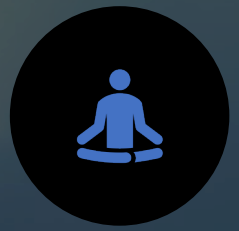

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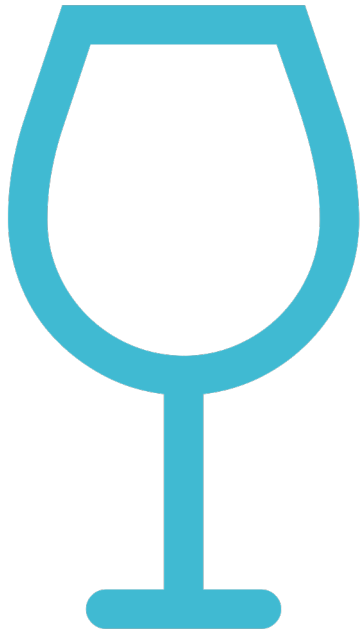
TORONTO REVIEW COURSE – DR. FRANCHUK

SUD GUIDELINES APA

DSM V



SUDs: Alcohol

RC Rounds Dr. A. Jewett

MCQs

- Which enzyme does disulfiram block?
  - Alcohol dehydrogenase
  - Acetate dehydrogenase
  - Acetaldehyde dehydrogenase
  - Acetaldehyde

MCQ

- What neurotransmitter primarily mediates ETOH withdrawal?
  - GABA
  - Glutamate
  - Serotonin
  - Dopamine

MCQ

- Which of the following is not part of the triad for Wernicke's Encephalopathy?
  - Ataxia
  - Confusion
  - Apraxia
  - Nystagmus

MCQ

- What is the most sensitive and readily available test to potentially identify a suspected ETOH use disorder?
  - Carbohydrate deficient transferrin (CDT)
  - Gamma-glutamyl transpeptidase (GGT)
  - Alanine transaminase (ALT)
  - Aspartate aminotransferase (AST)

Alcohol Use Disorder

- A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least. Two of the following, occurring within a 12 mo period
  - Alcohol is often taken in larger amounts or over a longer period than was intended
  - There is a persistent desire or unsuccessful efforts to cut down or control alcohol use
  - A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects
  - Craving, or a strong desire or urge to use alcohol
  - Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home
  - Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol
  - Important social, occupational, or recreational activities are given up or reduced because of alcohol use
  - Recurrent alcohol use in situations in which it is physically hazardous
  - Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol
  - Tolerance, as defined by either of the following:
    - A need for markedly increased amounts of alcohol to achieve intoxication or desired effect
    - A markedly diminished effect with continued use of the same amount of alcohol
  - Withdrawal, as manifested by either of the following:
    - The characteristic withdrawal syndrome for alcohol
    - Alcohol or a benzo is taken to relieve or avoid withdrawal symptoms
- Specify if in early remission (at least 3 mo but less than 12), or sustained remission (12 mo or longer) – none of the above met with exception that craving or a strong desire or urge to use alcohol may be met
- Mild – 2-3 sx, moderate 4-5 sx, severe 6 or more sx

Withdrawal 4-12 hrs after reduced intake
Sleep issues for months
15% liver cirrhosis or pancreatitis
Most common = low grade HTN
Contributes to suicide risk
4.6% 12-17, 8.5% adults, men 12.4%, 16.2% in 18-29

Alcohol Use Disorder

- In a controlled environment – in jails, therapeutic communities, locked hospital units
- Severity also related to days of use per mo, number of drinks per day, elevation of values in labs
- Withdrawal occurs 4-12 hrs after reduction of intake
- Sleep problems can persist at lower intensities for months and contribute to relapse
- Often associated to other substance use – used to alleviate unwanted effects of other substances or substitute for them when not available
- GI effects = gastritis, stomach or duodenal ulcers, and in 15% liver cirrhosis or pancreatitis
- Increased rate of cancer of the esophagus, stomach, and other parts of the GI tract
- One of the most commonly associated conditions is low grade hypertension
- Cardiomyopathy and other myopathies are less common but occur at an increased rate
- Increased triglycerides, LDL – increased risk of heart disease
- Peripheral neuropathy with weakness, paresthesias, decreased peripheral sensation
- Cognitive deficits, severe memory impairment, and degenerative changes in the cerebellum
- Related to direct effects of alcohol or trauma or vitamin deficiencies
- Important contributor to suicide risk during severe intoxication and in the context of temporary alcohol induced depressive and bipolar disorder
- 12 mo prevalence 4.6% in 12-17, 8.5% in adults 18 or older
- Rates greater among adult men (12.4%) than adult women (4.9%)
- Decreases in middle age, greatest among individuals 18-29 years old (16.2%) and lowest among individuals age 65 years and older (1.5%)

Older people and women more at risk of complications and intoxication
10% have onset over 40

Alcohol Use Disorder

- First episode intoxication likely to occur during mid teens
- Use disorder dx peaks in late teens or early to mid 20s, large majority by late 30s
- Earlier onset if conduct disorder, early onset of intoxication
- Variable course with periods of remission and relapse
- Typically promising prognosis, not an intractable condition in most unless severe
- In adolescents, conduct disorder and repeated antisocial behavior often co-occur with alcohol and other substance related disorders
- Most individuals with alcohol use disorder develop the condition before age 40, but 10% have later onset
- Older individuals – increased brain susceptibility to the depressant effects of alcohol, decreased rates of liver metabolism of a variety of substances, including alcohol, decreased percentages of body water → older people can have severe intoxication and problems at lower levels of consumption, more comorbid medical complications
- ETOH is the most frequently used intoxicating substance and contributes to considerable morbidity and mortality

40% of Asian groups have slow metabolism – lower risk of ETOH disorder
55% of fatal driving accidents = ETOH
BD, SCZ, ASPD highly associated

Alcohol Use Disorder

- Polymorphisms of genes for ETOH metabolizing enzymes alcohol dehydrogenase and aldehyde dehydrogenase most often seen in Asians and can affect the response to alcohol → flushed face and palpitations
- Occurs in 40% of Japanese, Chinese, Korean and related groups → lower risks of ETOH use disorder
- Males have higher rates of drinking, but because females weigh less, have more fat and less water in their bodies, and metabolize less alcohol in their esophagus and stomach, they have higher blood alcohol levels per drink than males – more vulnerable to physical consequences including liver disease
- Significant impairment occupationally, relationships, SES
- Most individuals continue to live with families and function within their jobs
- Significant increase in risk of accidents, violence and suicide
- 1/5 ICU admissions is related to alcohol, 40% of people experience an alcohol related adverse event in their lifetime, 55% of fatal driving events have ETOH involved
- Severe ETOH use disorder especially in ASPD associated with criminal acts including homicide
- Bipolar disorders, Scz, and ASPD are associated with a markedly increased rate of alcohol use disorder, and several anxiety and depressive disorders may relate to alcohol use disorder as well
- Can cause depression and suppress immune system

Risks = cultural attitudes toward drinking, availability, personal experiences, peers, exaggerated positive expectations of effects of ETOH, diff coping w stress, genes, low sensitivity to ETOH (high risk)
40-60% of risk = genetic influences
3-4x risk in relatives even when adopted out

Alcohol Use Disorder Risk Factors

- Cultural attitudes toward drinking and intoxication
- Availability and price of alcohol
- Acquired personal experiences with alcohol, stress levels
- Heavier peer substance use
- Exaggerated positive expectations of the effects of alcohol
- Suboptimal ways of coping w stress
- Runs in families with 40-60% of the variance of risk explained by genetic influences
- 3-4x higher in close relatives of individuals with alcohol use disorder – values highest for individuals with a greater number of affected relatives, closer genetic relationships, higher severity of the alcohol related problems
- 3-4 x increase in children w ETOH use disorder, even when children given up for adoption
- Low risk phenotypes = alcohol related skin flush in Asians
- High vulnerability with preexisting scz or bipolar disorder, impulsivity
- High risk associated with low level of response (sensitivity) to alcohol
- High levels of impulsivity = earlier onset, more severe disorder

At 200 mg/dL should be intoxicated
GGT >35
70% high GGT are persistent heavy drinkers
CDT most sensitive and specific but hard to access
GGT/CDT return to normal in days of stopping – can use to monitor abstinence
MCV marker but can't follow
Can cause hormonal problems, pregnancy
More likely to have seizures if epilepsy or prev TBI

Alcohol Use Disorder Diagnostic Markers

- Not for diagnosis but if seen, can highlight individuals in whom more info should be gathered
- Blood alcohol concentration – measure of tolerance to ETOH (ie. If 150 mg/dL – should show signs of intoxication, if they don't – have tolerance)
- At 200 mg/dL most people should be severely intoxicated
- Elevation or high normal levels of GGT (>35 units)
- At least 70% of high GGT are persistent heavy drinkers – 8 or more drinks daily on a regular basis
- CDT (carbohydrate deficient transferrin) with levels of 20 u or higher – more sensitive and specific
- Both GGT and CDT return toward normal within days to weeks of stopping drinking – can use to monitor abstinence; combo of both tests even better than alone
- Other useful tests are MCV (high due to toxic effects of alcohol on erythropoiesis) – poor method of measuring abstinence because of long half life of RBCs
- ALT and Alk Phos can reveal liver injury that is a consequence of heavy drinking
- Elevated lipids, high normal uric acid – nonspecific
- Medical sx = dyspepsia, nausea, bloating with gastritis, hepatomegaly, esophageal varices, hemorrhoids, tremor, unsteady gait, insomnia, erectile dysfunction
- Males may have decreased testicular size and feminizing effects associated with reduced testosterone levels
- Repeated heavy drinking in females can cause menstrual irregularities, spontaneous abortion, fetal alcohol syndrome if pregnant
- If epilepsy or previous head trauma, more likely to have alcohol related seizures
- **Withdrawal may cause nausea, vomiting, gastritis, hematemesis, dry mouth, puffy blotchy complexion, mild peripheral edema**

ETOH = slurred speech, incoordination, unsteady gait, nystagmus, impaired attention or memory, stupor or coma PLUS had ETOH and bad behavior or psych changes

Alcohol Intoxication

Recent ingestion of alcohol

Clinically significant problematic behavioral or psychological changes (ie. Inappropriate sexual or aggressive behavior, mood lability, impaired judgment) that developed during, or shortly after alcohol ingestion

One or more of the following signs or symptoms:

- Slurred speech
- Incoordination
- Unsteady gait
- Nystagmus
- Impairment in attention or memory
- Stupor or coma

Signs not from medical condition, another mental disorder, or another substance

Alcohol Intoxication

- Evidence – smelling alcohol on breath, hx from individual or observer, breath, blood or urine sample for tox
- Sometimes associated with amnesia for the events that occurred during the course of intoxication (blackouts) – related to high blood alcohol level and RAPIDITY with which this level is reached
- Mild usually after two drinks (20 mg/dL, 10-12 grams) - talkativeness, sensation of well-being, bright expansive mood
- Later, especially when blood alcohol levels are falling – more likely to be depressed, withdrawn, cognitively impaired
- At very high levels if not tolerant – fall asleep and enter first stage of anesthesia
- Over 300-400 mg/dL – inhibition or respiration and pulse and even death in nontolerant individuals
- Body is able to metabolize one drink per hour, so blood alcohol typically decreases at a rate of 15-20 mg/dL per hour
- Signs and symptoms of intoxication are more intense when blood alcohol level is rising than when it is falling
- Increased rate of suicidal behavior and completed suicide when intoxicated
- 70% of college students have been drunk in past year, 44% of 12th grade students
- Develops over minutes to hours and typically lasts several hours
- Highest prevalence 18-25 – frequency and intensity usually decrease with further advancing age
- Earlier the onset of regular intoxication, the greater the likelihood the individual will develop alcohol use disorder
- Increased rates with personality traits of sensation seeking and impulsivity, heavy drinking environment
- Cerebellar ataxia, MS, DKA can resemble intoxication

Blackouts = high BA level rapidly
300-400 = resp depression
Decreases at rate of 15-20 mg/dL/hr
Intoxication when levels rising
Lasts hours
Earlier onset regular drinking and drunkenness = more likely to develop d/o

w/d = autonomic hyperactivity, diaphoresis, tachycardia, hand tremor, insomnia, N and V, transient hallucinations – reality intact, agitation, anxiety, seizures (tonic clonic)

