PAINWEEK®

Vaping in the 21st Century: Is There a Safer Way to Deliver Drugs?

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Disclosures

- Nothing to disclose

Learning Objectives

- Examine the underlaying science behind vaping related to e-cigarette technology and its derivatives
- Describe smoking cessation and e-cigs (what was promised? What has been delivered")
- Review the "full spectrum CBD Liquid" and the "Entourage Effect of CBD and vaping
- Assess medical cannabis safety for your patient

Aerosolized Drug Delivery

- When we look at the various routes of drug delivery, we must consider two key elements
  - Speed of delivery
  - Quantity of drug delivered
- First, we need to examine some of the (practical) routes of administration in common use today.
  - Topical (including mucosal)
  - Oral
  - Percutaneous (SQ, IM, IV)
  - Pulmonary

Routes of drug delivery

- Topical
  - Not all drugs can be delivered cutaneously
  - Typically require a suitable vehicle (carrier) to carry the substance into the skin
  - Ultimately, it's a very slow "transcutaneous or transmucosal" delivery of drug into the venous system
- Oral
  - Somewhat faster onset but still uses the venous system to deliver the drug to the arterial system – for delivery to the brain
  - Subject to first pass effect through the presystemic metabolic pathway
    - *Usually* lowers drug effects unless it's a prodrug or active metabolites– ie metabolism is part or the drug effect

Routes of Administration

- Percutaneous
  - Much faster route with few limits on dose
  - Includes SQ, IM, IV (slowest to fastest)
  - Drug delivery begins at the point of injection, through the venous vasculature, through the right side of the heart, into the lungs, followed by the left side of the heart, and finally into the arterial system and the brain
  - This route is highly reinforcing, both in terms of precision and speed of delivery as well as the rituals associated with illicit parenteral drug use

Systemic Circulation

- Cardiac Circulation

Very Little Beats the pulmOnary System!

- Not only is inhalation a very fast way to deliver drugs to the brain, but it is also the most rewarding
  - IV drug users are often said to be “hooked on the needle”
    - This relates to the ritual of obtaining, preparing and ultimately using IV drugs
  - But pharmacologically, the “mechanics of reward” rest in the ability of the user to get exactly the amount of drug they want, at the instant they want it!
  - This is one of the reasons cigarette smoking is so highly reinforcing
    - It isn’t just the drug!
    - It’s the way it’s delivered

Aerosolized Drug

- Certain drugs can be subjected to combustion and still remain psychoactive
  - Nicotine is likely the best-known example
  - Δ-9-Tetrahydro cannabinol
  - Many opioids can be smoked
    - Historically – opium
    - Derivatives of opium – diacetyl morphine, oxycodone etc
  - Cocaine
    - Yes/no – cocaine salts have high melting points – decompose before vaporizing
      - Cocaine alkaloid ie “free base” ABSOLUTELY
  - But many more drugs can be aerosolized without combustion

The “Atomizer”

- A euphemism for a device to create an aerosol of micro droplets of liquid
  - The “perfume atomizer” uses pressure to break a scented liquid into fine droplets – these droplets are of varying size and remain in the air for extended periods of time
  - Ultrasonic vaporizers
    - Commonly used for non-toxic “smoke” effects
      - US humidifiers –characterized by leaving a fine white residue of minerals deposited on surfaces
  - Thermal Vaporizers
    - Certain liquids, when heated below their decomposition point, form copious amounts of smoke-like vapor
    - This is the basis of the e-cigarette and similar devices

Elements in Common for e-Cig System

- Power supply – single use battery or rechargeable (~3.7 volts)
- Microprocessor control – detects demand; voltage of battery (and alert the user when the battery reaches a specified value)
- Storage compartment – either a simple wick or actual liquid reservoir
- Atomizer/vaporizer unit
- Drip tube and user mouthpiece

Typical e-Cigarette

en.wikipedia.org/wiki/Construction_of_electronic_cigarettes.

