PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

Vape Technology: Addressing the Science and Safety Issues

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Disclosure

- Nothing to disclose

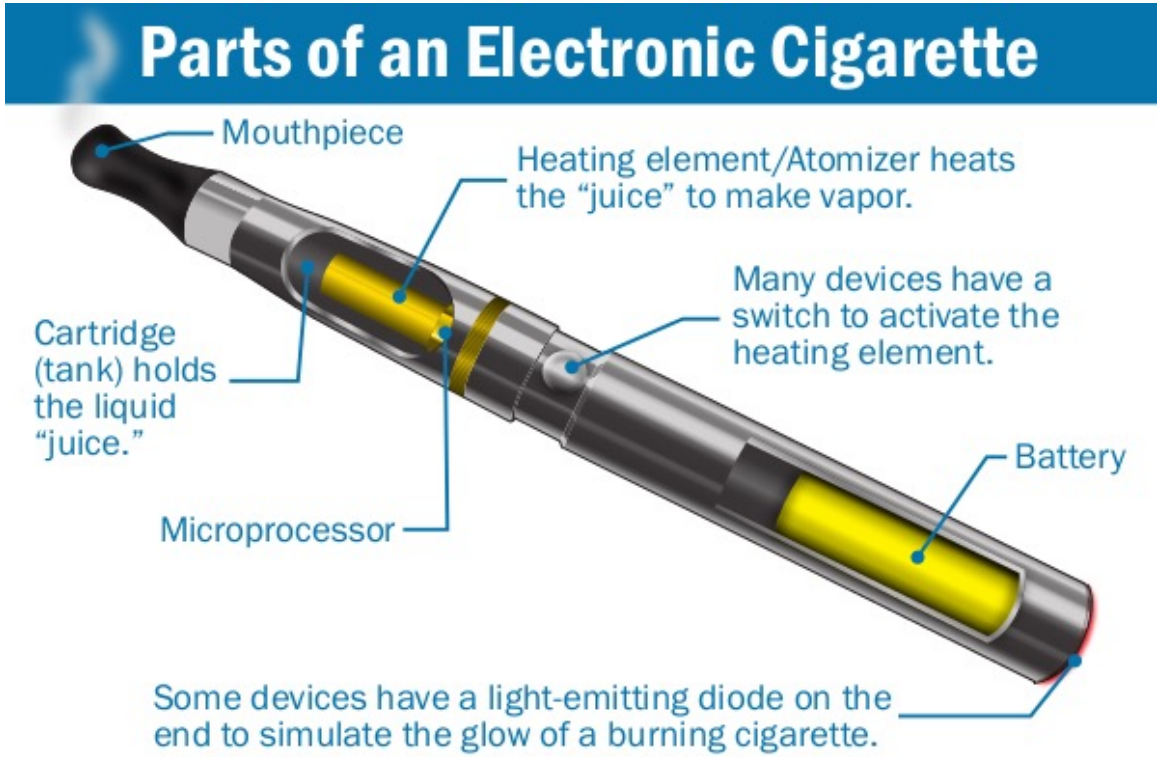
Learning Objectives

- Examine the underlaying science behind vaping related to e-cigarette technology and its derivatives
- Discuss 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
- Describe how to assess medical cannabis safety for a patient

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

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

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

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.

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.

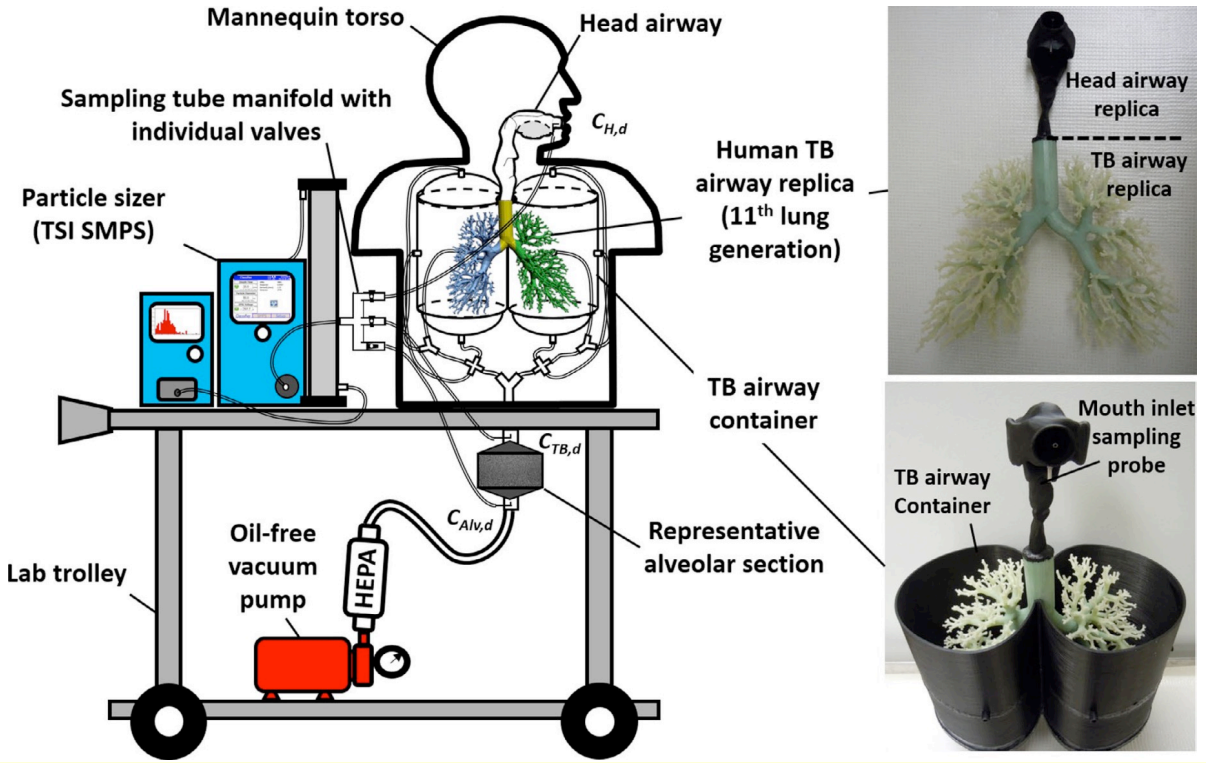
"Outbreak of Pulmonary Diseases Linked to Vaping"