Alcohol Withdrawal

- Cessation of (or reduction in) alcohol use that has been heavy and prolonged
- Two or more of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use described above:
  - Autonomic hyperactivity (sweating, pulse over 100 bpm)
  - Increased hand tremor
  - Insomnia
  - Nausea or vomiting
  - Transient visual, tactile, or auditory hallucinations or illusions
  - Psychomotor agitation
  - Anxiety
  - Generalized tonic clonic seizures
- The signs of symptoms in Criterion B cause clinically significant distress or impairment in social, occupational or other important areas of functioning
- Signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance
- Specify if with perceptual disturbances – relatively rare when hallucinations (usually visual or tactile) occur with intact reality testing, or auditory, visual, tactile illusions occur in the absence of a delirium

Develops in hours to days
Begin when BAC decline sharply (4-12 hrs)
Peak second day, improve by 4-5th
Anxiety, insomnia, autonomic dysfunction x 3-6 mo
Seizures 3%
Delirium – usually medical condition, 10%, heavy drinking, lasts 4-5 days → fam hx w/d, prior w/d, sedative hx

Alcohol Withdrawal

- When hallucinations occur in the absence of delirium, a diagnosis of ETOH induced psychotic disorder should be considered
- Develops within several hours to a few days after cessation of (or reduction in) heavy and prolonged alcohol use
- Symptoms can be relieved by administering alcohol or benzodiazepines (ie. Diazepam)
- Withdrawal symptoms typically begin when blood concentrations of alcohol decline sharply (ie. Within 4-12 hours) after alcohol use has been stopped or reduced
- Relatively fast metabolism of alcohol → sx of withdrawal peak in intensity in second day of abstinence and likely to improve markedly by the fourth or fith day
- Following acute withdrawal, symptoms of anxiety, insomnia and autonomic dysfunction may persist for up to 3-6 mo at lower levels of intensity
- Fewer than 10% of individuals who develop ETOH withdrawal will ever develop dramatic symptoms (severe autonomic hyperactivity, tremors, delirium)
- Tonic clonic seizures in 3%
- Alcohol withdrawal delirium may occur → confusion and changes in consciousness, can include hallucinations (DTs)
- When alcohol withdrawal delirium develops – likely that a clinically relevant medical condition may be present (ie. Liver failure, pneumonia, GI bleeding, sequelae of head trauma, hypoglycemia, an electrolyte imbalance, postoperative status)
- 50% of middle class, highly functional individuals with etoh use disorder have experienced a full ETOH withdrawal syndrome
- In people who are hospitalized or homeless, rates of withdrawal may be greater than 80%
- Less than 10% get delirium or seizures
- Lasts 4-5 days, only after extended periods of heavy drinking, relatively rare younger than 30
- Risk and severity increases with increasing age, increased quantity and frequency of consumption
- Enhanced risk if concurrent medical conditions, family history of withdrawal, prior withdrawal and people on sedatives or hypnotics
- Autonomic hyperactivity in the context of moderately high but falling blood alcohol levels and a history of prolonged heavy drinking indicate ETOH w/d

Other Alcohol Induced Disorders

- Can get **psychotic disorder, bipolar disorder, depressive disorder, anxiety disorder, sleep disorder, sexual dysfunction, NCD alcohol induced**
- Alcohol induced conditions are likely to improve without formal treatment in a matter of **days to weeks after cessation** of severe intoxication or withdrawal
- **Lifetime risk for MDE in person with ETOH use disorder is 40%,** but **only about 1/3-1/2** of these are **independent MDD** outside of intoxication
- **Similar rates of anxiety and sleep disorders**, psychosis is rare
- Most likely to improve relatively quickly, unlikely to last for more than 1 mo

APA AUD 2018 Guidelines

- Initial evaluation – include full substance use history, quantitative behavioral measure for alcohol use
- Physiological biomarkers used to identify and possible monitor alcohol use
- Assess co-occurring conditions
- Initial goals of treatment agreed upon with patient and clinician and documented
- **Naltrexone or acamprosate should be offered to patients with a moderate to severe ETOH use disorder who has a goal of reducing alcohol consumption or achieving abstinence, prefer pharmacotherapy or have not responded to non-pharm alone, and have no contraindications to these meds**
- Disulfiram should be offered to people who want abstinence, prefer disulfiram, or have not tolerated above, capable of understanding risks of using ETOH on disulfiram, no contraindications
- Topiramate or gabapentin should be offered if goal is reducing consumption or achieving abstinence, prefer these meds or haven't responded to acamprosate or naltrexone, no contraindication
- **Antidepressants shouldn't be used unless co-occurring disorder** that warrants it
- No to benzos too unless co-occurring disorder
- **Breastfeeding or pregnant women should not use pharmacological treatments unless acute withdrawal with benzos or another disorder**
- **Acamprosate not in severe renal impairment**
- **Naltrexone not in acute hepatitis or hepatic failure**
- **Naltrexone not if opioid user or may need opioids**
- If mild or moderate renal impairment, acamprosate should not be first line or if used, dose be reduced
- **Psychosocial tx – MET, CBT, behavioral therapies, TSF, marital and family therapies; second line group and third psychodynamic, IPT**

APA AUD 2018 Guidelines

- Biomarkers
  - Serum ethanol level – acute intoxication, normalizes within hours, **zero order kinetics**, one standard drink metabolized per hr
  - Ethyl glucuronide – conjugation product of alcohol, can be detected in urine or hair up to 2-5 days after last drink
  - Phosphatidylethanol – on erythrocyte cell membranes – requires a longer duration of alcohol use to become elevated, and remains elevated for 2-3 weeks after cessation of drinking; nearly 100% sensitivity for consumption but **cannot discriminate between low to moderate and heavy consumption**
  - **CDT – first FDA approved biomarker for alcohol**, form of transferrin, high sensitivity and specificity
  - GGT – reflects altered hepatic metabolism in setting of sustained heavy ETOH consumption, but variable in individuals, gender, age, **heavy caffeine use (lowers it);** normal GGT does not rule out heavy ETOH consumption, false positives if TCAs, warfarin, MAOis, phenytoin, thiazides, steroids
  - MCV – increased for 3-4 mo after abstinence, low sensitivity

APA Guidelines

- **Acamprosate**
  - 666 mg TID
  - Modulates **glutamate**
  - Studies show less likely to return to drinking after attaining abstinence and significant reduction in number of drinking days
  - Start treatment as soon as abstinence is attained and continue even if relapses
  - Lack of metabolism through the liver – **can be used in hepatic dysfunction**
  - **Measure Cr and do not use if CrCl is less than 30 or GFR less than 30 (renally cleared), reduce dose if mild renal failure**
- **Naltrexone**
  - Opioid receptor antagonist, greatest affinity for mu receptors
  - Reduced likelihood of return to drinking with fewer drinking days over all
  - **Decreased experience of craving**
  - Daily oral or monthly depot injection
  - 50 mg po daily up to 100 mg to achieve effect
  - Some studies suggested benefit for combined naltrexone with antidepressant in depression
  - Smokers may respond better too
  - **Potential GI effects occur more in women than men, abdo pain, diarrhea, nausea, vomiting, dizziness**
  - **Cannot use in acute hepatitis or liver failure**
  - **Cant use in opiate use**
- **Disulfiram**
  - Inhibits enzyme **aldehyde dehydrogenase** which breaks down acetaldehyde
  - Only for abstinence → causes tachycardia, flushing, headache, nausea, and vomiting
  - **Involving family member as observer is helpful**
  - **Reactions up to 14 days after taking it**
  - Not in seizure disorder, high risk of relapse, **recent MI**
- **Topiramate**
  - Cognitive dysfunction, weight loss
  - High doses in studies
- **Gabapentin**
  - Doses 900-1800 per day
  - **Increased rate of abstinence, NNT 8, reduction in heavy drinking days NNT 5**
  - Reduced craving, insomnia
  - **Adjust dose in renal impairment**

Canada's Low Risk Guidelines

- No more than **10 drinks per week for women, no more than 2 drinks per day most days**
- **15 drinks per week for men, no more than 3** per day most days
- Non drinking days every week are good
- No more than 3 drinks for women, 4 for men on single occasion
- Zero is the limit when driving, taking medicine that interacts, dangerous physical activity, mental or physical health problems, alcohol dependence, pregnant or planning to be pregnant, responsible for the safety of others, making important decisions
- Teens should never have more than 1-2 drinks at a time
- Drink slowly, **have no more than 2 drinks in 3 hrs**
- For every drink have one non-alcoholic drink
- Eat before and when drinking
- Do not start drinking for health benefits

Ottawa Review Course

- More hospitalizations for alcohol than for heart attacks
- **Most used, most disorders**
- Acts on ligand and voltage gated ion channels primarily **agonizing GABA-A and antagonizing glutamate**
- Alcohol → alcohol dehydrogenase → acetaldehyde → acetaldehyde dehydrogenase → Acetate; **zero order elimination (ADH quickly saturated, disulfiram blocks ALDH)**
- Predictors of use disorders = early onset of use, family history, being able to hold their liquor, peers, positive effect
- Treatment for intoxication = primarily supportive with airway protection, **IM thiamine then glucose, no charcoal or lavage**
- ETOH users have an absorption syndrome – can't absorb oral thiamine
- **Glutamate is neurotransmitter that primarily mediates alcohol withdrawal**
- **Intoxication = GABA**

Ottawa Review Course Management of Withdrawal

- **Withdrawal begins 6-24 hours after last drink, seizures in 24-48 hrs, DTs in 48-72 hrs**
- Increased sympathetic activity – increased HR, BP, diaphoresis, **pupillary dilation**
- Primarily treat with benzos – ie. Lorazepam, diazepam, chlordiazepoxide
- CIWA > 10 – suggestive of benzo use with taper
- **If serious prior withdrawal, put on regular benzos with taper rather than waiting**
- **If no severe LFT abnormalities – diazepam or chlordiazepoxide (ie. 50 mg/d) x 2-3 days**
- Diazepam slightly more of a buzz than chlordiazepoxide
- Try to avoid **antipsychotics → decrease seizure threshold**
- IM or IV thiamine
- **Refer to treatment (detox does not change tx outcome)**

Ottawa Review Course

- Wernicke-Korsakoff Syndrome:
  - Wernicke's Encephalopathy – **classic triad of nystagmus (and 6th nerve palsy), ataxia, and confusion (delirium)**
  - Due to vitamin B1 thiamine deficiency – critical co-enzyme in glucose metabolism
  - Exposure to factors that increase glucose metabolism worsen encephalopathy
  - Give IM or IV thiamine prior to any glucose load
  - **Korsakoff's Syndrome – if you don't treat Wernicke's, anterograde and retrograde amnesia with associated cognitive deficits (aphasia, apraxia, agnosia, or executive dysfunction) → give ongoing thiamine and nutrition**

Ottawa Review Course

- Wouldn't want to give disulfiram if lives alone, severe relapses
- Acamprosate not in renal failure
- APA 2018 guidelines – naltrexone and acamprosate should be offered in moderate to severe alcohol use disorder in specific circumstances (ie. When nonpharm have not had effect)
- Disulfiram for when family involved, unable to tolerate naltrexone and acamprosate
- Topiramate and gabapentin suggested if do not respond or preferred
- **Leading cause of death in people with substance use disorders – smoking related illness**

Ottawa Review Course Treatment

Naltrexone

50 mg/day

Limits euphoria, blunted response when they do drink

Opioid antagonist

Potential risk of liver toxicity – avoid in hepatitis and liver failure

People with **family history of ETOH use do better w naltrexone** than those w no fam hx

Does not predispose to depression

Compliance (motivation, craving, SE) predicts outcome

Targets craving

NNT 9, depot naltrexone and oral nalmefene have comparable effects

50 RCTs – reduced risk to heavy drinking, heavy drinking days, total drinking days, consumed amounts of alcohol and GGT

Acamprosate

Affects glutaminergic and GABAergic activity indirectly (not specific to NMDA receptor)

24 RCTs – acamprosate significantly reduced risk of any drinking and significantly increased cumulative abstinence duration

NNT 9

May modulate acute and protracted withdrawal states

No anxiolytic, antidepressant or anticonvulsant effect

Can impair sleep and sex drive, cause diarrhea

Renally cleared – avoid in renal disease and renal failure

666 mg TID

Need to stop drinking before use it

Disulfiram

250 mg/day

Concern about inhibition of dopamine beta hydroxylase theoretically worsening psychosis, but not found in studies

Can sustain cocaine high

Beneficial in context of **supervised administration (ie. Supportive relationship) with behavioral contracting**

