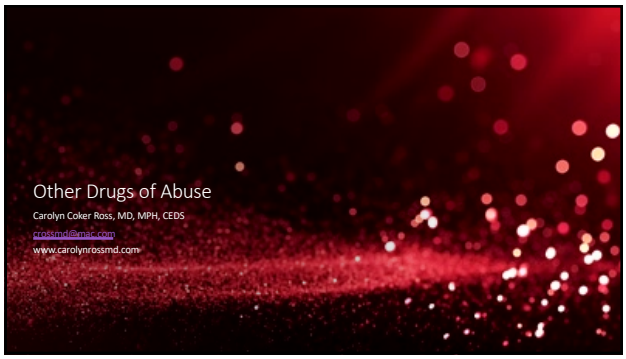


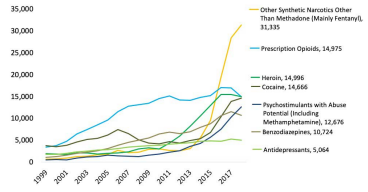
Myths about Drug Use

1. Opioids are the Most Common Drugs of Abuse
2. Most Drugs come across the border from Mexico (or the US)
3. Males with addiction are more likely to die than females
4. The drug problem is getting worse all over the world
5. Canada is not a major drug producer

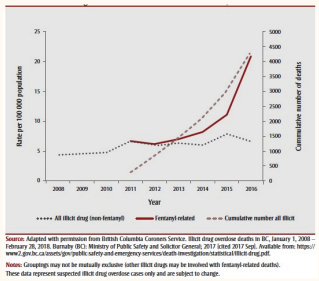
Other Drugs of Abuse

National drug overdose deaths – 1999-2018

Figure 2. National Drug Overdose Deaths
Number Among All Ages, 1999-2018



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2018 on CDC WONDER Online Database, released January, 2019



Source: Adapted with permission from British Columbia Coroners Service. Illicit drug overdose deaths in BC, January 1, 2008 – February 28, 2018. Burnaby (BC): Ministry of Public Safety and Solicitor General; 2017 cited 2017 Sept. Available from: https://www2.gov.bc.ca/assets/gov/public-safety-and-emergency-services/death-investigation/statistics/illicit-drug.pdf.

Notes: Groupings may not be mutually exclusive (either illicit drugs may be involved with fentanyl-related deaths).
These data represent suspected illicit drug overdose cases only and are subject to change.

Figure 1

Illicit drug overdose death rates in British Columbia, 2008–2016

Cannabis

- THC is the major psychoactive component
- The unpollinated female plants are called hashhish
- Cannabinoids are compounds that are structurally similar to THC
- Marijuana refers to cannabis leaves and other crude parts of the plant
- Cannabis oil (hashish oil) is a concentrate of cannabinoids obtained by solvent extraction of the crude plant material or of the resin.

Cannabis

147 million people

2.5% of world population

vs.

0.2% for cocaine
0.2% for opiates

Chronic Health Effects

- Selective changes in cognitive function
- Development of a cannabis dependence syndrome
- Exacerbation of schizophrenia
- Airway and lung inflammation or injury
- Use by pregnant women can lead to low birth weight babies

Therapeutic Benefits

- Treatment of nausea and vomiting in HIV / Cancer
- Treatment of asthma and glaucoma
- Antidepressant, anti-spasmodic, appetite stimulant and anti-convulsive

Cannabis

In most countries, cannabis is legal for medical purposes.

Canada recently legalized recreational cannabis.

Marijuana is legal in 11 states for adults over the age of 21, and legal for medical use in 33 states.

Cannabis

- Contemporary strains can be highly potent
  - Severe intoxication
  - Greater risk of use disorder
  - Cognitive impairment, "amotivational syndrome"
- Common among patients with opiate use disorder including those on MAT
- No specific treatment other than CBT
- Cannabis withdrawal and opioid withdrawal syndromes share features, including irritability, insomnia, anxiety
- Patients report taking cannabis to help with sleep or anxiety
- Difficult to quantify abuse or use disorder due to differences in potency

Cannabis Use - Canada

- Most prevalently used illicit drug
- 2015- past year use = 12% (2013 = 11%)
  - Males (15%) > Females (10%)
  - Increase in use by females from 7% in 2013
  - Age at initiation – 17 years of age
- 24% report using cannabis for medical reasons
- 33% consume daily
- Used varied by Province
  - 8% use in PEI
  - 17% in BC

Canadian Alcohol and Drug Use Monitoring Survey.

Synthetic Cannabinoids

- Synthetic cannabinoids are a class of synthetic molecules that bind to cannabinoid receptors in the brain and body (the same receptors to which THC and CBD attach).
- They are "designer drugs" that are usually smoked and have been marketed as herbal incense, or "herbal smoking blends".
- They are sold under common names like **K2, Spice, Black Mamba, Kronic and Synthetic Marijuana**.