Propylene Glycol and Vegetable Glycerin

- The Food and Drug Administration (FDA) has **classified propylene glycol** as an additive that is "generally recognized as **safe**" for use in food. ... It may exist in air in the vapor form, although **propylene glycol** must be heated or briskly shaken to produce a vapor. **Propylene glycol** is practically odorless and tasteless
- **Vegetable glycerin**
  - By-product of soap manufacturing
  - Common use in cosmetics
  - Generally considered safe in low concentrations – concerns emerging re pulmonary effects
- **But when heated, toxicity changes dramatically***

*Jensen. *N Engl J Med*. 2015;372(4):392-394.

So, Where Did the e-Cigarette Come From?

- Herbert A Gilbert, a 2 pack per day smoker patented a smokeless nontobacco cigarette in 1965… but it never caught on
  - But in 2003, Hon Lik in China developed and patented the "e-cigarette" to address the massive smoking problem in China*
  - Now, it's a $10 billion/yr worldwide industry
- Originally, the nicotine containing liquid was in free-base form**
  - "Big tobacco" has known for years this is not the most efficient way to deliver nicotine to the brain but through existing tobacco chemistry, the development of nicotine salts has become the norm
    - "Better bang for the buck"
    - Higher nicotine concentrations delivered to the brain
    - Cheaper replacement "e-juice" for vapor systems

*patents.google.com/patent/EP1618803A1/en?inventor=Lik+Hon&sort=old.
**Barrington-Trimis. *N Engl J Med.* 2018;379(12):1099-1102.

PG + VG (heat) = VAPOR

- Relative ratio of PG/VG determines quality of the 'vapor'
  - Higher PG = thinner liquid, greater 'smoke hit' in throat
  - Higher VG = more viscous, greater volume of smoke
  - Other variables include temperature of the atomizer and quantity of liquid
    - ie, capillary action of original e-cig = limited vapor
    - "drip" delivery of PG/VG to heater element = huge volumes of smoke*

- What ever substances are present in the vape liquid will play a role in what is in the vapor (including PG/VG)
  - Diacetyl is a flavoring chemical: it and oxidation products appear in the vapor, ie, acetic acid
  - Pesticides (in far greater concentrations after concentrating)
  - Thermal decomposition of propylene glycol and flavoring agents create toxic aldehydes**

*Krishnan-Sarin. *Pediatrics*. 2017;139(3):e20163224.
**Khlystov. *Environ Sci Technol*. 2016;50(23):13080-13085.

In a Perfect World….

- Vaping would involve taking pure compounds of vehicle (PG/VG) and active ingredient (nicotine/THC/CBD, etc) in precise concentrations, applied to a heating element held to exacting standards to deliver ONLY the desired elements of the mixture

BUT…

- In reality…. The starting materials are rarely pure and typically contain >1 flavoring agents, the proportions may/may not be clearly defined and, as a result of a number of variables, the compound(s) delivered may contain trace heavy metals, undesired oxidation products of both known and unknown toxicity, and device modifications that are impossible to control

Even the major vendors are problematic

- Alaina K Holt et al* examined 3 different flavored tobacco products from a major vendor (Juul.) Samples were obtained from the manufacturer, a local vape shop and a "3rd party." only one of the flavors, "Virginia Tobacco" was found to contain 0.37mg/ml of gamma-butyrolactone (GLB)

- GBL is a precursor to GHB. It is converted in the human body to GHB. GBL is more potent and faster onset
  - Safety studies by on GBL by inhalation are unknown
- The identification of GBL in an e-cigarette product purportedly compliant with federal regulation continues to demonstrate public health and public safety concerns.

- *Alaina K Holt, Justin L Poklis, Caroline O Cobb, Michelle R Peace, Identification of Gamma-Butyrolactone in JUUL Liquids, *Journal of Analytical Toxicology*, 2021

But Vaping Isn't the Only Technology

- Noncombusted tobacco/cannabis systems
  - Herbal cannabis vaporizer
    (The Volcano™ Hybrid – undoubtedly the most expensive)
  - Heat-not-burn cigarettes – several brands

IQOS –(**I** **Q**uit **O**rdinary **S**moking)

Ubelacker. The Canadian Press.
Published August 15, 2017.