Difficult to find as industry did not pick up contract to produce

Abstinence focus

Helps relationships

Topiramate

100-150 mg BID

Two studies – significant reductions in decreasing craving or euphoria

Significant cognitive impairment, also paresthesias, metabolic acidosis, kidney stones

Can be used when patient still drinking

Not antimanic but may be useful add on for **bipolar patients** or target patients with mood instability

Gabapentin

900-1800 mg/day

Benzo like effect – **can get diverted**

Increased rate of abstinence, reduction in heavy drinking days, reductions in drinking quantity and frequency, GGT, craving, mood, insomnia

Renally cleared – avoid in renal impairment or failure

NNT 5 for heavy drinking days, NNT 8 for abstinence

Ottawa Review Course

- Screening in history:
  - Repeated absences from work and school especially on Mondays
  - Frequent trauma and accidental injuries
  - Persistent depression or anxiety despite tx
  - Sexual dysfunction
  - Lack of motivation
  - Cognitive impairment
  - Recurrent sleep problems
  - Younger age (18-44 yrs)
  - Other drug use (ETOH, nicotine)
- Physical:
  - Odor, conjunctiva, tremor, burn marks on hands, stigmata alcohol use
  - Risk of all cause mortality, especially cancers rises with increasing levels of consumption
- Ask in alcohol:
  - How much do you drink rather than do you drink
  - Clarify type of drink – what is your drink
  - Hard more likely use disorder
  - Daily more likely use disorder
  - Taking months off
  - Over 4 drinks in one sitting highly indicative
  - Consequences – blackouts, withdrawal, driving violations, public intoxication, others worried
  - Prior tx history
  - CAGE – cut down, annoyed, guilty, eye opener → if positive do more screening
  - Other option – ever had drinking problems? Any alcohol in last 24 hours – if both yes, 92% chance of current ETOH problem
  - AUDIT – 10 questions in office
- Tests:
  - **GGT most readily available**

Toronto Review Course

- **Acamprosate can be used with opioids**
- Different types of AUD
  - Type 1/A = mild, later onset, over 25, less childhood behavioral problems, less novelty seeking, increased harm avoidance
  - **Type 2/B = severe, earlier onset, under 25, family history, increased risk taking, novelty seeking**
- **LOT for liver impairment and ETOH withdrawal**
- Average rate of alcohol metabolism is 3.25 mmol/L per hr or **15 mg/dL per hr**
- Women have **lower activity of aldehyde dehydrogenase in stomach** – more vulnerable to damage, also have smaller body water – more intoxication
- Transtheoretical model by Prochaska – stages of change
- **Glutamate plays key role in mediating cravings**
- Substances directly or indirectly affect the **VTA firing**, **NA in salience**

AUD Guidelines BC

Table 1 Summary of Guideline Recommendations[a]

		Quality of Evidence	Strength of Recommendation
	Screening and Brief Intervention		
1	Clinicians should provide education about Canada's Low-Risk Alcohol Drinking Guidelines to all adult and youth patients.	LOW	STRONG
2	All adult and youth patients should be screened annually for alcohol use above low-risk limits.	MODERATE	STRONG
3	All patients who are drinking alcohol above low-risk limits but do not have an alcohol use disorder (AUD)[b] should receive a brief counselling intervention.	MODERATE	STRONG
	Withdrawal Management		
4	Clinicians should use the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) to assess the risk of severe complications of alcohol withdrawal in patients with AUD, in order to select the most appropriate withdrawal management pathway.	MODERATE	STRONG
5	Patients at low risk of severe complications of alcohol withdrawal (PAWSS<4) who have no other concurrent conditions that would require inpatient management should be offered outpatient withdrawal management.	HIGH	STRONG
6	Clinicians should consider prescribing non-benzodiazepine medications, such as gabapentin, carbamazepine, or clonidine, for the outpatient management of patients at low risk of severe complications of alcohol withdrawal.	MODERATE	STRONG
7	Patients at high risk of severe complications of withdrawal (PAWSS≥4) should be referred to an inpatient facility (i.e., withdrawal management facility or hospital) where they can receive a benzodiazepine treatment regimen under close observation, and emergency care can be administered immediately if needed.	HIGH	STRONG
8	All patients who complete withdrawal management should be connected to continuing AUD care.	LOW	STRONG
	Continuing Care		
9	Adult patients with moderate to severe AUD should be offered naltrexone or acamprosate as a first-line pharmacotherapy to support achievement of patient-identified treatment goals. A. Naltrexone is recommended for patients who have a treatment goal of either abstinence or a reduction in alcohol consumption. B. Acamprosate is recommended for patients who have a treatment goal of abstinence.	MODERATE	STRONG
10	Adult patients with moderate to severe AUD who do not benefit from, have contraindications to, or express a preference for an alternative to first-line medications, can be offered topiramate or gabapentin.	MODERATE	STRONG
11	Clinicians should provide motivational interviewing-based counselling to all patients with mild to severe AUD to support achievement of treatment goals.	MODERATE	STRONG
12	All patients with mild to severe AUD can be provided with information about and referrals to specialist-led psychosocial treatment interventions.	MODERATE	STRONG
13	All patients with mild to severe AUD can be provided with information about and referrals to peer-support groups and other recovery-oriented services in the community.	LOW	STRONG

[a] *The GRADE approach[1] was used to assess the quality of evidence (possible categories include: high, moderate, low, or very low) and strength of recommendation (possible categories include: strong or weak). Please refer to the Development and Approval of Recommendations section for more information on how the GRADE criteria were applied and an explanation of the quality of evidence and strength of recommendation scores that have been assigned.*

[b] *As per DSM-5 Diagnostic Criteria for Alcohol Use Disorder and Severity (Mild, Moderate, Severe)[2]*

AUD Guidelines BC

Table 2 Summary of Principles of Care

1	Alcohol use, high-risk drinking, and AUD should be viewed within a larger societal framework that is shaped by inequities in the social determinants of health. Clinicians should aim to address disparities in the social determinants of health by connecting patients with resources that meet these needs (e.g., housing, food/nutrition, financial assistance, employment).
2	Clinicians should be familiar with and incorporate the principles of harm reduction, trauma- and violence-informed care, and Indigenous cultural safety in the care and clinical management of patients with AUD.
3	AUD is understood to be a chronic, relapsing condition. As with other chronic disorders, a longitudinal care approach is recommended.
4	Patients should be offered a full range of evidence-based pharmacotherapies, psychosocial treatment interventions, and recovery supports to support achievement of their treatment goals.
5	A stepped and integrated approach to management of AUD is recommended, where mode of treatment is regularly adjusted to meet patient needs, circumstances, and preferences over time.
6	AUD should be managed within a broader framework of comprehensive medical care and support, including routine and ongoing medical, mental health, and psychosocial assessments.
7	Treatment plans should be individually tailored, patient-centered, and recovery-oriented, with the understanding that "recovery" can look different to each person.
8	Family and social circle[h] involvement in treatment planning and decision-making should be encouraged whenever possible, and when deemed appropriate by the patient and their care team.

[h] *This guideline uses the term "family" to encompass all relations that are important to the patient within their social circle, which may include romantic partners, close friends, and other people of significance who may or may not be legally recognized as family.*

AUD Guidelines BC

Recommendation 1 Awareness of Canada's Low Risk Alcohol Drinking Guidelines

Clinicians should provide education about Canada's Low-Risk Alcohol Drinking Guidelines to all adult and youth patients.

Quality of Evidence: LOW	Strength of Recommendation: STRONG

Remarks

- This recommendation has been graded as strong despite limited research evidence. It is the consensus of the committee that all patients could potentially benefit from increased knowledge and awareness of Canada's Low-Risk Alcohol Drinking Guidelines.
- Cultural safety is critical when talking to Indigenous patients and families about alcohol use. Some patients may have experienced stigma and discrimination, or been subject to harmful stereotypes about Indigenous peoples and alcohol in the health care system in the past. Using culturally safe approaches can minimize unintended harms and strengthen the therapeutic relationship.
- Clinicians should be mindful that some patients may be in recovery or abstinent from alcohol for personal reasons, such as a family history of alcohol-related issues. These types of disclosures should be handled with sensitivity and support to avoid causing distress or other unintended consequences in patients.

AUD Guidelines BC

4.2.5 Clinical Indications for Alcohol Use Screening

This guideline recommends universal screening of all adult and youth patients in primary care. However, there are a number of common clinical scenarios that should trigger alcohol screening regardless of whether or when a patient was last screened. These include:

- Signs of intoxication or detection of alcohol on breath
- Before prescribing a medication known to interact with alcohol
- Patient reports non-medical use of opioids, benzodiazepines, or illicit substances
- Patients with chronic non-cancer pain
- Laboratory investigations show elevated liver enzymes (increased GGT, AST:ALT ratio > 2:1), or MCV > 96 fL on CBC panel[k]
- Patients who are pregnant or planning to become pregnant
- Recent and/or repeated physical trauma, burns, injuries, accidents, or falls
- Recent, historical, or recurrent psychological trauma, intimate partner or family violence
- Significant life event (death of spouse or family member, divorce)
- Signs of workplace dysfunction (unexplained time-off, loss of employment)
- High-risk behaviours (problem gambling, unplanned or unprotected sex, impaired driving)
- Diagnosis or worsening of health conditions that may be associated with alcohol use:
  - Depression
  - Anxiety
  - Insomnia
  - Seizures
  - Psychosis
  - Anaemia
  - High blood pressure
  - Cardiovascular disease
  - Gout
  - Memory issues
  - Pancreatitis
  - Gastrointestinal disorders
  - Hepatitis, cirrhosis

Additionally, patients presenting to care because they are concerned about their alcohol use or suspect they have an AUD can undergo a full diagnostic interview immediately.

Box 2 The 5As Model for Delivering Alcohol Use Brief Interventions [48,148]

Ask	Screen and document alcohol use for every patient. Identify individuals who are drinking above low-risk limits.
Advise	In a clear, strong, and personalized manner, advise individuals that they are drinking above low-risk limits, and may be at risk of alcohol-related harms.
Assess	Is the individual willing to make a change at this time? Confirming/excluding a diagnosis of AUD is advised, as BI alone is not effective for individuals with an AUD.
Assist	For the patient willing to reduce or stop alcohol use, develop a treatment plan using a shared decision-making framework. Provide supportive counselling and advice, and referrals to community resources.
Arrange	Schedule a follow-up visit, preferably within a week of the planned "change date".

4.4.2 Brief Intervention

There is a robust evidence base to support the use of BI for high-risk drinking in adults and youth (aged 11-25 years).[128,149] Several high-quality systematic reviews have demonstrated that BI results in clinically meaningful reductions in high-risk drinking behaviours, including heavy episodic drinking, high daily or weekly levels of alcohol consumption, and drinking that exceeds recommended alcohol consumption limits, and have concluded that overall, there is a moderate beneficial effect of BI.[143,150-153] For example, a 2018 meta-analysis (69 RCTs, n=33,642) reported moderate-quality evidence that alcohol-related BIs administered in primary care and emergency settings led to sustained reductions in alcohol use up to one year later: on average, participants consumed 1.5 fewer drinks[1] per week than participants who received minimal or no intervention.

Although a 2012 systematic review reported larger effect sizes with multi-contact brief interventions, (i.e., multiple 10-15 minute BI sessions delivered over a timespan of up to 1 year);[117] other reviews have found that extending the duration and frequency of brief interventions does not appear to confer significant advantages.[143,154] A consistent finding across multiple reviews is that even a single, 5-minute session incorporating the core principles of MI is likely to be effective in reducing alcohol consumption among individuals at higher risk of alcohol-related harms.[149] A 2016 meta-analysis of 52 RCTs (n=29,891) found that provider type did not impact outcomes, with some evidence that BI delivered by nurses was more effective than physician-, counsellor- or peer-delivered BIs in reducing the quantity of alcohol consumed by individuals with high-risk drinking patterns.[155] Thus, if physician and nurse practitioner time is limited, delegation of screening and BI to other trained members of the care team or staff can be considered.

Brief Interventions

More BI

Ask

The first step of the 5As intervention is asking patients about their alcohol use—screening—which is covered in Appendix 1.

Advise

Clearly describe the screening result and its implications on the patient's health, and provide direct personalized recommendations. Where possible, relay relevant health risks in reference to patient's concerns, laboratory investigations, and medical findings (e.g., anxiety, insomnia, liver function tests, gastroesophageal reflux disease, blood pressure).