- 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:I2219.

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**

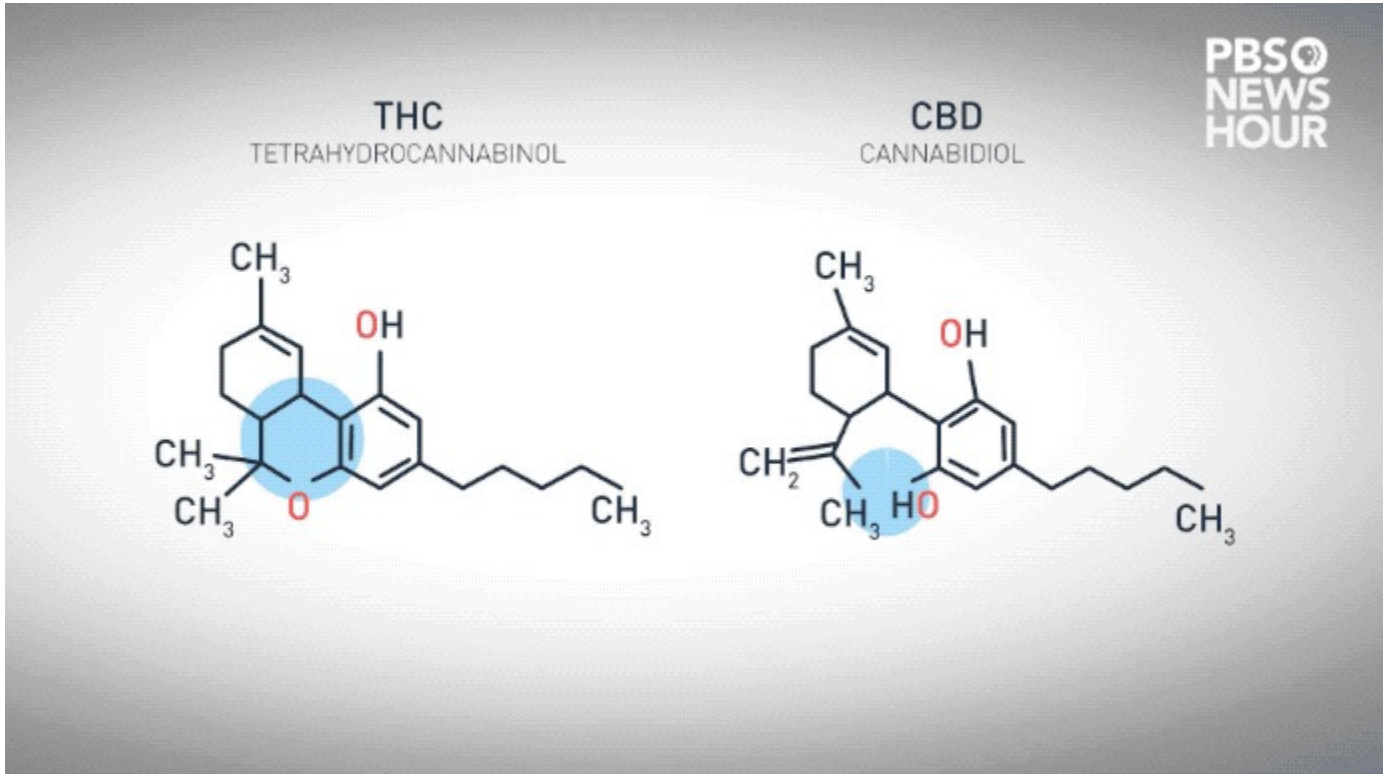
*www.icrp.org/publication.asp?id=ICRP%20Supporting%20Guidance%203.