Heat-not-Burn Drug Delivery

- Both the Volcano® and the IQOS® both heat plant material to vaporize the active alkaloids
  - Ie cannabinoids or nicotine alkaloids
- In these products, the temperature is set to the vaporization point of the desired alkaloid (~338C to 379C for Cannabis/~350C vs ~900C for combusted products)
- Alkaloids delivered by a Heat-not-Burn delivery system have a very limited visible vapor

Heat-not-burn technology

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- These devices use a resistive “blade” to heat the tobacco-paste in the filtered “tobacco stick”
- What is contained in the ‘paste’ beyond nicotine will likely be a trade secret

Smoking Cessation

- In Canada, e-cigarette use is increasing, especially among youth*
  - Use in Canadians age 16-17 increased from 29.3% in 2017 to 37% in 2018
    - Moreover, prevalence and frequency of vaping increased among never and experimental smokers in parallel with market rise of higher nicotine concentration delivery systems
  - E-cigarette use is strongly associated with initiation and ongoing use of cigarette smoking
    - 14–30-year-old nonsmokers who use e-cigarettes have a >3-fold increased risk (23.2% vs 7.2%) of initiation of cigarette smoking (1 in 6)
  - E-cigarettes are an additional smoking cessation tool
    - Randomized clinical trial (Hajek. *N Engl J Med*. 2019;380(7):629-637.)
  - E-cigarettes are unregulated products with potentially dangerous health effects
  - Clinicians should ask every patient about e-cigarette use

*Aloosh. *CMAJ*. 2019;15;191(41):E1136.

Smoking Cessation

- E-cigarettes were initially marketed as “safe, effective” smoking cessation devices.
  - There were few regulations except for purchase age for any nicotine-products
    - 18 years of age was the minimum age for sale of nicotine containing products, including e-cigarettes BUT
    - That does not include “nicotine-free” products
    - Legal age varies highly based on jurisdiction
  - While there is evidence of effectiveness in smoking cessation, the issue of safety is anything but settled
  - In fact, nicotine-containing products are clearly targeted toward the youth-market
  - At present, regulations are in a state of flux but in 2022, Canada will be the first country to totally ban all flavored vape products except tobacco, mint/menthol

Flavored or Plain?

- >99% of vape juice sold in Canada is Flavored*
  - Studies in Europe show a negligible market for unflavored products.
- In a 2018 public opinion survey that investigated reasons for using vaping products, those who said they vaped because of the flavours were predominantly younger
- Vapers aged 15–19 years (51%);
- Vapers aged 20–24 years (54%); and
- Vapers aged 25+ years (30%).
- Data from the 2019 Wave 3 International Tobacco Control Youth Tobacco and Vaping Survey indicates that, of youth in Canada aged 16–19 who had vaped in the past 30 days, 40% reported they use vaping products "for the flavour" among their top five reasons. The other four reasons included "for fun/I like it" (50%), "curiosity/to try something new" (39%), "for the nicotine" (24%) and "to deal with stress or anxiety" (35%).**

- *Euromonitor International. *Study of the Market Size, Characteristics, and Growth Trends of the Vaping Products Market in Canada*. A custom report for Health Canada. February 2020. (Euromonitor International did not report any measurable market for flavourless vaping products.)
- **Unpublished results provided by Dr. David Hammond, School of Public Health and Health Systems, University of Waterloo, Canada.

Is Vaping Safe?

- This is a ***relative*** question
  - Is it safer than…
    - Combusted tobacco products? – consensus is YES
    - Combusted cannabis products? – probably
  - Is it a "safe" way of smoking? – NO
    - "Safer" ≠ "Safe!"
- Vaping is a relatively 'new' method of widespread drug delivery
  - It will likely take years to realistically assess intrinsic risk of the method vs other risks yet to be considered, ie contamination of e-liquids
  - Until then, we will have anecdotes to examine and limited studies to review

Vaping Cardiovascular Health Risks

- Peruzzi et al published an “umbrella review” of the cardiovascular risks of electronic vaping and “heat-not-burn” cigarettes and concluded they may represent a “lesser evil” than traditional combusted tobacco products
  - Even though vaping increases overall cardiovascular risk!
  - Benefit most likely seen when used as a ***temporary*** strategy for smoking cessation

Peruzzi. *Curr Emerg Hosp Med Rep*. 2020 Jun 16;1-7.