Sample Script:

> *"You are drinking more than is medically safe.*
> *I think your drinking is putting your health at risk and is not good for you."*
> *"I strongly recommend that you cut down or stop drinking."*

Assess

Engage patient in a brief conversation to assess their motivation and ability to reduce or discontinue their alcohol use at this time.

Sample Questions:

> *"Are you willing to consider making changes in your drinking?"*
> *"How do you feel about my recommendation? Do you have any questions?"*
> *"What do you think? Would that work for you? Does that make sense?"*

Assist

If patient expresses readiness to change:

- Express your support and offer encouragement.
- Affirm your confidence in patient's motivation and ability to change.
- Collaboratively set goals that are meaningful to the patient. Goals do not have to be limited to reducing or stopping alcohol use.
- Agree on a specific plan and a change date or schedule.
- In line with the patient's goals, provide a menu of options, including pharmacotherapy, psychosocial interventions, recovery-oriented and community-based supports.
- Provide educational material and referrals to social supports and community resources.
- Schedule a follow-up visit.

If patient does not express readiness to change:

- Restate your concern about patient's health.
- Ask about any barriers to change the patient may be experiencing, and invite the patient to consider how these could be navigated.
- Encourage the patient to take time to reflect on the conversation.
- Reaffirm your willingness to support when patient is ready.
- Offer educational material and referrals to relevant health care and community resources.
- Follow-up. Repeat screening and brief intervention regularly.

Arrange

Schedule follow-up visits at the end of a screening and brief intervention session. In follow-up visits, document alcohol use and assess if patient has been able to meet and sustain planned goals.

If patient has met planned intervention goal:

- Congratulate, reinforce, and support continued change.
- Coordinate care with referral partners if the patient has accessed additional support. Communicate with external/community agencies on patient's progress.
- Assess and address any co-occurring medical conditions and mental health symptoms (e.g., insomnia, depression, anxiety) noting that these may improve with reduction in alcohol use.
- Set new goals and schedule follow-up appointments.

If patient has been unable to meet planned intervention goal:

- Acknowledge that change is difficult.
- Relate drinking to problems a patient may be experiencing (e.g., health, psychological, social) as appropriate.
- If the following measures are not already being taken, consider:
  - Referring patient to external or community-based resources (e.g., peer support groups).
  - Recommending the involvement of family (if appropriate).
  - Offering pharmacotherapy to patients with AUD.
  - Reassessing or adjusting current treatment.
- Continue to assess and address any co-occurring medical conditions and mental health symptoms (e.g., insomnia, depression, anxiety).
  Note: Pharmacological management of depression and anxiety is less effective while the patient continues to use alcohol.
- Schedule follow up appointments.

Outpatient withdrawal management can be considered for patients who meet all of the following criteria:

- PAWSS score <4
- Absence of contraindications including, but not limited to:
  - Severe or uncontrolled comorbid medical conditions (e.g., diabetes, COPD, heart disease, decompensated cirrhosis)
  - Acute confusion or cognitive impairment
  - Acute illness or infection requiring medical intervention
  - Co-occurring serious psychiatric symptoms or disorders (e.g., suicidal ideation, psychosis)
  - Co-occurring severe drug use disorder (excluding tobacco)
  - Pregnancy
- Ability to attend daily medical visits for first 3-5 days, and alternating day visits thereafter
  - For patients and/or practices in rural or remote areas where daily in-person visits are not feasible, remote follow-up options such as telemedicine, or secure phone or video calls, are acceptable alternatives (but see notes below)
- Ability to take oral medications
- Has a reliable family member or community-based contact who can monitor symptoms during acute withdrawal period (i.e., 3-5 days) and support adherence to medications*
- Any other medical or social condition that, in the treating clinician's best judgment, would present serious risks to patient safety if alcohol withdrawal was managed on an outpatient basis

Note: Patients who do not have support from family or community should not be denied treatment. If inpatient treatment is not an option due to scarcity of beds or patient preference, patients with minimal social supports should be accommodated and treated through alternative strategies such as daily clinic visits, home visits, or connection to a local pharmacist. A patient's track record of reliability and adherence to clinical recommendations should be considered as a factor in this decision.

Box 6 General Considerations for Outpatient Withdrawal Management

- Schedule withdrawal management in consideration of available coverage and patient circumstances. Starting treatment on a weekend may minimize disruption to a patient's work. If weekend service is unavailable, schedule treatment for Monday or Tuesday to ensure access to service in the following days.
- See the patient daily during the stabilization phase of withdrawal (i.e., 3-5 days), evaluate and adjust the visit schedule thereafter as appropriate. If appropriate, consider remote follow-up options (i.e., phone or video calls and connection to a local pharmacist) for patients residing in remote areas or those with mobility impediments.
- Provide patients with a phone number or alternative contact that they can call in the event of an emergency.
- Where possible, request that a reliable family member or friend is available to provide support, help with treatment schedules, track symptoms and response to medications, and accompany or transport the patient to appointments.
- Provide patients, families and caregivers with educational resources detailing withdrawal symptoms, medications, side effects, and safety issues.
- Advise patients not to drive until their withdrawal symptoms subside.
- Recommend over-the-counter vitamins including thiamine and folate.
- Recommend increased fluid and electrolyte intake, restricted diet consisting of mild foods, and minimal exercise.
- Review risks and benefits of natural remedies, caffeine, or any activity that increases sweating (e.g., hot baths, showers, or saunas), with respect for and understanding of the important role that Indigenous and traditional approaches to healing have for some patients (e.g., sweat lodges).
- Assess vital signs, withdrawal symptoms, hydration, cognition, emotional status, general physical condition, and sleep at each daily visit.
- Provide encouragement and referrals to community resources, support groups, or employee assistance programs.
- Reassess patient's recovery goals regularly.
- Monitor for relapse, and collaboratively explore the cause of relapse and correct if possible; if unable to address the cause, refer for inpatient management.
- BC physicians and nurse practitioners are encouraged to call the Rapid Access to Consultative Expertise (RACE) line (Vancouver area: 604-696-2131; toll-free: 1-877-696-2131; Monday to Friday, 0800-1700) or use the RACE line app (www.raceconnect.ca) to connect with an addiction medicine specialist for advice and guidance.

AUD Guidelines BC

Table 5 Comparison of Pharmacotherapy Options for Outpatient Management of Alcohol Withdrawal [m]

	Benzodiazepines[257]	Carbamazepine[244]	Gabapentin[258]	Clonidine[259]	Valproic Acid[260]
Efficacy	Over 60 RCTs (n>4000) report superior efficacy in the suppression of withdrawal symptoms compared to placebo and other active treatments.[229] Over 20 RCTs (n>2000) report superior efficacy for prevention of seizures compared to placebo and active treatments.[227-229]	Six RCTs (n=558) of carbamazepine report equal[238-241] or superior[242,243] efficacy in the reduction of withdrawal symptom severity compared to benzodiazepines. Insufficient evidence for prevention of seizures or delirium tremens.	Two RCTs (n=126) reported that gabapentin is as effective as benzodiazepines in suppressing mild to moderate withdrawal symptoms, and may be superior for treating insomnia and anxiety symptoms.[246,247] Insufficient evidence for prevention of seizures or delirium tremens.	Two RCTs (n=50) reported that clonidine was as effective as benzodiazepines in reducing mild to moderate withdrawal symptoms.[254,255] Does not prevent seizure or delirium tremens.	Limited evidence of efficacy. Two open-label trials (n=27) suggest a faster reduction of withdrawal symptoms with valproic acid compared than benzodiazepines.[251,252] Insufficient evidence for prevention of seizures or delirium tremens.
Concurrent Alcohol Use	Potentiates the effects of alcohol; concurrent alcohol use can result in serious safety risks, including over sedation, falls, delirium, respiratory depression (e.g., non-fatal or fatal overdose), and need for prolonged hospitalization.	No safety risk if taken concurrently with alcohol (i.e., in the event of lapse/relapse).	Abstinence is recommended after starting treatment due to potential risk of additive CNS-depressive effects. **Note:** Studies suggest concomitant use of alcohol and gabapentin (at therapeutic doses) does not increase sedation or motor impairment.[261]	Can have an additive effect on lowering blood pressure if taken with alcohol. Patients and families should receive education on signs and symptoms of hypotension.	No safety risk if taken concurrently with alcohol (i.e., in the event of lapse/relapse).
Contraindications	1. Severe respiratory insufficiency 2. Hepatic disease 3. Sleep apnea 4. Myasthenia gravis 5. Narrow angle glaucoma	1. Hepatic disease 2. Bone marrow depression 3. Serious blood disorder 4. Atrioventricular heart block	Hypersensitivity to gabapentin	1. Sinus node function impairment 2. Severe bradyarrhythmia 3. Galactose intolerance	1. Mitochondrial disease 2. Hepatic disease or dysfunction 3. Urea cycle disorders
Cautions	1. Lactose intolerance 2. Renal impairment 3. Breast feeding	Has been associated with rare blood dyscrasias and Stevens Johnson Syndrome with longer-term use. **Note:** Patients of Asian ethnicity are at increased risk of carbamazepine toxicity due to higher prevalence of the HLA-B*1502 allele. Genetic testing to exclude those at high-risk must be performed before prescribing to this patient population.[245]	Renal impairment	May cause hypotension in patients with a history of low blood pressure.	1. Pregnant or intending to become pregnant 2. Geriatric patients (> 65 years of age)
Side Effects	Common side effects are drowsiness, dizziness. Less common side effects include changes in skin colour, nausea, headache, blurred vision, tremors, hypotension, GI disturbances. Memory loss may also occur.	Side effects may include dizziness, pruritus, ataxia, headache, drowsiness and nausea. These side effects are often minor and temporary.	Higher doses may cause ataxia, slurred speech and/or drowsiness. Favourable side effect profile in comparison to other anticonvulsants.	Hypotension, dry mouth, dizziness, fatigue, headache, nausea, vomiting, constipation, malaise, sleep disorder, sedation and erectile dysfunction.	Somnolence, GI disturbances, confusion and tremor.
Other Considerations	Potential for non-medical use, diversion, and dependence. Potential for drug-drug interactions leading to excess sedation, impaired psychomotor and cognitive functioning. Due to safety concerns, exercise caution when considering this medication for outpatient use.	Has no potential for non-medical use, diversion, or dependence. Some side effects resemble withdrawal symptoms; clinician should ascertain the source of symptoms before dose adjustments. Baseline and periodic evaluations of hepatic function must be performed in elderly patients and patients with a history of liver disease.	Potential for non-medical use, diversion, and dependence. Toxicity profile parallels that of alcohol. Easy to transition from withdrawal management to long-term relapse prevention.	Should only be used for treating mild-moderate withdrawal symptoms in patients at low risk of severe complications. Safe to use as adjunct to benzodiazepines or other anticonvulsants. Patients should receive education on the signs and symptoms of hypotension.	Due to the lack of high-quality evidence, should only be considered when other options are contraindicated. Associated with risk of fetal harm and birth defects (e.g., neural tube defects, craniofacial defects, cardiovascular malformations, hypospadias). Women of reproductive age should be advised to use an effective contraceptive.

[m] *Contraindications, cautions, and side effects have been abstracted in part from Health Canada-approved product monographs for specific clinical indications. Only benzodiazepines have been approved for the treatment of alcohol withdrawal in Canada. Duration and dosages used for indicated conditions (e.g., seizure disorders, hypertension) may differ from those used for off-label indication of alcohol withdrawal management. Data should be interpreted with this caution.*

Pharmacologic Options in Withdrawal

Recommendation 6 Pharmacotherapy for Management of Mild to Moderate Withdrawal

Clinicians should consider non-benzodiazepine medications, such as carbamazepine, gabapentin, or clonidine, for outpatient withdrawal management in patients at low risk of severe complications of alcohol withdrawal.

Quality of Evidence: MODERATE	Strength of Recommendation: STRONG

Remarks

- Selection of an appropriate medication should be made through shared decision-making by patient and provider in consideration of a patient's goals, needs, and preferences.
- Contraindications, side effects, feasibility (dosing schedules, out-of-pocket costs), and patient history should also be taken into account in selecting a medication.
- Carbamazepine is contraindicated in patients with hepatic disease, bone marrow depression, serious blood disorder, and atrioventricular heart block.
  - People of Asian descent are at increased risk of serious cutaneous adverse drug reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis [TEN], maculopapular rash) due to a higher baseline prevalence of the HLA-B*1502 allele, a marker for carbamazepine toxicity. Carbamazepine should be avoided in this population unless genetic testing is available and has excluded risk.[245]
- Gabapentin is contraindicated in patients with hypersensitivity to this medication. Caution is advised for patients with renal impairment. Gabapentin should not be combined with opioids.
- Clonidine is contraindicated in patients with sinus node function impairment, severe bradyarrhythmia, and galactose intolerance. Caution is advised for patients with a history of hypotension.