Synthetic Cannabinoids

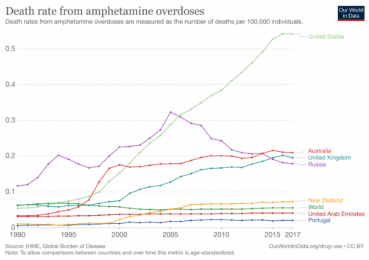
- Usually smoked or brewed as a tea
- Also used in e-cigarettes
- Not easily detected with standard drug tests
- Grouped as "new psychoactive substances"
- The active ingredients are made in lab (not natural)
- Can be addictive.
- Can produce stronger effects than THC
- Chemical composition is unknown and ever-changing
- Effects:
  - Elevated mood and relaxation
  - Altered perception
  - Symptoms of psychosis
  - Other
    - Rapid heart rate and blood pressure
    - Vomiting
    - Violent behavior
    - Suicidal thoughts

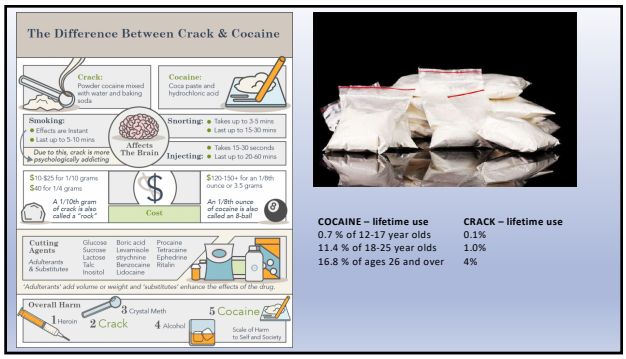
CBD

- CBD stands for cannabidiol and it is derived from cannabis, marijuana and hemp.
- CBD is the main ingredient in hemp and the second main ingredient in marijuana after THC.
- **CBD is not a psychoactive substance**
- Marijuana contains much more THC than hemp, while hemp has more cannabidiol (CBD).
- ***Patients using CBD may test positive for THC***

Stimulants

Stimulants





COCAINE – lifetime use
0.7 % of 12-17 year olds
11.4 % of 18-25 year olds
16.8 % of ages 26 and over

CRACK – lifetime use
0.1%
1.0%
4%

Cocaine and the brain

Cocaine

Short Term Effects
- constricted blood vessels
- dilated pupils
- nausea
- raised body temperature and blood pressure
- fast or irregular heartbeat
- tremors and muscle twitches
- restlessness

Long Term Effects
- *snorting:* loss of smell, nosebleeds, frequent runny nose, and problems with swallowing
- *smoking:* cough, asthma, respiratory distress, and higher risk of infections like pneumonia
- *consuming by mouth:* severe bowel decay from reduced blood flow
- *needle injection:* higher risk for contracting HIV, hepatitis C, and other bloodborne diseases, skin or soft tissue infections, as well as scarring or collapsed veins
- Parkinson's disease
- Paranoia
- Auditory hallucinations

Methamphetamine versus Cocaine

Methamphetamine	Cocaine
Stimulant	Stimulant and local anesthetic
Man-made	Plant-derived
Smoking produces a long-lasting high	Smoking produces a brief high
50% of the drug is removed from the body in 12 hours	50% of the drug is removed from the body in 1 hour
Increases dopamine release and blocks dopamine re-uptake	Blocks dopamine re-uptake
Limited medical use for ADHD, narcolepsy, and weight loss	Limited medical use as a local anesthetic in some surgical procedures

- Stimulant drug – pill or powder form
- Crystal methamphetamine – a form of the drug that looks like glass fragments or shiny bluish white rocks
- Chemically similar to amphetamine

Methamphetamine

Methamphetamines

- Other common names for methamphetamine include *blue, crystal, ice, meth,* and *speed*.
- Taken by:
  - smoking
  - swallowing (pill)
  - snorting
  - injecting the powder that has been dissolved in water/alcohol
- Binge / Crash pattern

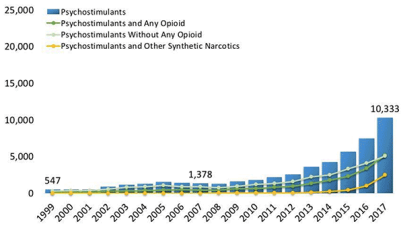
Methamphetamine Use

- 2017 Statistics:
  - .6% of the population (1.6 million) used in past year
  - Average age of first use = 23.3 years
  - 0.4% had a methamphetamine use disorder in 2017
  - Use of methamphetamine by adolescents has declined significantly since 1999
  - Nationwide treatment admissions for methamphetamine misuse dropped from 68 per 100,000 individuals in 2005 to 49 per 100,000 in 2015
  - U.S. drug overdose deaths involving methamphetamine more than doubled from 2010 to 2014.

National Survey on Drug Use and Health: Trends in Prevalence of Methamphetamine for Ages 12 or Older, Ages 12 to 17, Ages 18 to 25, and Ages 26 or Older; 2018 (in percent)[a]

Drug	Time Period	Ages 12 or Older	Ages 12 to 17	Ages 18 to 25	Ages 26 or Older
Methamphetamine	Lifetime	5.40	0.30	2.50	6.50
	Past Year	0.70	0.20	0.80	0.70
	Past Month	0.40	0.10	0.30	0.40

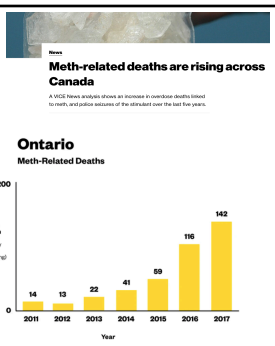
Figure 6. **National Drug Overdose Deaths Involving Psychostimulants With Abuse Potential (Including Methamphetamine), by Opioid Involvement**
Number Among All Ages, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Dea 1999-2017 on CDC WONDER Online Database, released December, 2018