"Outbreak of Pulmonary Diseases Linked to Vaping"

- A recent editorial in the *British Medical Journal* commenting on an outbreak of >450 cases of severe pulmonary disease (over a 2-month period) in the US associated with vaping make several observations
  1. There is strong consensus that vaping is substantially less harmful than smoking and that established smokers switching to vaping lower their health risk, but there is less consensus around absolute risks of vaping among nonsmokers
  2. The circumstances of the outbreak suggest this is likely due to faulty devices or contaminants being vaped rather than general effects of vaping
  3. Toxic exposure from e-cigarette products can be highly variable depending on
     - The device
     - The liquid
     - How the device is operated

Hammond. *BMJ*. 2019;365:l2219.

Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin – Final Report

- Study involving chart reviews (n=98) of males who had used an e-cigarette device in the 90 days before symptoms occurred, median age 21 who presented with respiratory symptoms (97%), gastrointestinal symptoms (77%), and constitutional symptoms (100%)
  - 95% were hospitalized, 26% intubated/ventilated and 2 deaths
  - 89% used THC products vape devices but all had used a variety of e-products and e-devices
  - Comparing June through August 2019, this represented a doubling of rate observed over same period in 2018

  - Layden, J et al. Pulmonary illness related to e-cigarette use in Illinois and Wisconsin – Final Report. NEJM 382;10 2020

What About 2nd Hand Effects of Vaping?

- Is it even possible to answer this question?
  - MALDA: Mobile Aerosol Lung Deposition Apparatus

.

Su. *Indoor Air*. 2021;31(2):348-356.

Passive e-Cigarette Effects

- MALDA provides a useful tool for real-life studies of passive exposure to aerosols of the size seen with e-cigarettes
  - Data collected aligns closely with the ICRP convention curve for Human Respiratory Tract Model* both in the head-to-TB region and the alveolar region
- Current studies have shown that SP-A (surfactant protein-A) as well as other proteins are negatively impacted by passive exposure**

*www.icrp.org/publication.asp?id=ICRP%20Supporting%20Guidance%203.
**Rosenkilde Laursen. *Eur Clin Respir J*. 2020;8(1):1861580.

In Reality…

- The vaping industry has been largely uncontrolled
  - Since 2016, regulations introduced limiting access to e-cigs by age have pushed e-cigarette user to turn to traditional cigarettes
- Flavoring agents – agents and drug concentrations remain unregulated: flavorings are clearly targeting youth
- Equipment – rebuildable/modifiable atomizers/aerosolizers
- Alternative methods of use:
  - Dripping – direct contact of "juice" with heating element = huge volumes of vapor
  - Use of nicotine salts in refillable e-cigs designed for nonsalt based juices
    - Results in much higher pulmonary nicotine delivery so possible nicotine toxicity
    - "The Nicotine Wars"

Counterfeit e-Liquids and Pods

- CBD and THC oils are viscous: “the thicker the liquid, the higher the concentration”
  - UNLESS it has been adulterated or “diluted” with a cheaper material with similar viscosity to cannabis oils, ie, “vitamin E oil”*
  - Why do it? MONEY!
- The replacement pods are all available from the manufacturers in China – regardless of brand name

*Boudi. *Cureus*. 2019;11(12):e6350.

Is It Pure or Adulterated: CBD and THC?

Marketing

- Is it a surprise that the major e-cigarette companies are being bought out by big tobacco? Such as RJ Reynolds
- The marketing is clearly aimed at youth, as are the flavors