Recommendation 7 Withdrawal Management for Patients at High Risk of Severe Complications

Patients at high risk of severe complications of withdrawal (i.e., PAWSS≥4) should be referred to an inpatient facility (i.e., withdrawal management facility or hospital) where they can receive a benzodiazepine treatment regimen under close observation, and emergency care can be administered immediately if needed.

Quality of Evidence: HIGH	Strength of Recommendation: STRONG

Remarks

- Conditions that could indicate inpatient withdrawal management regardless of PAWSS score include:
  - Multiple unsuccessful attempts at outpatient withdrawal management
  - Failure to respond to medications after 24-48 hours
  - Unstable medical conditions
  - Unstable psychiatric disorders
  - Chronic, complex pain disorders
  - Concurrent use of other CNS depressants (e.g., prescribed or nonmedical use of Z-drugs, benzodiazepines, barbiturates, opioids)
  - Severe liver compromise (e.g., jaundice, ascites, decompensated cirrhosis)
  - Pregnancy
  - Lack of a safe, stable, and substance-free setting and/or caregiver to dispense medication
- If a patient has a PAWSS≥4 but inpatient treatment is not feasible due to patient preference or scarcity of beds, clinicians should arrange for community-based monitoring and support during treatment (home withdrawal programs, intensive outpatient programs (DayTox), connection with community pharmacist, involving family members or caregivers) and monitor patient closely (daily phone calls, frequent clinical visits).

Withdrawal Mgmt

Benzos

<table>
<tr><th colspan="2">Benzodiazepines[257]</th></tr>
<tr><td>Contraindications</td><td>1. Severe respiratory insufficiency
2. Hepatic disease
3. Sleep apnea
4. Myasthenia gravis
5. Narrow angle glaucoma</td></tr>
<tr><td>Cautions</td><td>1. Lactose intolerance
2. Renal impairment
3. Breast feeding
4. Potential for non-medical use, diversion, and dependence</td></tr>
<tr><td>Side Effects</td><td>• The most common side effects of benzodiazepines are drowsiness and dizziness.
• Less common side effects include changes in skin colour, nausea, headache, blurred vision, tremors, hypotension, GI disturbances, and memory loss.</td></tr>
<tr><td>Coverage</td><td>Benzodiazepines are eligible for full coverage under Fair PharmaCare, and PharmaCare Plans C and W.</td></tr>
<tr><td>Concurrent Alcohol Use</td><td>Benzodiazepines potentiate the effects of alcohol; concurrent alcohol use can result in serious safety risks including oversedation, falls, delirium, respiratory depression (e.g., non-fatal or fatal overdose), and need for prolonged hospitalization.</td></tr>
<tr><td>Safety Considerations</td><td>• If benzodiazepines are selected for outpatient withdrawal management, consider a fixed dosing schedule to limit risks. Benzodiazepines should be discontinued after withdrawal symptoms have resolved (typically 5-7 days).
• All patients and families should be aware of the risk of dependence and tolerance, and receive education on safe use, the signs of an overdose, and emergency contact information.
• Where appropriate, consider the following strategies to reduce risk: daily dispensing from a pharmacy, involving family members or caregivers to administer medication and monitor patient response, frequent follow-up visits, or daily check-ins by phone.</td></tr>
<tr><td>Sample Dosing Protocol[207,212]</td><td>Example four-day fixed and flexible protocols for diazepam (Valium)
<table><tr><th>SCHEDULE</th><th>DAY 1</th><th>DAY 2</th><th>DAY 3</th><th>DAY 4</th></tr><tr><td>Fixed</td><td>10 mg QID</td><td>10 mg TID</td><td>10 mg BID</td><td>10 mg at bedtime</td></tr><tr><td>Flexible*</td><td>10 mg every 4 to 6 hours as needed based on symptoms**</td><td>10 mg every 6 to 8 hours as needed</td><td>10 mg every 12 hours as needed</td><td>10 mg at bedtime as needed</td></tr></table>* Flexible dose schedules should only be prescribed to patients with proven reliability and adherence to clinical recommendations. Enlisting family members or caregivers to assess symptom severity and dispense medication is recommended.
** Symptoms: Pulse rate >100 beats per minute, diastolic BP >90 mmHg, or signs of withdrawal.
Abbreviations: QID – four times per day, TID – three times per day, BID – two times per day.</td></tr>
</table>

PAWSS

Box 12 Prediction of Alcohol Withdrawal Severity Scale (PAWSS)[195]

PART A: THRESHOLD CRITERIA — Yes or No, no point	
Have you consumed any amount of alcohol (i.e., been drinking) **within the last 30 days**? **OR** Did the patient have a positive (+) blood alcohol level (BAL) on admission?	
If the answer to either is YES, proceed to next questions.	
PART B: BASED ON PATIENT INTERVIEW — 1 point each	
1	Have you been recently **intoxicated/drunk**, within the last 30 days?
2	Have you **ever** undergone alcohol use disorder rehabilitation treatment or treatment for alcoholism? (i.e., in-patient or out-patient treatment programs or AA attendance)
3	Have you **ever** experienced any previous episodes of alcohol withdrawal, regardless of severity?
4	Have you **ever** experienced blackouts?
5	Have you **ever** experienced alcohol withdrawal seizures?
6	Have you **ever** experienced delirium tremens or DTs?
7	Have you combined alcohol with other "downers" like benzodiazepines or barbiturates, **during the last 90 days**?
8	Have you combined alcohol with any other substance of abuse, **during the last 90 days**?
PART C: BASED ON CLINICAL EVIDENCE — 1 point each	
9	Was the patient's blood alcohol level (BAL) greater than 200 mg/dL? (SI units 43.5 mmol/L)* **OR** *Have you consumed any alcohol in the past 24 hours?
10	Is there any evidence of increased autonomic activity? e.g., heart rate >120 bpm, tremor, agitation, sweating, nausea

*Due to the common absence of a BAL the committee has added this modification. Please see next page.

Interpretation

Maximum score = 10. This instrument is intended as a SCREENING TOOL. The greater the number of positive findings, the higher the risk for the development of alcohol withdrawal syndrome (AWS).

A score of ≥4 suggests HIGH RISK for moderate to severe (complicated) AWS; prophylaxis and/or inpatient treatment are indicated.

Pearls from BC Guidelines

- Predictors of a positive response to naltrexone = high levels of craving and family hx of AUD, ? Those who use tobacco
- Naltrexone contraindicated in acute hepatitis and liver failure, those taking or expected to need opioids or OAT
- Common SE naltrexone = somnolence, nausea, vomiting, decreased appetite, abdo pain, insomnia, dizziness
- Naltrexone = less likely to engage in heavy drinking, less drinking days per month
- Some studies show efficacy when taken as needed
- Acamprosate – reduced return to drinking and increased duration of abstinence, persisted effects for 3-12 mo after discontinuation
- However in NA study, no better than placebo
- Strongest predictors of success of acamprosate are completing withdrawal management or being abstinent prior to starting, and having abstinence as a treatment goal
- Other predictors of success with acamprosate are – higher anxiety levels, a physiological dependence on alcohol, a lack of family history of AUD, and a later age of AUD onset (over 40)
- In 2014 meta-analysis – no sig differences between acamprosate and naltrexone
- Naltrexone may be better at reducing heavy drinking, and acamprosate may be better at supporting abstinence

Naltrexone vs. Acamprosate

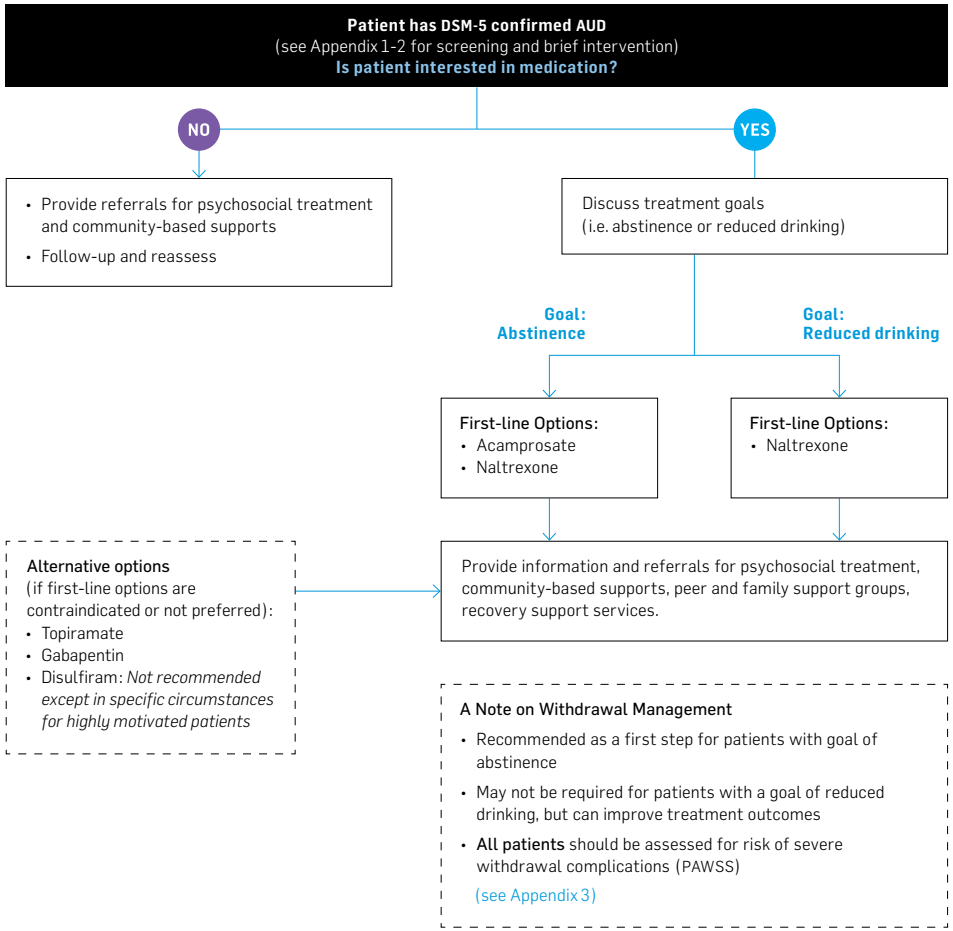
Table 6 Comparison of First-Line Pharmacotherapies for AUD

	Naltrexone[309]	Acamprosate[310]
Efficacy	Established evidence base for safety and efficacy in reducing relapse rates and alcohol consumption compared to placebo (53 RCTs; n=9,140).[178] A 2014 meta-analysis estimated that the NNT to prevent return to any drinking (relapse) was 20 (95%CI, 11 to 500), and the NNT to prevent return to heavy drinking was 12 (95%CI, 8 to 26).[178]	Established evidence base for safety and efficacy reducing relapse rates compared to placebo (27 RCTs; n=7,519).[178] A 2014 meta-analysis estimated that the NNT to prevent return to any drinking (relapse) was 12 (95%CI, 8 to 26), but that acamprosate was not associated with an improvement in alcohol consumption.[178]
Concurrent Alcohol Use	Safe to start while patients are using alcohol, but may be more effective and potential side effects minimized if started upon completion of withdrawal management (3-7 days of abstinence from alcohol use).[178,179]	Safe to start while patients are using alcohol, but may be more effective if started following completion of withdrawal management.[177,178]
Contraindications	1. History of sensitivity to naltrexone 2. Current opioid use or opioid use disorder (analgesia, opioid agonist treatment, or non-medical use) 3. Acute opioid withdrawal 4. Acute hepatitis or liver failure	1. History of hypersensitivity to acamprosate 2. Severe renal impairment (creatinine clearance ≤30mL/min) 3. Breastfeeding
Cautions	1. Renal impairment 2. Hepatic impairment 3. Concomitant use of other potentially hepatotoxic drugs 4. Pregnancy and breastfeeding* 5. Pediatric patients (<18 years)*	1. Moderate renal impairment (creatinine clearance of 30-50mL/min) 2. Pregnancy* 3. Pediatric and geriatric (>65 years) patients*
Side Effects	Nausea, headache, and dizziness are the most commonly reported side effects. Generally, these are mild, subside over time, and can be avoided if naltrexone is started at a lower dose and/or if the patient is abstinent from alcohol.	Diarrhea is the most commonly reported side effect; vomiting and abdominal pain are reported less frequently. Side effects are usually transient and resolve quickly.
Coverage	Collaborative Prescribing Agreement is required; eligible for full coverage under Fair PharmaCare, and PharmaCare Plans C, G, and W.	Collaborative Prescribing Agreement is required; eligible for full coverage under Fair PharmaCare, and PharmaCare Plans C, G, and W.
Safety and Other Considerations	• Liver function tests (LFT) should be assessed at treatment initiation, and again at 1, 3, and 6 months. If LFTs are elevated at baseline, more frequent monitoring is indicated. • Patients should be advised of the risk of hepatic injury and to stop use of medication if they experience symptoms of acute hepatitis (fatigue, anorexia, nausea, and vomiting).	• No dose adjustment is required for patients with mild renal impairment (creatinine clearance 50-80mL/min). • Dose reduction is required for patients with moderate renal impairment (creatinine clearance 30-50mL/min). • No known hepatic toxicities.