Stimulant Use - Canada

- 1% of Canadians (338,000) over age 15 (no change from 2013) reported past year use of stimulants
- Males = Females
- Highest among those
  - Ages 15-19 (5%)
  - Ages 20-24 (4%)
- From 2016-2017- 22% jump in methamphetamine deaths.
  - BC with highest rates of opioid overdose deaths saw a 32% rise in meth overdoses
  - 84% increase in Manitoba


News

Meth-related deaths are rising across Canada

A VICE News analysis shows an increase in overdose deaths linked to meth, and police seizures of the stimulant over the last five years.

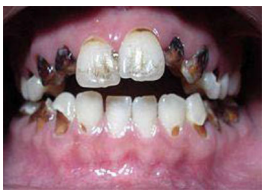
Ontario

Meth-Related Deaths

Methamphetamines

- 1000% increase in brain dopamine
- Reinforces drug-taking behavior
- Short-term effects:
  - Increased wakefulness and physical activity
  - decreased appetite
  - faster breathing
  - rapid and/or irregular heartbeat
  - increased blood pressure and body temperature
- Long term effects:
  - Risky sex → HIV/Hep B and C
  - May worsen the progression of HIV / AIDS
  - extreme weight loss
  - addiction
  - severe dental problems ("meth mouth")
  - intense itching, leading to skin sores from scratching
  - anxiety
  - changes in brain structure and function
  - confusion
  - memory loss
  - sleeping problems
  - violent behavior
  - *paranoia*—extreme and unreasonable distrust of others
  - *hallucinations*—sensations and images that seem real though they aren't

Crystal Methamphetamine



- Changes in the brain reward system
  - Poor coordination
  - Impaired verbal learning
  - Affects emotional and memory centers of the brain
- Some changes may reverse after a year
- Other changes may not recover
  - Increased risk of Parkinson's disorder

Methamphetamine

- 2017 – 15% of drug overdose deaths involved crystal meth
  - 50% of these also involved opiates (esp. fentanyl)
- Treatment of overdose
  - restoring blood flow to the affected part of the brain (stroke)
  - restoring blood flow to the heart (heart attack)
  - treating the organ problems
- Withdrawal symptoms:
  - anxiety
  - fatigue
  - severe depression
  - psychosis
  - intense drug cravings
- There is no MAT for methamphetamine addiction
- Treatment with CBT and motivational incentives

Methamphetamine

Promising new therapy

- A monoclonal antibody (mAb) that is intended to interact with methamphetamine and decrease its ability to enter the brain. They have successfully tested the antibody, called IXT-m200, *in vitro* and in animals and have now advanced its development to the second, penultimate stage of clinical trials. If all continues to go well, they hope to make it available to clinicians and patients in 3 to 5 years.
  - Stevens et al. 2014

- Is a stimulant and also a hallucinogen
- It is a synthetic drug / formerly a "club drug"
- producing feelings of increased energy, pleasure, emotional warmth, and distorted sensory and time perception.
- Can be taken as tablet, dissolved in liquid or snort the powder.
- Molly refers to the crystalline form can be contaminated with bath salts
- Effects last 3-6 hours

MDMA / ECSTASY / Molly

MDMA

- MDMA can affect the body's ability to regulate temperature. This can lead to a spike in body temperature that can occasionally result in liver, kidney, or heart failure or even death.
- MDMA can promote trust and closeness, its use—especially combined with sildenafil (Viagra)—may encourage unsafe sexual behavior.
- Side effects include:
  - nausea
  - muscle cramping
  - involuntary teeth clenching
  - blurred vision
  - chills
  - sweating

MDMA increases the activity of three brain chemicals:

- Dopamine—produces increased energy/activity and acts in the reward system to reinforce behaviors
- Norepinephrine—increases heart rate and blood pressure, which are particularly risky for people with heart and blood vessel problems
- Serotonin—affects mood, appetite, sleep, and other functions. It also triggers hormones that affect sexual arousal and trust. The release of large amounts of serotonin likely causes the emotional closeness, elevated mood, and empathy felt by those who use MDMA.

Case

- 25 y.o. male with history of opiate use disorder on buprenorphine. Also drinks 2-4 beers / day and takes 1 mg of Xanax before bedtime.
- The patient now begins to produce cocaine positive urines. He says he takes cocaine in the morning to combat fatigue and get to work on time. He also says his work is often tedious and the cocaine helps him stay focused. He denies all symptoms of a cocaine use disorder. He asks for a prescription for Adderall (immediate release), mentioning that several years ago a doctor diagnosed him with ADHD and treated him with Adderall. Childhood history yields no indication of problems with performance or behavior at school.