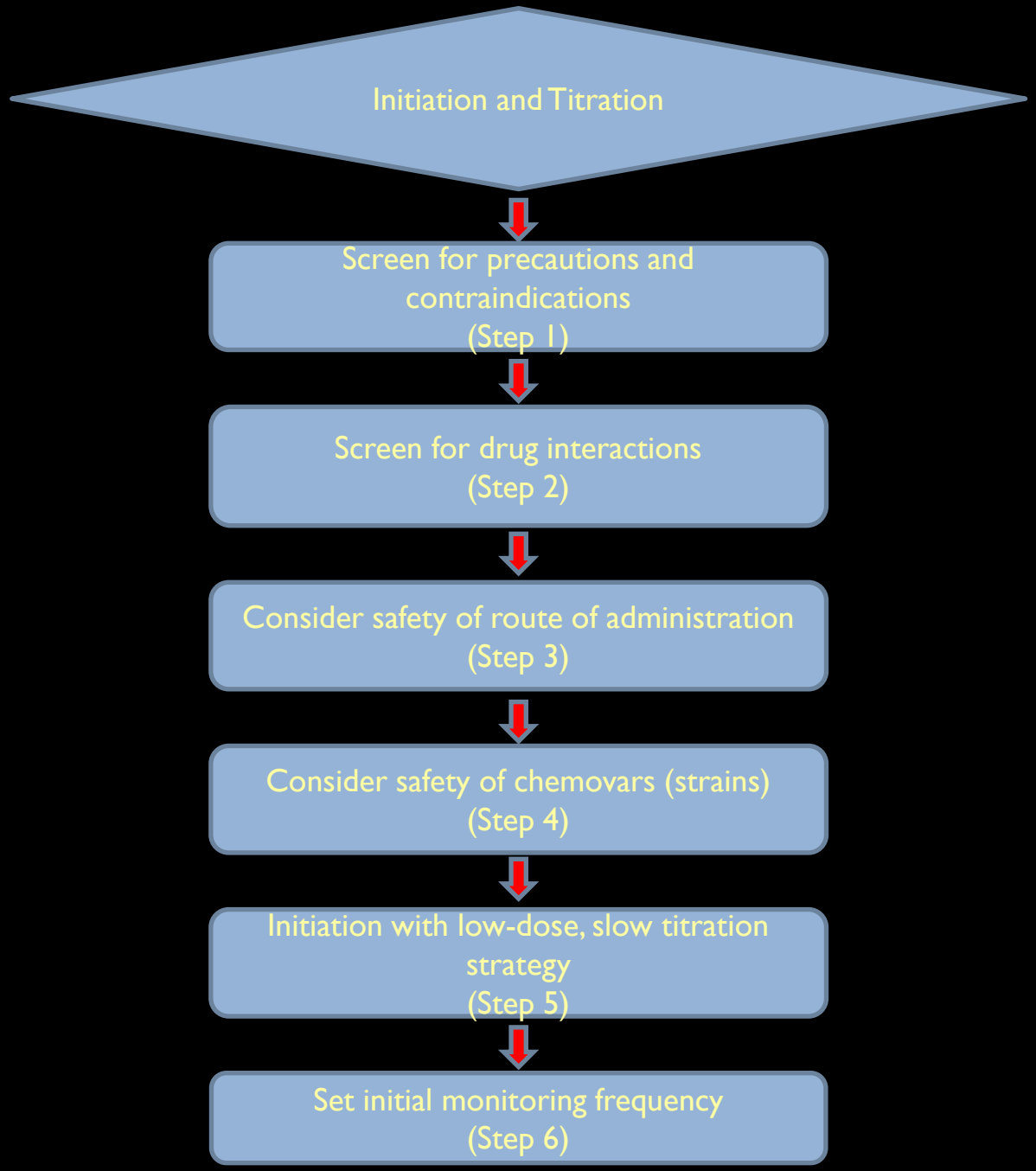
So, Who Wins?

- The only real winner so far is big tobacco
  - As e-cigs are more heavily regulated, regular users of these previously available sources of nicotine will turn to traditional tobacco products
    - 'People don't simply stop using because the legal age for use has been raised'
  - In some respects, this has been the perfect answer to over regulation by the government. 'Let peer pressure be the initiator, and poorly thought through regulations be the driver toward regular tobacco use'

Is Medical Cannabis Safe for My Patient?*

- One of the most difficult assessments for many primary care clinicians to make
  - Very little published evidence to support the few recommendations that exist in the literature, especially in the context of 'herbal' cannabis products
  - Despite this, many jurisdictions have had to re-examine a simple prohibitionary approach to this problem
  - The issue is further complicated by a somewhat arbitrary distinction between cannabis and (pharmaceutical) cannabinoids
    - Can we really consider smoking ANYTHING a 'healthy' behavior?
    - Is the non-combusted route of administration intrinsically 'safer' that the combusted route? (yes)
  - ***"Can medical cannabis be used safely in this patient?"***
    - *What strategies can we implement to mitigate any potential/emerging harms resulting?*

*MacCallum. *Eur J Intern Med*. 2021;89:10-18.