** Safety and efficacy of these medications has not been fully established in these patient populations and their use would be at the discretion of the treating clinician. Specialist consultation, careful assessment of benefit and risks, fully informed patient consent, and regular monitoring and assessment is advised in these cases.*

Pathway

Figure 3 Continuing Care Pathway for Adult Patients with AUD



Other Pharm Options

Table 7 Comparison of Select Alternative AUD Pharmacotherapy Options[n] (continued)

	Topiramate[356]	Gabapentin[258]	Disulfiram[352]
Cautions	1. Concomitant use of valproic acid 2. Conditions or therapies that predispose patients to acidosis (renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diets, certain drugs)	1. Geriatric (>65 years of age) and pediatric patients (<18 years of age)* 2. Pregnant and breastfeeding patients* 3. Concomitant use of opioids and other CNS depressants 4. Compromised respiratory function 5. Neurological disease or cognitive impairment 6. Renal impairment	1. Pregnant and breastfeeding patients* 2. Pediatric patients* 3. Disorders including diabetes mellitus, hypothyroidism, seizure disorders, cerebral damage, chronic or acute nephritis, hepatic cirrhosis or insufficiency, abnormal EEG results, or co-occurring drug use disorders
Side Effects	Side effects are most often CNS-related, and may include psychomotor slowing, difficulty concentrating, speech/language problems, somnolence, fatigue, and mood disturbance (irritability, depression). Most are mild to moderate in severity, and occur early in therapy. Starting at a low dose with slow titration up to a stable dose over a period of several weeks is recommended to avoid or reduce severity of side effects.	Side effects include ataxia, slurred speech, and drowsiness. Most are mild to moderate in severity, and occur early in therapy.	In the absence of alcohol, most common side effects are drowsiness, skin eruptions (acne, dermatitis), fatigue, erectile dysfunction, headache, and a metallic or garlic-like aftertaste. A less common but serious side effect is hepatic toxicity (cholestatic or fulminant hepatitis, hepatic failure resulting in transplantation or death), which has been reported in patients taking disulfiram with and without prior history of abnormal liver function.
Safety and Other Considerations	Due to risk of fetal harm, women of reproductive age should be advised to use an effective contraceptive. Safe to use in patients with liver disease. Patients should be monitored for signs of hyperammonemia (unexplained vomiting, lethargy, confusion, changes in mental status, hyperthermia) and metabolic acidosis (hyperventilation, fatigue, anorexia, cardiac arrhythmias, stupor).	Safe to use in patients with liver disease. Requires conservative dosing in patients with renal impairment.	The disulfiram-alcohol reaction can present as an emergency situation. It is recommended that patients carry an identification card on their person listing symptoms of disulfiram-alcohol reaction and their clinician's contact information in the event of emergencies. Due to risk of hepatotoxicity, it is recommended to perform baseline and follow-up LFTs and to monitor CBC and blood chemistries. Patients and families should be advised to immediately report early signs or symptoms of hepatitis.

** Note: Safety and efficacy of these medications has not been fully established in these patient populations and their use would be at the discretion of the treating clinician. Specialist consultation, careful assessment of benefit and risks, fully informed patient consent, and regular monitoring and assessment is advised in these cases.*

Table 7 Comparison of Select Alternative AUD Pharmacotherapy Options[n]

	Topiramate[356]	Gabapentin[258]	Disulfiram[352]
Efficacy	Seven RCTs (n=1,125) of topiramate have reported small to moderate effects on abstinence and heavy drinking outcomes compared to placebo.[316-322] Three clinical trials (n=439) have reported that topiramate is as effective or superior to naltrexone for abstinence, heavy drinking and craving outcomes.[323,324]	Three RCTs (n=131) of immediate-release gabapentin have reported small to moderate effects on abstinence and heavy drinking outcomes, craving, mood, and insomnia compared to placebo.[326,328,357] One RCT (n=346) of extended-release gabapentin found no difference in alcohol consumption or craving compared to placebo.[330]	Five RCTs (n=528) found that disulfiram was no more effective than placebo in supporting abstinence or preventing relapse.[358-362] A 2014 meta-analysis of 17 open-label trials (n=2,104) concluded that disulfiram is effective in supporting abstinence if administered under structured and supervised conditions.[354]
Concurrent Alcohol Use	Safe to start while patients are using alcohol; has been studied for the reduction of alcohol consumption in non-abstinent individuals.[316-318] Outcomes do not appear to differ for patients who complete withdrawal management prior to starting treatment compared to those who do not.[315] Completion of withdrawal management is not required prior to treatment start.	Safe to start while patients are using alcohol, but outcomes may be improved if patient has been abstinent for ≥3 days.[261] Abstinence is recommended after starting treatment (where possible) due to potential risk of combined CNS-related side effects, although studies suggest concomitant use of alcohol and therapeutic doses of gabapentin does not increase sedation or motor impairment.[261] Completion of withdrawal management is not required prior to treatment start.	Due to severity of disulfiram-alcohol reaction, **patients should not consume alcohol while taking disulfiram.** Disulfiram must never be administered to a patient without their full knowledge and consent, and patients and families must receive education on side effects and risks associated with the disulfiram-alcohol reaction. Disulfiram should never be administered to a patient until they have abstained from using alcohol for at least 12 hours.
Contraindications	1. Hypersensitivity to topiramate 2. Pregnant or planning to become pregnant 3. Narrow angle glaucoma 4. History of nephrolithiasis	Hypersensitivity to gabapentin	1. Concurrent or recent use of metronidazole, alcohol, or alcohol containing preparations 2. Alcohol intoxication 3. Severe myocardial disease, coronary occlusion 4. Active psychosis 5. Hypersensitivity to disulfiram or to other thiuram (rubber) derivatives

[n] Contraindications, cautions, and side effects have been abstracted in part from Health Canada-approved product monographs for specific clinical indications. Only disulfiram has been approved for the treatment of AUD in Canada. Duration and dosages used for indicated conditions (e.g., seizure disorders) may differ from those used for off-label indication of AUD treatment. Data should be interpreted with this caution.

Box 7 Considerations for Referral to Inpatient Treatment Programs[517,521,522]

- Individuals who have not benefited from multiple previous treatment attempts
- Individuals with co-occurring substance use or mental health disorders
- Individuals with concurrent medical conditions
- Individuals in an unstable social environment or circumstances
- Pregnant individuals
- Indigenous peoples — some inpatient treatment programs offer cultural interventions and tailored programming

Table 11 The FRAMES Model for MI-Based Brief Interventions[144,146]

Feedback	Provide individualized *feedback* on screening or assessment results. Asking open-ended questions about how the patient feels or thinks about the feedback can aid discussion.
Responsibility	Using a strengths-based, patient-centred approach, emphasize that *responsibility* for making the choice to change behaviour ultimately rests with the individual.
Advice	Seek permission from the patient first before giving advice. Provide clear *advice* that cutting down or stopping alcohol use will reduce risk of future problems. Many patients are unaware that their current drinking patterns could potentially lead to health or other problems, or make existing problems worse. Increased awareness of their personal risk can provide reasons to consider changing behaviour.
Menu	Review a "*menu*" of different options for reducing alcohol use and encourage patient to choose the strategies that they feel best fit their circumstances and needs. Providing choice reinforces a patient's sense of control and responsibility and can strengthen motivation to change. Using a shared-decision making framework, set goals that are realistic and meaningful to the patient.
Empathic	Use a warm, *empathic* counseling style, which involves listening, understanding, and reflecting that understanding back to the patient (e.g., "reflective listening"), and is associated with improved BI outcomes.
Self-Efficacy	Encourage and reinforce the patient's *self-efficacy* and confidence in their ability to change. Individuals who believe that they can make changes are much more likely to do so than those who feel powerless or helpless to change their behaviour.

Helpful Tables

Clinical Institute Withdrawal Assessment for Alcohol-Revised might be an unreliable tool in the management of alcohol withdrawal

- ***Objective alcohol withdrawal scale***
- *The objective alcohol withdrawal scale is applied as follows:*
- *Score 1 point for each of*
  - *-systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 90 mm Hg;*
  - *-heart rate ≥ 90 beats/min;*
  - *-tremor;*
  - *-diaphoresis; and*
  - *-agitation*
- *If total ≥ 2 give 1 mg oral lorazepam (or 10 mg of diazepam)*
- *If total ≥ 3 give 2 mg oral lorazepam (or 20 mg of diazepam)*
- *Reassess every hour until score is < 2 for 3 consecutive measures, then reassess every 6 hours for 24 hours, then every 24 hours for 72 hours, then discontinue*
- Highlights:
  - CIWA can be heavily subjective, only 3/10 components can be rated by observation alone
  - Issues arise when language barrier, confusion, delirium, acute psychosis, dementia, mechanical communication problems
  - NOT intended as alternative to CIWA but rather an approach to treatment that may be useful when other validated tools cannot reliably be applied
  - Can modify – ie. If HTN at baseline, use higher BP cut off
  - HR may be excluded if uncontrolled a fib or sepsis
  - Tremor excluded if essential tremor
  - Can increase cut offs if concern with benzo toxicity

K and S

- **15% of ETOH use disorder die by suicide**
- 30-40% lifetime MDD in ETOH users
- Genetics in 60%
- Intoxicating effects higher when blood levels rising
- **90% ETOH metabolized in liver**, remainder in lungs and kidneys
- **Alcohol causes decreased REM, decreased deep sleep, more sleep fragmentation**
- **Tremors in 6-8 hrs, psychosis in 8-12 hrs, seizures in 12-24 hrs, DTs in 72 hrs, but monitor for one week**
- Withdrawal seizures = stereotyped, generalized and tonic clonic
- If **delirium tremens – 20% mortality** – physical illness usually predisposes
- Atypical antipsychotics decrease seizure threshold
- Avoid restraints
- Wernicke's has vestibular dysfunction, horizontal nystagmus, lateral orbital palsy and gaze palsy
- **If sluggish reaction to light and anisocoria think Korsakoff's**
- **Only 20% recover from Korsakoff's, still give thiamine**
- ETOH blocks consolidation of new memories into old memories
- **3% of people experience hallucinations/delusions – in context of clear sensorium unlike DTs, tx with benzos**
- **Alcoholic pellagra encephalopathy – confusion, myoclonus, hypertonia, fatigue, apathy, irritability, anorexia, insomnia – treat with niacin**
- **FASD has 35% risk in F with ETOH use disorder**
- Anxiety prominent in withdrawal – **80% up to 4 weeks; can consider acamprosate**
- **Do not use disulfiram if CAD, heart issues, impulsive, psychosis, epilepsy, hepatic dysfunction – bad in pregnancy, can cause hepatitis, optic neuritis, neuropathy**
- **Naltrexone reacts with yohimbine**
- **In acamprosate – concern about suicide, lots of GI side effects, decreased libido**

Resources

- DSM V
- K and S
- Ottawa Review Lecture – Dr. Crockford
- Toronto Review Lecture – Dr. Franchuk
- Clinical Institute Withdrawal Assessment for Alcohol-Revised might be an unreliable tool in the management of alcohol withdrawal, Knight and Lappalainen, Canadian Family Physician, 2017
- Guidelines:
  - APA AUD Guidelines 2018
  - Canada's Low Risk Guidelines
  - Provincial Guideline for the Clinical Management of High Risk Drinking and Alcohol Use Disorder, BC Centre on Substance Use