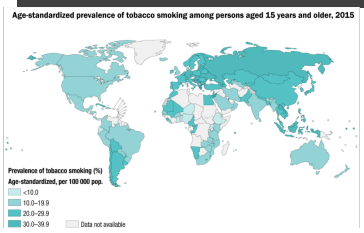
Case questions

- What would be the most appropriate next step in his treatment?
  1. Institute Contingency Management, where cocaine positive urines trigger reductions in buprenorphine dose
  2. Prescribe Adderall, immediate release
  3. Prescribe Adderall, extended release
  4. Counsel that ongoing alprazolam and alcohol use may contribute to his fatigue
  5. Obtain collateral history from his mother about his childhood years

Tobacco Use Disorder DSM-5 305.1 (Z72.0) (F17.200)

1. Larger quantities of tobacco over a longer period then intended are consumed.
2. Tolerance for nicotine
3. Withdrawal symptoms upon cessation of use

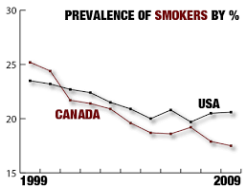
Tobacco



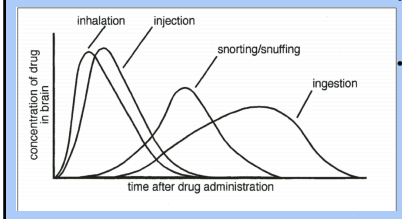
- The leading cause of death, injury and impoverishment
- Causes > 8 million deaths / year with 1.2 million of these deaths due to second hand smoke worldwide
- Kills over half its' users
- 80% of smokers live in low- and middle-income countries
  - World Health Organization

Canada

- Prevalence of cigarette smoking in 2015 = 13% (3.9 million smokers)
  - Decreased from 15% in 2013
  - Males (16%) > Females (10%)
- Variable by Provinces
  - Low of 10% in BC
  - High of 18% in Newfoundland, Labrador and Nova Scotia



Tobacco

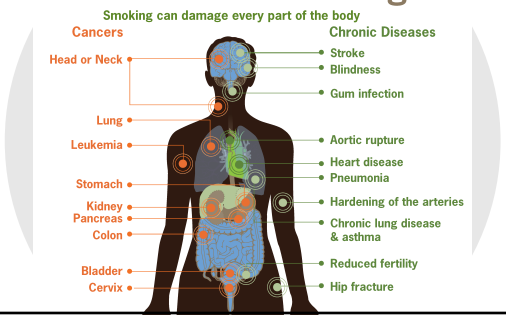


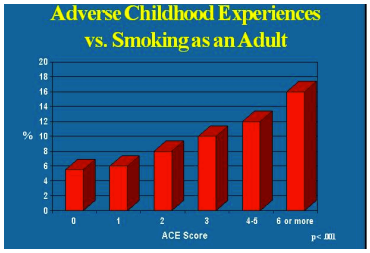
- Smoking is the fastest route for drug administration
- **Heaviness of smoking index:** AM (upon awakening) Time to First Cigarette (TTFC)
  - TTFC < 30 minutes = moderate
  - TTFC = < 5 minutes = severe

Cigarettes

- Cigarette smoke has greater than 7000 compounds (cyanide, carbon monoxide, formaldehyde, acetone, etc.
- Greater than 65 Carcinogens

Risks from Smoking





63 % of smokers have at least one ACE

Persons with 5 or more ACEs are 3 times more likely to smoke or have lung disease

Woman and Smoking

- Increased deaths
  - Emphysema and bronchitis 12X increased risk
  - Tracheal, lung or bronchus cancer – 12 X
- Deaths from lung cancer (1960-1990) increased by 500%
- Lung cancer surpassed breast cancer as leading cause of death in US women
- Increases mortality from coronary heart disease in middle-aged women by 5 X

Effects of second-hand smoke

- Adults: heart disease and lung cancer
- Infants: increase in sudden infant death syndrome
- Children: respiratory diseases / asthma, ear infections
- Pregnant women: low birth weight and pregnancy complications
- 65,000 children die each year as the result of second-hand smoke
- Over 40% of children in the world have at least 1 smoking parent
- Children accounted for 31% of the 600,000 premature deaths attributable to second-hand smoke in 2004
- Neither ventilation nor filtration (or both) can counter the effects of second-hand smoke.

E-Cigarettes (Electronic nicotine delivery systems (ENDS))

- Often used with 1 or more tobacco products
- Aerosols contain numerous toxic products harmful to users and non-users
- Minors who use ENDS double their chances of becoming cigarette smokers later in life
- Increase risk of heart disease and lung disorders
- EVALI (E-cigarette or vaping associated lung injury)
  - Most linked to THC products from "informal sources"
  - Vitamin E acetate
  - 2,668 hospitalizations (median age is 24 y.o.)
  - 68 deaths in 29 states and DC
  - Median age of those who died: 49.5, Range is from 15-75 y.o.

- May be beneficial for adult smokers as a complete substitute for other tobacco products
- Not safe for youth, pregnant women
- 4th generation "pod mods" use nicotine salts (vs. free-base nicotine) → higher levels of inhaled nicotine
- E-cigarette aerosol generally contains fewer toxic chemicals than the what is released from cigarettes.
- However it can contain harmful and potentially harmful substances, including nicotine, heavy metals like lead, volatile organic compounds, and cancer-causing agents.

- E-liquid is what's converted into aerosol with an e-cig product
- It is typically a mixture of water, food grade flavoring, a choice of nicotine levels, cannabis (THC, CBD), propylene glycol (PG) or vegetable glycerin (VG).
- PG and VG are humectants used in e-liquid to produce aerosols that simulate combustible tobacco cigarette smoke.
- The ratio of PG and VG in the e-liquid can change based on whether flavor (higher levels of PG) or plume (higher levels of VG) is desired.