Initiation and Titration
Screen for precautions and contraindications (Step 1)
Screen for drug interactions (Step 2)
Consider safety of route of administration (Step 3)
Consider safety of chemovars (strains) (Step 4)
Initiation with low-dose, slow titration strategy (Step 5)
Set initial monitoring frequency (Step 6)

Cannabis Precautions and Considerations

- **Considerations**
  - Immunocompromised
  - Chronic renal disease
  - Older adults
  - Concurrent medical conditions
  - Polypharmacy/potential drug interactions
- **Precautions**
  - Concurrent mood/anxiety disorders
  - Risk factors for cardiovascular disease
  - Tobacco use/e-Cigarette use
  - Severe liver dysfunction/disease
  - Medications with sedation/cognitive impairment
  - Driving or other safety sensitive occupations
- **Relative Contraindications**
  - Under the age of 25
  - Current or past cannabis use disorder
  - Current or past substance use disorder
- **Contraindications**
  - Unstable cardiovascular disease
  - Personal or strong family history of psychosis or bipolar disorder
  - Pregnant, planning on becoming pregnant, or breastfeeding

So, What Is the Message to Your Patients?

- If you don't smoke: DON'T START (including e-cigs)
  - If you are a smoker, get professional, knowledgeable help to quit
- If you chose vaping as a drug delivery system – for nicotine, CBD, or THC – make sure you are aware of the risks
  - Stay away from the net – the "Wild West" is not the place to entrust your health
  - Find a local vendor you can trust and get to know them
    - Cheapest isn't always best, especially if you factor a double lung transplant into the equation
- Avoid flavored "juices" – the flavoring agents may be more dangerous than the active ingredients

Route of Administration – Start Low, Go Slow

- Inhaled vs oral (ignoring topical)
  - Inhalation is the fastest way to deliver a drug with the shortest onset times and greatest efficiency
    - It's faster than parenteral (SC/IM/IV) routes
    - Greatest ability to titrate to effect
    - Most reinforcing!
  - Oral route
    - Slower onset
    - Least reinforcing
    - Least effective per mg dose (first pass effect)
    - **Greatest risk of adverse effects related to overdose – "once you take it, you're stuck with it!"**

Conclusions

- The lungs are an efficient way to deliver drugs to the brain, but they are also one of our most structurally fragile systems
  - Time will tell how “safe” it is as a recreational drug delivery system
- Currently, the use of e-cigarettes to quit smoking may be effective in the short term but lacks evidence to support it as a safe, long-term practice
  - But regulatory changes are already moving “non-smoking” youth from vaping to combusted tobacco products
- Until we know for sure, assume this is less safe than advertised!

References

- Contact:
  - Douglas Gourlay MD, MSc, FRCP(C), DFASAM
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- Pokhrel P, et al Young adult e-cigarette users' reasons for liking and not liking e-cigarettes: a qualitative study. *Psychol Health*. 2015;30(12):1450-1469.
- Breitbarth A, et al. E-cigarettes—An unintended illicit drug delivery system. *Drug Alcohol Depend*. 2018;192:98-111.
- Budzyńskaa E, et al. Analysis of e-liquids for electronic cigarettes using GC-IMS/MS with headspace sampling. *Talanta*. 2020;209:120594.
- Aloosh M, et al. E-cigarettes. *CMAJ*. 2019;191:E1136.
- Krishnan-Sarin S, et al. E-Cigarettes and "Dripping" Among High-School Youth. *Pediatrics*. 2017;139(3):e20163224.
- Chand HS, Muthumalage T, Maziak W, et al. Pulmonary toxicity and the pathophysiology of electronic cigarette, or vaping product, use associated lung injury. *Front Pharmacol*. 2020;10:1619.