RC ROUNDS DR. A JEWETT

OPIATE USE DISORDERS

MCQ

- When is an opioid dependent patient most likely to die from an overdose?
  - After completing detox
  - During heavy use
  - When combining with stimulants
  - When on methadone

MCQ

- Which treatment has evidence in prescription opioid use disorders?
  - Methadone
  - Suboxone
  - Methadone and Suboxone
  - Clonidine

MCQ

- 30 year old woman, pregnant, on methadone in the 3rd trimester. What do you do with her methadone dose?
  - Switch to Suboxone
  - Decrease the dose because she will deliver soon and you want to avoid NAS
  - Keep the same dose
  - Increase the dose as renal clearance increases and plasma concentration of methadone decreases

MCQ

- 35 year old surgeon recently completed rehabilitation for an IV opiate use disorder. He wants treatment to stay abstinent so he can keep operating. What would you use?
  - Clonidine
  - Suboxone
  - Naloxone
  - Naltrexone

OPIOID USE DISORDER

- A problematic pattern of opioid use leading to clinically significant impairment or distress as manifested by at least two of the following, occurring within a 12 mo period:
  - Opioids are often taken in larger amounts or over a longer period than was intended
  - There is a persistent desire or unsuccessful efforts to cut down or control opioid use
  - A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
  - Craving, or a strong desire or urge to use the opioid
  - Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
  - Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
  - Important social, occupational, or recreational activities are given up or reduced because of opioid use
  - Recurrent opioid use in situations in which it is physically hazardous
  - Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused by the substance
  - Tolerance, as defined by either of the following:
    - A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    - A markedly diminished effect with continued use of the same amount of an opioid
    - Do not use this criterion if taking opioids under medical supervision
  - Withdrawal as manifested by either of the following:
    - The characteristic opioid withdrawal syndrome
    - Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms
- Specify if early remission (3-12 mo), sustained remission (>12 mo), on maintenance therapy, in a controlled environment

OPIOID USE DISORDER

Used for no legitimate medical purpose, or if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition

Often have conditioned responses to drug related stimuli – often contribute to relapse, are difficult to extinguish, and typically persist long after detox is completed

Can be associated with drug related crimes, in health care professionals – diversion, marital difficulties, employment issues

12 mo prevalence 0.37% 18 and older (may be an underestimate – large number of incarcerated individuals)

Higher in males than females (1.5:1 for non-heroin and 3:1 for heroin)

Female adolescents may have a higher likelihood of developing opioid use disorders

Prevalence decreases with age, highest among adults 29 or younger

Usually onset in late tends or early 20s

Relapse following abstinence is common

Mortality 2% per year

20-30% of people achieve long term abstinence

Military service personnel who became dependent on opioids in Vietnam – over 90% achieved abstinence after they returned, but had increased ETOH or amphetamine use disorder, increased suicidality

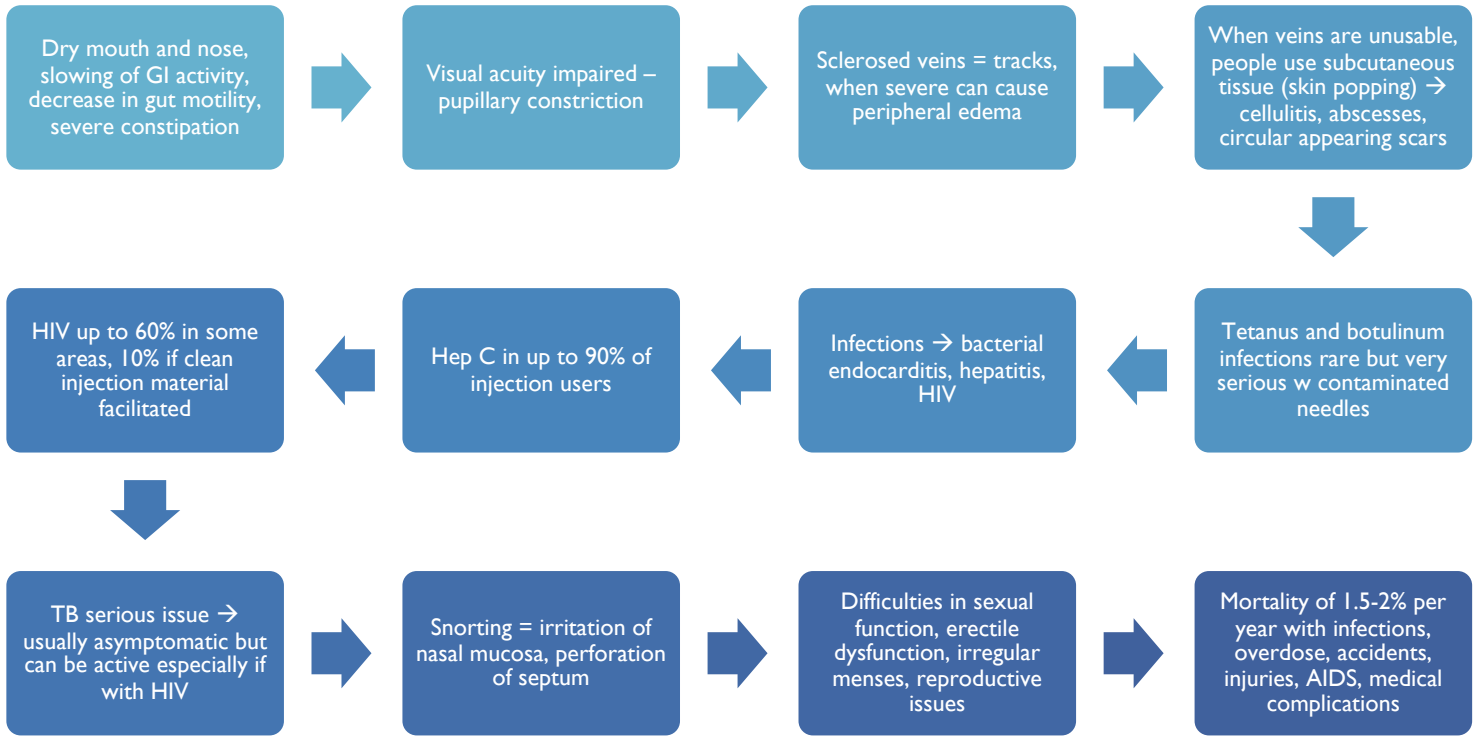
0.37% prevalence
M>F especially for heroin
F adolescents more likely to develop opioid use disorders
Onset 20s
Mortality 2% per year
20-30% achieve long term abstinence

OPIOID USE DISORDER

Increasing age is associated with a decrease in prevalence as a result of early mortality and remission of symptoms after age 40	Risks: • Genetic factors – impulsivity and novelty seeking temperament • Peer factors	Seen more increasingly in white middle-class individuals, especially females	Medical personnel with access may be at increased risk	Urine tests remain positive for most opioids for 12-36 hours after administration
Fentanyl not detected by standard urine tests but can be identified by more specialized procedures for several days	Methadone, buprenorphine, and LAAM have to be specifically tested for and will not cause a positive test on routine labs – can be detected for several days up to one week	Screening test results for hep A, B and C are positive in as many as 80-90% of opioid users – active infection or past	HIV prevalent in injection opioid users as well	Mildly elevated liver function test results common – either resolving hepatitis or toxic injury from contaminants of injected material
Subtle changes in cortisol secretion patterns and body temperature regulation have been observed for up to 6 mo following detox	Heightened risk of suicide attempts and completed suicides	Accidental and deliberate opioid overdoses	Can have opioid withdrawal or intoxication induced depression w completed suicides as result	Nonfatal accidental overdose and suicide attempt are not the same

Urine + for 12-36 hrs after admin
Heightened risk suicide

CONSEQUENCES OF OPIOIDS IN BODY



Dry mouth, slowed GI, poor visual acuity, pinpoint pupils, cellulitis

Hormonal issues

Mortality secondary to infxn, OD, accidents, injuries, AIDS

CONSEQUENCES OF OPIOIDS IN BODY

1. In some areas, violence has more deaths than overdose or HIV
2. Physiological dependence in ½ of infants with moms with opioid use disorder – can produce severe withdrawal syndrome requiring treatment
3. Opioids are less likely to produce symptoms of mental disturbance than other drugs, more depression
4. Pupil constriction and response to naloxone → how you can tell it isn't ETOH or sedative intoxication
5. Withdrawal = rhinorrhea, lacrimation, pupillary dilation, anxiety and restlessness, nausea, vomiting, diarrhea, abdominal cramps
6. Most common medical comorbidity = viral (HIV, hepatitis) and bacterial infections – less in prescription use
7. Other substance use disorders common = tobacco, alcohol, cannabis, stimulants, benzos
8. Risk of depression, especially in chronic intoxication or stressors
9. Insomnia common especially during withdrawal
10. ASPD much more common in opiate use disorder
11. Higher rates of PTSD, conduct disorder

Physiological dependence in 50% of babes born to moms w OUD
w/d = fluids, big pupils, pain
Other SUDs common
Viruses, ASPD, PTSD, Conduct

OPIOID INTOXICATION

- Recent use of an opioid
- Clinically significant problematic behavioral or psychological changes (ie. Initial euphoria followed by apathy, dysphoria, psychomotor agitation or retardation, impaired judgment) that developed during, or shortly after, opioid use
- Pupillary constriction (or **dilation due to anoxia from severe overdose**) and one or more of the following signs or symptoms developing during or shortly after opioid use:
  - **Drowsiness or coma**
  - **Slurred speech**
  - **Impairment in attention or memory**
- Signs and symptoms are not from another medical condition, substance, mental disorder
- Specify if with perceptual disturbances (hallucinations with intact reality testing in absence of delirium)

OPIOID WITHDRAWAL

- Presence of either of the following:
  - Cessation of (or reduction in) opioid use that has been heavy and prolonged (ie. Several weeks or longer)
  - Administration of an opioid antagonist after a period of opioid use
- Three or more of the following developing within **minutes to several days** of above:
  - **Dysphoric mood**
  - **Nausea or vomiting**
  - **Muscle aches**
  - **Lacrimation or rhinorrhea**
  - **Pupillary dilation, piloerection, or sweating**
  - **Diarrhea**
  - **Yawning**
  - **Fever**
  - **Insomnia**
  - Signs or symptoms cause clinically significant distress or impairment
  - Not from another medical condition, mental disorder, substance

OPIOID WITHDRAWAL

- Withdrawal syndrome can be precipitated by administration of an opioid antagonist (naloxone or naltrexone), or administration of opioid partial agonist such as buprenorphine to a person currently using a full opioid agonist
- First anxiety, restlessness, achy feeling in back and legs → irritability and increased sensitivity to pain
- **Piloerection and fever are more severe withdrawal – advanced**
- **Speed and severity of withdrawal depends on half-life of opiate**
- Physiologically dependent on short acting drugs like **heroin – withdrawal sx in 6-12 hours after last dose, peak in 1-3 days, subside in 5-7 days**
- Symptoms may take 2-4 days to emerge in the case of longer acting drugs like methadone, LAAM, or buprenorphine
- Less acute withdrawal symptoms can last for weeks to months; **more chronic sx = anxiety, dysphoria, anhedonia, insomnia**
- **Males may experience piloerection, sweating and spontaneous ejaculations while awake**
- Can occur in medical management of pain
- 60% of individuals who had used heroin at least once in past 12 mo had withdrawal
- Typical in course of disorder – can be escalating pattern