Benefits of quitting

- 12 hours – drop in carbon monoxide in the body
- 2-12 weeks – lung function and circulation increases
- 1 year – risk of coronary heart disease decreases by 50%
- 5 years – stroke risks decreases to that of a nonsmoker
- 10 years – risk of lung cancer falls to 50% of nonsmoker; risk of other cancers drops
- 15 years – heart disease risk is same as non-smoker
- Quitting after a heart attack, reduce their chances of having another by 50%
- Decreases impotence
- Reduces difficulties getting pregnant, pre-term births, low birth weight babies and miscarriage

Tobacco Withdrawal Symptoms

- Depressed mood
- Insomnia
- Irritability, frustration or anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased appetite or weight gain

Mental Health and Smoking Cessation

Meta-analysis 26 studies (gen pop and mental health)

Table 1| **Effect of smoking cessation on mental health. Sensitivity analysis after removal of studies of low quality (me Newcastle-Ottawa scale)**

Outcome	No of studies included	No of studies excluded	Standardised mean difference (95% CI)	
			Effect estimate	Original effect estimate
Anxiety	4	0	−0.37 (−0.70 to −0.03)	−0.37 (−0.70 to −0.03)
Depression	9	1	−0.29 (−0.42 to −0.15)	−0.25 (−0.37 to −0.12)
Mixed anxiety and depression	4	1	−0.36 (−0.58 to −0.14)	−0.31 (−0.47 to −0.14)
Psychological quality of life	4	4	0.17 (−0.02 to 0.35)	0.22 (0.09 to 0.36)
Positive affect	1	2	0.68 (0.24 to 1.12)	0.40 (0.09 to 0.71)
Stress	2	1	−0.23 (−0.39 to −0.07)	−0.27 (−0.40 to −0.13)

Smoking Treatment (Not Cessation)

BRIEF INTERVENTION
- 2As and R (Ask, Advise and Refer)
- Do you use Tobacco? How much? What kinds?
- Document tobacco use at visits
- How do you feel about quitting?
- Can I give your name to someone to get more information?

Principles of co-occurring disorders treatment
- Integrated mental health and addiction services
- Comprehensive services
- Treatment matched to motivational level
- Long-term treatment perspective
- Continuous assessment of substance use
- Motivational interventions
- Psychopharmacology
- Case management

Not easy to quit

- 55% make a serious attempt once a year
- Less than 5% are successful without treatment
- 6 month quit rate = 25% **with treatment**

- It's hard to quit because:
  - Smoking is very addictive
  - Treatment options are limited
    - Some medications
    - Brief counseling support
    - No levels of care
  - Treatment utilization is poor
    - Don't take medications long enough
    - Don't get counseling

Smoking Treatment – Predictors of Abstinence

- Lower level of dependence
- Higher SES, education, insured
- Older age
- No co-occurring behavioral health issue
- Don't have a lot of smokers in their social network
- Quit in first 7 days / Have longer periods of abstinence
- Use of cessation treatment

Best Practices = Counseling + Medication

- Skills training
- Relapse prevention
- Problem solving
- Stress management
- Avoid high risk situations
- Maximize social support

Effectiveness of meds or counseling alone vs. combination

Treatment	No of Studies	Est Odds Ratio (95%ci)	Estimated Quit Rate (%)
Medication alone	8	1.0	22
Meds plus counseling	39	**1.4** (1.2-1.6)	28

Treatment	No of Studies	Est Odds Ratio (95%ci)	Estimated Quit Rate (%)
Counseling alone	11	1.0	15
Meds plus counseling	13	**1.5** (1.3-2.1)	22

2008 US Public Health Service Guideline Update

Medication – Nicotine replacement therapy

- Nicotine replacement therapy
  - Patch, Gum or Lozenge = Over the counter
  - Inhaler / Nasal spray
- Need to use in a scheduled way (not as needed)
- Can be combined with other medications
- Must use for long enough period
- No drug-drug interactions
- Safe enough to be over the counter

Oral forms of nicotine replacement therapy

- Dose frequently – every 1=2 hours
- Slow, buccal absorption
- Acidic foods may decrease absorption
- Mild side effects: mouth and throat irritation
- GI upset if swallowed
- Need prescription for inhaler

Nicotine replacement therapy

Nasal Spray
- Rapid delivery through nasal mucosa
- Has the most side effects: runny nose, nasal irritation, watering eyes
- 2 sprays = 1 dose
- Up to 40 doses / day
- Some risk of dependence

Nicotine inhaler – "Nicotrol"

- 6-16 cartridges per day
- Puff for 20-30 minutes
- Oral puffer
- Acidic beverages decrease absorption
- Mild side effects: throat and mouth irritation

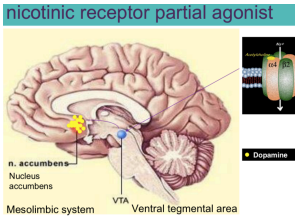
Medications

Buproprion SR
- Most effective dose is 150 – 300 mg / day
- Works on norepinephrine and dopamine systems
- Start 2 weeks before quit date
- Side effects: headache, insomnia
- Contraindication: Hx of Seizures or Eating Disorders
- Efficacy similar to NRT
- Less weight gain with higher dose