References

- Chen L, et al. Vaping associated pulmonary nontuberculous mycobacteria. *Lung.* 2021;199(1):21-27.
- Amin AA, Haught E, Mousattat Y. Do not huff, puff, or vape that stuff: interstitial airspace disease in a teenager. *Case Rep Pediatr*. 2020;2020:8822362.
- Xie Z, Li D. cross-sectional association between lifetime use of electronic cigarettes with or without marijuana and self-reported past 12-month respiratory symptoms as well as lifetime respiratory diseases in U.S. adults. *Nicotine Tob Res.* 2020;22(Suppl 1):S70-S75.
- Aldy K, et al. E-cigarette or vaping product use-associated lung injury (EVALI) features and recognition in the emergency department. *J Am Coll Emerg Physicians Open.* 2020;1(5):1090-1096.
- Patten T, De Biasi M. History repeats itself: role of characterizing flavors on nicotine use and abuse. *Neuropharmacology.* 2020;177:108162.
- Jonas A, Raj R. Vaping-related acute parenchymal lung injury: systematic review. *Chest.* 2020;158(4):1555-1565.

References

- MacCallum CA, Lo LA, Boivin M. "Is medical cannabis safe for my patients?" A practical review of cannabis safety considerations. *Eur J Intern Med.* 2021;89:10-18.
- MacCallum CA, et al. Practical Strategies Using Medical Cannabis to Reduce Harms Associated With Long Term Opioid Use in Chronic Pain. *Front Pharmacol.* 2021;12:633168.
- Bhaskar A, et al. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *J Cannabis Res*. 2021;3(1):22.
- Hammond D, et al. E-cigarette Marketing Regulations and Youth Vaping: Cross-Sectional Surveys, 2017-2019. *Pediatrics*. 2020;146(1).

Question 1

- A 19-year-old, previously well college student became acutely short of breath. On arrival to the ER, he was tachycardic with a shallow pattern of breathing (RR 28) with decreased breath sounds. He is afebrile and in obvious distress.

- He is immediately placed on 100% oxygen mask
- Anesthesia and Respiratory Technology were called for probable intubation
- A chest x-ray was ordered:

Question 1 cont.

- Pre-intubation x-ray

.

Question 1 cont

- His oxygen saturation rose to 90% on 100% oxygen

The parents volunteered he had recently began using e-Cigarettes to help stop smoking (~ 6 months)

- The most likely cause of his respiratory condition is:
  - 1) acute bronchial pneumonia
  - **2) acute bronchiolitis– so called "pop corn lung" - ? d/t history of vaping**
  - 3) Chronic Obstructive Pulmonary Disease due to smoking
  - 4) aspiration pneumonitis

Question 2

- The long-term use of vape technology has been shown to be safer than smoking
  - True
  - **False**
- **Question 3**
- In the heat-not-burn nicotine delivery system, tobacco is heated by the
  - **A) The resistive Blade**
  - B) The match
  - C) The juice
  - D) The friction from pushing in the heatstick into the device

Question 4

- Of the following routes of administration, which has the slowest onset?

1. Inhalation
2. Subcutaneous
3. **Oral**
4. Intravenous

Question 5

A 22yo woman, with history of bulimia is considering nicotine as an appetite suppressant. She has had treatment for her eating disorder in the past, with significant success but feels that if she just cuts down on calories, she'll be fine. She never has been a tobacco user.

Which of the following is likely to have the greatest chance of success?

1. Reassure her that she looks great. No need to change a thing
2. Caution her that while vaping is "Safe", her parents might not approve
3. **Listen reflectively, asking her to consider exploring this issue with the eating disorder team.**
4. Suggest that baggie cloths are very stylish these days!

Question 6

Which of the following has been reported as a vaporizer adulterant:

1. **Vitamin E**
2. Motor Oil
3. Niacin
4. Olive Oil

Question 7

- Of the following routes of administration, which has the fastest onset of action?
  1. Oral
  2. Topical
  3. Intravenous
  4. **Inhalation**

Question 8

There is no evidence of harmful 2nd hand vaporization because the particles are too small.

1. True
2. **False**

Question 9

- The MALDA acronym stands for:
  1. **Mobile Aerosol Lung Deposition Apparatus**
  2. Multisystem Accurate Lung Deflation Array
  3. Male Alternative Lung Disease Assessment
  4. Mothers' Against Lung Disease Algorithm

Question 10

The poor regulatory framework for e-cigarettes has played a role in adolescent smoking of traditional, combusted tobacco products

1) **True**
2) False