OTHER OPIOID INDUCED DISORDERS

DEPRESSION, ANXIETY, SLEEP DISORDER, **SEXUAL DYSFUNCTION**, DELIRIUM

METHADONE AND PREGNANCY – COLLEGE OF PHYSICIANS AND SURGEONS, DR. RIEB 2016

- Opioid use can interfere with fertility – heroin 60-90% have menstrual irregularities; in methadone the majority resume regular menses by 6-12 mo
- Opioids are not physical teratogens, but heroin can be cut with them (ie. Quinine, cocaine, amphetamine)
- Opioid use is not what endangers in utero but withdrawal and associated risks do endanger fetus
- Heroin can result in abruption, abortion, premature labor, IUGR, decreased birth weight and head circumference, increased NAS and SIDS and feeding problems, more illegal activity, sex trade, needle use, STDs, viremia, maternal mortality, family disruption
- Methadone stops withdrawal cycle, decreases prematurity rates, increased birth weight and head circumference, decreased infant mortality, better prenatal care and nutrition, babies w normal milestones by 18 mo, less maternal mortality, less risk of infections, increased family cohesion
- However methadone can cause sweating, constipation, libido, sleep and nausea issues for mom and increased risk of more prolonged and pronounced NAS, SIDS in baby
- If female pregnant pt is on heroin, convert to methadone or buprenorphine – in hospital is recommended, faster; do not use clonidine, naloxone, naltrexone
- Many women are most stable if maintained on methadone through delivery and six months postpartum
- In second and third trimester, pregnant women have increased weight and blood volume and may need increased dose once daily; or become rapid metabolizers and need split dose
- Best dose is lowest dose that keeps woman out of withdrawal
- Tapering is possible but risk of relapse high, go very slowly
- In labor – continue methadone, avoid fentanyl, cannot give Narcan to baby due to seizure risk
- Can have epidural or NO if appropriate
- Postpartum may gradually lower methadone dose
- In neonate – observe for NAS, rx morphine if needed
- MOTHER study – compared methadone to buprenorphine perinatally and observed infant outcomes; both safe and effective
- Buprenorphine use led to less morphine needed to treat baby, shorter length of hospital stay; methadone provided greater retention in tx
- Methadone is still gold standard
- If patient is on suboxone, change to pure buprenorphine
- Breastfeeding is not contraindicated with methadone, but is if HIV positive or active drug use

Opioid not teratogen but contaminants and risks are
Methadone = better baby outcomes, but risk of NAS, SIDS
Get pregnant lady on methadone ideally in hospital and maintain
Increase dose as pregnancy go on
In labor – continue methadone, don't Narcan baby – seizures, can use epidural
Lower dose gradually postpartum
Can give baby morphine for NAS
MOTHER study – both buprenorphine and methadone good, methadone greater retention, gold standard
No naloxone component
Can breastfeed on methadone, but not if active drug use or HIV+

MANAGEMENT OF OPIOID USE DISORDERS – A NATIONAL CLINICAL PRACTICE GUIDELINE 2018 CMAJ

- Initiate opioid agonist treatment (with **buprenorphine-naloxone whenever feasible**) to reduce the risk of toxicity, morbidity, and death, and to facilitate safer take-home dosing
- **For individuals responding poorly to buprenorphine-naloxone, consider transition to methadone**
- Initiate opioid agonist treatment with methadone when treatment with Suboxone not the preferred option
- For individuals with a successful and sustained response to methadone who express a desire for treatment simplification, consider transition to suboxone because its **superior safety profile allows for more routine take-home dosing and less frequent medical appointments**
- In patients for whom first and second line treatment options are ineffective or contraindicated, opioid agonist treatment with **slow release oral morphine (once daily witnessed)** can be considered
- Offering **withdrawal management alone (detox without transition to long term addiction treatment) should be avoided – increased rates of relapse, morbidity and death**
- When withdrawal management (without transition to opioid agonist treatment) is pursued, **provide supervised slow (>1mo) opioid agonist taper** (in an outpatient or residential treatment setting) rather than a rapid (<1 week) taper; patients should be transitioned to long term treatment to help prevent relapse and associated health risks
- For patients with a successful and sustained response to opioid agonist treatment who wish to discontinue treatment, **consider a slow taper approach (months to years);** ongoing addiction care after cessation
- **Psychosocial treatment interventions and supports should be routinely offered but not viewed as mandatory** for accessing opioid agonist treatment
- **Oral naltrexone can be considered as an adjunct medication if cessation of opioid use is achieved (weak recommendation - ie. Physician)**
- Information and referrals to **take home naloxone programs and other harm reduction services (ie. Provision of clean drug paraphernalia)** as well as other general health care services, should be routinely offered as part of standard care for opioid use disorders

MANAGEMENT OF OPIOID USE DISORDERS – A NATIONAL CLINICAL PRACTICE GUIDELINE 2018 CMAJ

- Suboxone = partial agonist, ceiling effect, lower resp depression, better safety (6x), less drug interactions, less sex dysfunction, less QT prolongation, can be take home dosing, up to 1-2 weeks worth of meds at a time
- Half life methadone 24-36 hrs, suboxone 24-69 hrs
- Relapse rates without agonist therapy = 60-90%

- **Suboxone is partial opioid agonist, methadone is full**
- Suboxone has reduced risk of fatal overdose because of **lower potential for respiratory depression**
- **6 x safer than methadone in terms of overdose** risk in one study
- **Methadone has more adverse reactions and drug-drug interactions (ie. Anti-retrovirals, antibiotics, antidepressants)**
- Methadone has substantial **QT prolonging effects**, especially at higher doses
- Methadone has **more male sexual dysfunction**
- **Suboxone can safely be provided for take home dosing** as soon as clinical stability is achieved – often within 7-10 days of treatment initiation, can have rapid titration to therapeutic dose
- **Suboxone needs patient to be in moderate withdrawal** before induction to avoid precipitated withdrawal
- No significant difference among buprenorphine-naloxone, methadone, and alpha—adrenergic agonists in terms of severity of withdrawal symptoms, adverse effects, withdrawal completion, and poor sustained abstinence rates in the absence of linkage to long term addiction treatment
- **If withdrawal management is offered, suboxone taper may offer faster symptom relief and higher rates of withdrawal completion**
- In pregnant women → monoproduct buprenorphine may be similarly safe and effective for treatment; **most evidence is for methadone**; **no naloxone as theoretical risk of harm to fetus from elevation of cortisol levels**
- **Relapse rates without agonist therapy 60-90%,** increased risk of morbidity and death
- For all treatment – harm reduction should be offered → **education regarding safer use of sterile syringes and needles, access to supplies, access to take home naloxone kits, access to supervised consumption sites**
- Methadone has long elimination half life = **24-36 hrs on average**
- Buprenorphine is long acting partial mu opioid receptor agonist – **half life 24-69 hours (average 37)** – higher affinity for opioid receptor enables it to displace other opioids but maximal effect is lower than full agonists due to **limiting activated effect on mu receptor (ceiling effect – lowers risk of respiratory depression, side effects, better safety**)
- **Naloxone has no effect when taken sublingually, but if injected will precipitate withdrawal symptoms**
- No evidence for psychosocial treatment, but should be offered
- **With methadone – weekly visits when stable, monthly UDTs, take home after >4 weeks on stable dose and 12 weeks negative UDT, begin with one take home dose per week; most have two witnessed doses per week with remaining as carries**
- **With suboxone – induction 2-4 mg, stable 8-12 mg, once at stable dose, can consider alternate day dosing (double dose MWF, single dose Sun), UDTs at least monthly then 4 per year, can increase carries until 1-2 weeks worth of meds at one time**

Methadone	Suboxone
Advantages	
Potentially better treatment retention, especially if higher intensity opioid use disorder – long hx of opioid use, injection heroin use, high tolerance and frequent use, high risk of dropping out May be more effective for withdrawal symptom control in chronic, severe opioid use disorder Treatment initiation easier **No maximum dose** **Approved for pain control in Canada**	**Health Canada exemption not required to prescribe in most provinces** Lower risk of overdose due to partial agonist properties and ceiling effect for respiratory depression (in absence of benzos and ETOH) **Lower risk of public safety harms if diverted** Milder adverse effect profile **Easier to transition from suboxone to methadone if unsuccessful** **Shorter time to achieve therapeutic dose (1-3 days)** Lower risk of toxicity and drug-drug interactions **Milder withdrawal symptoms when discontinuing treatment – good for lower intensity opioid dependence and people planning to taper off in a relatively short period** Optimal for **rural and remote locations** where access to care is limited, daily witnessed not feasible More flexible dosing schedules (alternate day dosing, earlier provision of 1-2 week take home prescriptions) – **support patient autonomy** and **reduce costs** **Easier to adjust and re-titrate following missed doses due to partial agonist properties**
Disadvantages	
Health Canada exemption required to prescribe Higher risk in overdose More witnessed doses, slow graduated schedule for take-home (ie. 1 take home dose per week x 4 weeks) **More severe adverse effect profile (somnolence, ED, cognitive blunting)** **Longer time to achieve therapeutic dose (weeks)** **Hard to go from methadone to suboxone** Higher risk if **diverted** Higher potential for drug drug interactions Associated with **QTc prolongation and increased risk of arrhythmia** in higher doses Can be more expensive with more dispensing and witnessing	Lower treatment retention, especially in higher intensity opioid use disorder May cause withdrawal if protocols not followed **Suppression of withdrawal symptoms may not be adequate for high opiate tolerance users** Reversing effects of overdose can be challenging because of pharm of buprenorphine (high affinity and long half life) Patients require education on how to take sublingual doses correctly – **hold under tongue til dissolved, up to 10 min, do not drink or smoke, minimize swallowing** Nonadherence to treatment may require frequent reinductions

MANAGEMENT OF OPIOID USE DISORDERS – A NATIONAL CLINICAL PRACTICE GUIDELINE 2018 CMAJ

OTTAWA REVIEW COURSE – DR. CROCKFORD

CAMH → 1 = alcohol (18% disorder, 50-60% teens use), 2 = cannabis, 3 = rx opioids, 3 = tobacco

- **Highest risk of death after completing detox – tolerance down**
- Synthetic very bad – fentanyl
- Pain and intoxication effects mediated by brain opioid receptors – primarily **mu** (also kappa and delta)
- **Subjective experiences adapt faster than respiratory suppressive effects**
- Higher risk of death **after detox**, combining use with respiratory suppressants (ie**. Benzos**) or **high potency agents (fentanyl)**
- **Prescription opioids second most common type of drug use disorder in Canada**
- Risks in prescribing: **prior addiction history, psychiatric history, family history of addiction, antisocial personality, non-specific pain source, preference for specific agent (opioid risk tool)**
- Functional improvement vs. cognitive impairment and depression
- Intoxication = sedation, pinpoint pupils, respiratory suppression, cognitive impairment, coma, death, **respiratory suppression (direct effects on brainstem) – protect airway!** – identify drug, amount, time of use and route
- **IV naloxone 0.4-0.8 mg – repeat if no response**
- **High potency or long action will require higher or repeat doses**
- If long acting (methadone) – will drop down again after naloxone wears off
- Refer to addiction tx

Brainstem less tolerance than euphoria – respiratory depression
Give Naloxone in OD – if it doesn't work, do it again, may need repeats
Highest risk of death after detox

OTTAWA REVIEW COURSE – DR. CROCKFORD

Treatment:

- **Buprenorphine/Naloxone first line, methadone second line**
- Withdrawal management w abstinence focus NOT recommended for opioid use disorders unless very mild or required by patient
- **Worse outcomes than no treatment – relapse, morbidity, death**
- If desired by patient, need **slow taper and ongoing addiction treatment**

Suboxone

- Naloxone not absorbed only if injected
- Partial mu agonist with high receptor affinity – less abuse and overdose potential than methadone
- Usual dosing **8-16 mg daily**, ceiling effect
- Must be in opioid withdrawal to start (COWS) to avoid precipitated withdrawal
- **Evidence in prescription opioid use disorders**
- **If use street opioids on suboxone – get less high, binds preferentially to receptor**
- Some patients with high tolerance to opioids may respond poorly –they need methadone
- Avoid benzos

Methadone

- **Additive effect if other opioids also used – overdose**
- Full opioid agonist
- Extensive research data supporting use particularly for IV opioid use and high tolerance
- No trials for prescription opioid use disorders
- Problematic administration arrangement
- QT interval prolongation potential
- Typical dosing of **60-120 mg/day**
- **More data than buprenorphine for pregnancy**

TORONTO REVIEW COURSE

- **In methadone, EDDP is metabolite that can be used to measure compliance**
- Nalmefene – not yet approved in Canada, newer med similar to naltrexone but longer duration of action, no liver impairment
- Vivitrol – not yet in Canada, depot naltrexone for 1 mo
- Baclofen – off label use, GABA B receptor agonist – can decrease cravings and ETOH consumption, no effects on liver function, no interactions with opioids
- Pregabalin – off label – curbs withdrawal sx

K AND S

- **15% of opiate users attempt suicide**
- In opioid withdrawal – insomnia, bradycardia, **temperature dysregulation**, and cravings can continue for months
- **No opiates and MAOIs – drug reaction, death**
- **Naltrexone is 72 hr antagonist**

RESOURCES

- Management of opioid use disorders – a national clinical practice guideline 2018 CMAJ
- Methadone and pregnancy – CPSBC, Dr. Rieb 2016
- CRISM National Guideline for the Clinical Management of Opioid Use Disorder
- DSM V
- K and S
- Ottawa Review Course – Dr. Crockford
- Toronto Review Course – Dr. Franchuk