Combination therapy
- Long acting patch + short acting gum/lozenge/inhaler
  - Delivers higher dose
  - Immediate relief of cravings
- Patch + gum or spray – odds ratio = **1.9**
- OR Patch + Buproprion – odds ratio= 1.3
  - Improved abstinence
  - Decreased withdrawal
  - Well tolerated
- Varenicline+NRT = not recommended

Varenicline

- For adults 18 and over
- Partial agonist→some dopamine release at nucleus accumbens
- Antagonist – blocks nicotine binding at a4B2
- Contraindications
  - Severe kidney disease
- Common Side Effects
  - Nausea
  - Insomnia
  - Abnormal dreams
  - Constipation
  - Flatulence
  - Vomiting



Effectiveness of medications

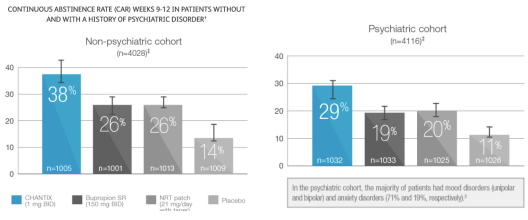
- Patients who achieved abstinence for at least 7 days at the end of 12 weeks and continued Varenicline, had greater abstinence at weeks 13-24.
  - Tonstad, et al. 2006

Results from meta-analyses comparing to placebo (6 month F/U

Medication	No. Studies	OR	95% CI
Nic. Patch (6-14 wks)	32	**1.9**	1.7-2.2
Nic. Gum (6-14 wks)	15	**1.5**	1.2-1.7
Nic. Inhaler	6	**2.1**	1.5-2.9
Nic. Spray	4	**2.3**	1.7-3.0
Bupropion	26	**2.0**	1.8-2.2
Varenicline (2mg/day)	5	**3.1**	2.5-3.8

2008 US PHS Update

Abstinence Rates – EAGLES Study



Athenelli, et al. 2016

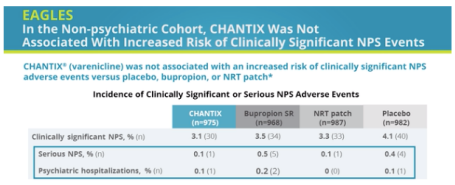
Side Effects and Safety

- NO increased risk of suicide
- NO increased risk of suicidal ideation
- No increased risk of depression
- No increased risk of irritability
- No increased risk of aggression
- Increased risk of sleep disorders
- Increased risk of insomnia
- Increased risk of abnormal dreams
- Reduced risk of anxiety

- Thomas, et al. 2015

Complementary and Alternative Therapies

- 2005 – 6% of smokers used acupuncture, 13% used hypnotherapy
- Meta-analysis comparing CAM vs. Placebo
  - OR for acupuncture = 3.5
  - OR for hypnotherapy = 4.55
- Cochrane Review
  - Acupuncture has RR = 1.18
    - less effective than nicotine replacement therapy
    - No firm conclusions could be drawn



CHANTIX LABEL UPDATE

Boxed Warning Removed and NPS Warning Retained and Updated

Warning Retained and Updated

- Serious neuropsychiatric adverse events have been reported in patients being treated with CHANTIX. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide
- Observe patients for the occurrence of neuropsychiatric adverse events. Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior

Additional HCP Guidance

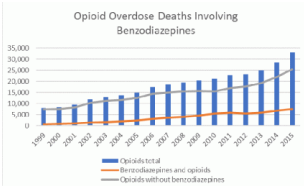
- The healthcare provider should evaluate the severity of the symptoms and the extent to which the patient is benefiting from treatment, and consider options including dose reduction, continued treatment under closer monitoring, or discontinuing treatment

- The most common adverse reactions include nausea (30%), abnormal dreams, constipation, flatulence, and vomiting. Patients should be informed that they may experience vivid, unusual, or strange dreams during treatment with CHANTIX. Patients should be advised to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.
- Safety and efficacy of CHANTIX in combination with other smoking cessation drug therapies have not been studied. Dosage adjustment with CHANTIX is recommended in patients with severe renal impairment or in patients undergoing hemodialysis.
- Smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, such as theophylline, warfarin, and insulin. Dosage adjustment for these drugs may be necessary.

Benzodiazepines

Benzodiazepines (BZD)

- More than 30% of overdoses involving opioids involve BZD
- Overdose mortality is 10X higher with opioids + BZD
- BZD - used for treatment of anxiety and work by increasing GABA in the brain
- Common BZD: Valium, Xanax, Klonopin, Ativan
- Increase in prescriptions for BZD by 67% from 1996-2013 from 8 million to 13 million. Increase in dosage



BZD

- RED FLAGS for misuse or diversion
  - Symptoms of intoxication or withdrawal
  - **Demands for a particular, usually fast acting, medication (alprazolam)**
    - "Extended-release doesn't work for me"
    - "Only Xanax works for me"
  - Repeated lost prescriptions
  - Discordant pill count
  - Excessive preoccupation with securing medication supply
  - Multiple prescribers
- Legitimate use
  - Low dose, no escalation
  - Stable pattern, taken as prescribed
  - Good therapeutic response
  - Even if use appears legitimate, monitor closely and seek non-addictive alternatives
- Misuse (risky use)
  - Not as prescribed, or illicitly procured
  - Higher doses, taking more than prescribed
- Use Disorder

Signs and Symptoms of Dependence

- Weakness
- Blurred vision
- Drowsiness
- Poor judgment or thinking
- Doctor shopping
- Asking friends, family, others for pills
- Unable to cut back
- Mood changes
- Risky behaviors (driving under the influence
- Combining BZD with alcohol or other drugs

Diagnosis requires 2 of 11 symptoms within a 12 month period:

- The sedative is taken in a higher volume or over a longer time period than first intended.
- Considerable time is spent getting the drug, using it, and recovering from its effects.
- When the drug is not in a person's system, the person experiences withdrawal, which can include cravings for the drug.
- Over time, more of the drug is needed to achieve the familiar desired effects (i.e., tolerance).
- The person experiences impaired performance at home, work, or school due to the drug's effects.

Abuse potential depends on Pharmacokinetics

- Rapid absorption = more rapid onset, more "high"
  - Alprazolam (Xanax) and diazepam (Valium) are rapidly absorbed orally
  - Clonazepam (Klonopin), lorazepam (Ativan), chlordiazepoxide (Librium), oxazepam (Serax) more slowly absorbed
- Rapid absorption also = more rapid onset of anxiolysis, which can be beneficial therapeutically
- Shorter half-life = greater risk of withdrawal effects
  - Benzodiazepine withdrawal resembles alcohol withdrawal, including **risk of seizures and delirium**
  - Withdrawal also drives drug seeking and use disorder
- *Alprazolam (rapid absorption, short half life) is the most popular illicit or abused benzodiazepine*

Sleep medications

- "Z drugs": Zolpidem (Ambien®), etc.
- Supposedly less abuse potential due to subunit selectivity at GABA receptors
- But, in practice more similar to benzodiazepines than different
- Rapid absorption, short half-life
- Rebound insomnia and sleep-walking are common,
- Withdrawal effects
- Use with caution in patients with opioid use disorder
- Also implicated in overdose deaths

- Alternatives for sleep
  - Sleep hygiene and CBT for sleep
  - Treat the underlying causes of sleep disturbance
    - Mood or anxiety disorders
    - Opioid withdrawal, stimulant intoxication, other substance effects
  - Sedating antidepressants
    - E.g. trazodone (but beware of priapism in men),
    - mirtazapine (Remeron®),
    - tricyclic antidepressants at low doses (e.g. doxepin, amitriptyline) or
    - antihistamines
  - Melatonin and melatonin agonists (Ramelteon)

Xanax - Effects

- ***Anxiety***: The lack of Xanax during withdrawal causes the opposite of a benzodiazepine-calm.
- ***Concentration difficulties***: Research has found that people can have cognitive problems for weeks after stopping Xanax.
- ***Depression***: Individuals have reported feeling deeply depressed and sorrowful.
- ***Hallucinations***: Although rare, some people have reported that when they suddenly stop using Xanax, they experience hallucinations.
- ***Insomnia***: Overtaken by anxiety and stress, individuals who are in withdrawal from Xanax may have trouble sleeping at night.
- ***Memory problems***: Research shows that long-term Xanax abuse can lead to dementia and memory problems in the short-term. Typically, memory functioning is restored within a few months of the initial withdrawal.

- ***Mood swings***: Unpredictable shifts in mood have been reported, such as quickly going from feeling elated to being depressed.
- ***Nightmares***: This side effect of withdrawal is often reported.
- ***Suicidal thinking***: The anxiety, stress, and excessive nervousness that can occur during withdrawal can lead to or coexist with suicidal thoughts.
- ***Psychosis***: Though rare, this may occur when a person stops using Xanax altogether, rather than being weaned off it.

Treatment options

- **Be aware that not all BZD are picked up on urine drug screens**
- Poor evidence for treatment
- CBT (cognitive behavior therapy) may be helpful
- Taper or detox
- Evaluate underlying causes (mood and anxiety disorders)
- Consider inpatient treatment if BZD use is high or overdose risk (use of opiates with BZD)

Valerian

- Best when used continuously rather than acutely
  - Dosage 300-600 mg / day
- Can be used to treat insomnia during BZD withdrawals
- Animal studies, valerian has been shown to relieve withdrawal symptoms from BZD
- Multicenter, RCT – valerian is as good as valium for sleep
  - (Andreatini and Leite, 1994)
- Small study in humans showed valerian to be effective for withdrawal symptoms (esp. middle insomnia)
  - (Poyares et al., 2002)
- Double-blind, placebo controlled study showed improvement in sleep latency and sleep quality
  - Leathwood, et al. 1982

Treatment

- TAPER
  - Substitute a benzodiazepine with lower abuse potential and long half life (e.g. clonazepam or chlordiazepoxide) or phenobarbital
  - Taper dose slowly over period of weeks to months
  - Oxazepam is a good choice if there is substantial liver impairment
  - Anticonvulsants(e.g.carbamazepine,pregabalin) may be useful as adjuncts to benzodiazepine taper

Drug	Dose (mg)
Alprazolam (Xanax™)	0.5 -1
Chlordiazepoxide (Librium™)	10-25
Clonazepam (Klonopin™)	0.25-0.5
Diazepam (Valium™)	5-10
Lorazepam (Ativan™)	1-2
Oxazepam (Serax™)	15-30

Case

- 35 year old man with opioid use disorder, on buprenorphine 16mg per day, illicit opioid abstinent, urines intermittently positive for benzodiazepines
- He has been under financial stress and may be depressed. He buys alprazolam (2mg "sticks") from his former heroin dealer and takes a half (1mg) at night to sleep
- His wife, who does not drink or take drugs and seems reliable, says she is aware of his alprazolam use for sleep, is worried about his alcohol use, but has not witnessed severe intoxicationor loss of consciousness while drinking
- He is holding down a job with no lateness or absences. He wants to stop drinking and buying drugs from the dealer, but says he has tried and been unable to stop either alcohol or alprazolam.

Case questions

- Which medication treatment would be the most appropriate first choice to help him stop drinking?
  1. Naltrexone
  2. Disulfuram
  3. Acamprosate
  4. Gabapentin

Case Questions

- What would be the most appropriate next step in managing his benzodiazepine use?
  1. Admit for inpatient benzodiazepine detoxification
  2. Prescribe alprazolam, 1 mg at bedtime with a taper schedule
  3. Prescribe clonazepam, 1 mg at bedtime, and continue until cause of insomnia better understood
  4. Prescribe low dose (10 to 25 mg) doxepin and tapering doses of clonazepam

References

- U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014
- U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004
- World Health Organization. Smokeless Tobacco and Some Tobacco-Specific N-Nitrosamines pdf icon[PDF–3.18 MB]external icon. International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 89. Lyon, (France): World Health Organization, International Agency for Research on Cancer, 2007

References

- Taylor G. Changes in mental health after smoking cessation. *BMJ* 2014;348:g1151
- Foulds J, et al. Factors associated with quitting smoking at a tobacco dependence treatment clinic. 2006. Am J Health Behav. Jul-Aug;30(4):400-12.
- Edwards VJ, Anda RF, Gu D, Dube SR, Felitti VJ. Adverse childhood experiences and smoking persistence in adults with smoking-related symptoms and illnessexternal icon. *Perm J.* 2007;11:5–7.
- Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, Williamson DF, Giovino GA. Adverse childhood experiences and smoking during adolescence and adulthoodexternal icon. *JAMA.* 1999;282:1652–1658.

References

- Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR; Varenicline Phase 3 Study Group. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA.* 2006;296(1):64-71.
- Thomas Kyla H, Martin Richard M, Knipe Duleeka W, Higgins Julian P T, Gunnell David. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis *BMJ* 2015; 350 :h1109
- Arthenelli RM, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet (London, England), 387(10037)

References

- **Hajek P, Stead L.F.** Aversive smoking for smoking cessation.*Cochrane Database Syst Rev.* 2004; (CD000546)
- **White A.R., et al.** Acupuncture and related interventions for smoking cessation.*Cochrane Database Syst Rev.* 2011; **1** (CD000009)
- Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Can electronic cigarettes help people stop smoking, and are they safe to use for this purpose?external icon Published 13 September 2016.
- Caraballo RS, Shafer PR, Patel D, Davis KC, McAfee TA. Quit Methods Used by US Adult Cigarette Smokers, 2014–2016external icon. Prev Chronic Dis 2017; 14:160600.
- Bjartveit K, Tverdal A. Health Consequences of Smoking 1-4 Cigarettes Per Day. Tobacco Control 2005;14(5):315–20.
- QuickStats: Cigarette Smoking Status Among Current Adult E-cigarette Users, by Age Group — National Health Interview Survey, United States, 2015external icon. MMWR Morb Mortal Wkly Rep 2016;65:1177.

References

- Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. *Am J Prev Med.* 2008;35(2):158–176. doi:10.1016/j.amepre.2008.04.009
- Stevens, M.W., Tawney, R.L., West, C.M., et al. Preclinical characterization of an anti-methamphetamine monoclonal antibody for human use. *mAbs* 6(2):547-555, 2014.
- Centers for Disease Control and Prevention (CDC). National Vital Statistics System, Mortality. CDC WONDER Online Database. https://wonder.cdc.gov/. Published 2017. Accessed April 4, 2017.
- Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996-2013. *Am J Public Health.* 2016;106(4):686-688. doi:10.2105/AJPH.2016.303061
- Centers for Disease Control and Prevention (CDC). Multiple Cause of Death, 1999-2015. CDC WONDER Online Database. https://wonder.cdc.gov/mcd-icd10.html. Accessed April 4, 2017.
- Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. *BMJ.* 2017;356:j760.

References

- Andreatini R, Leite JR. Effect of valepotriates on the behaviour of rats on the elevated plus maze during benzodiazepine withdrawal. Eur. J. Pharmacol., 260 (1994), pp. 233–235.
- Poyares DR, Guilleminault C, Ohayon MM, Tufik S. Can valerian improve the sleep of insomniacs after benzodiazepine withdrawal? Prog Neuropsychopharmacol Biol Psychiatry. 2002 Apr;26(3):539-45.
- Leathwood PD, Chauffard F, Heck E, Munoz-Box R. Aqueous extract of valerian root (Valeriana officinalis L.) improves sleep quality in man. *Pharmacol Biochem Behav*. 1982;17:65–71.