**Rosenkilde Laursen. *Eur Clin Respir J*. 2020;8(1):1861580.

Cannabinoid Delivery Systems

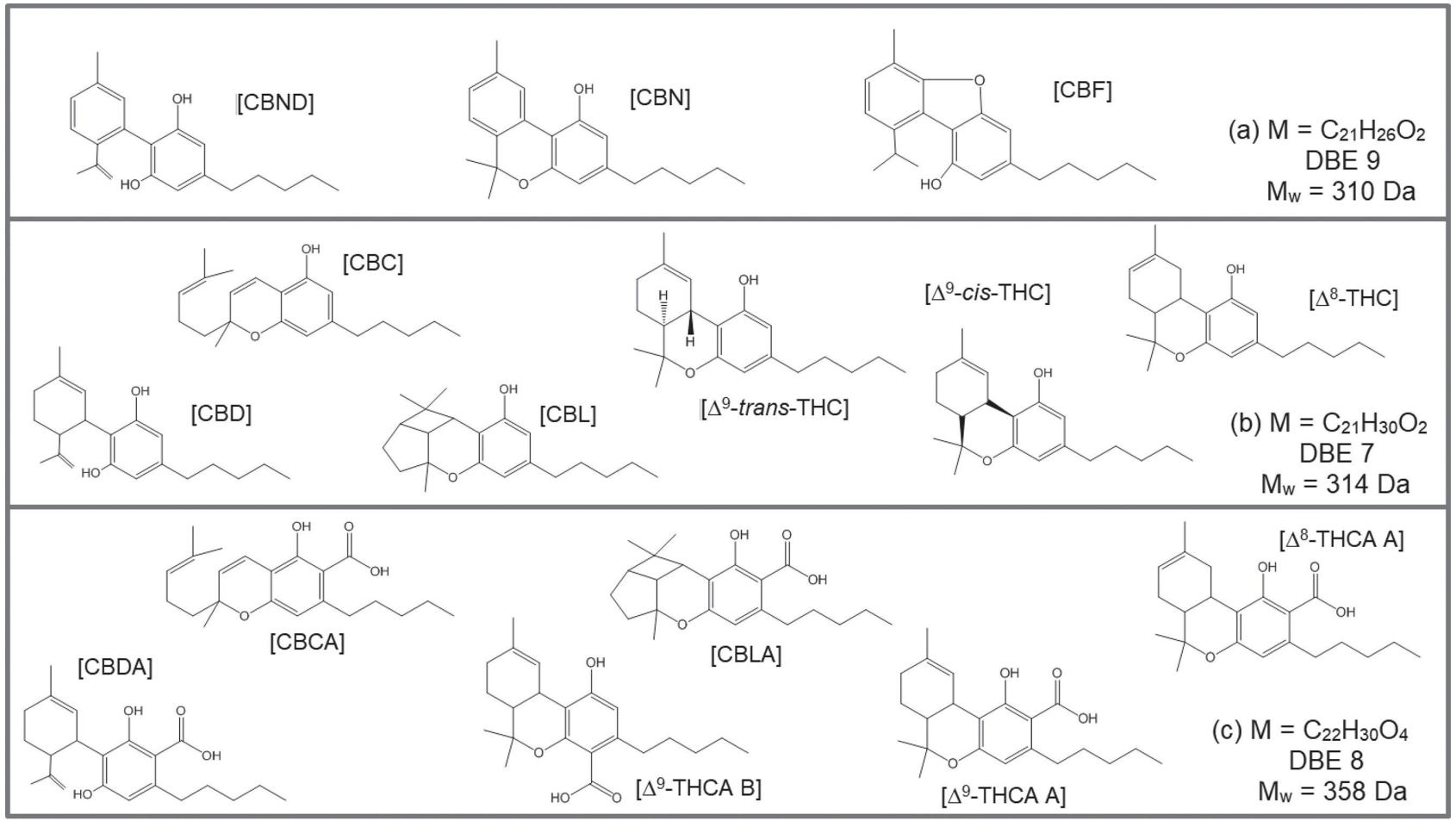
- The recent state legalization of medical marijuana and, in some cases, recreational marijuana has resulted in the search for “safer” and more efficient drug delivery systems
  - Many thought of vaping as a “less harmful” way to use cannabis: Not true!
    - **E**-cig **V**aping **A**ssociated **L**ung **I**njury (EVALI)
  - Evidence on medical effectiveness is unclear
    - Even use of CBD in pediatric epilepsy is coming into question
  - Mounting evidence of significant risk intrinsic to the vaping process
    - Bronchiectasis obliterans, ie, popcorn lung
    - Flavoring agents causing harm
    - Insecticides, etc

The Active Ingredients – But There Are Many More



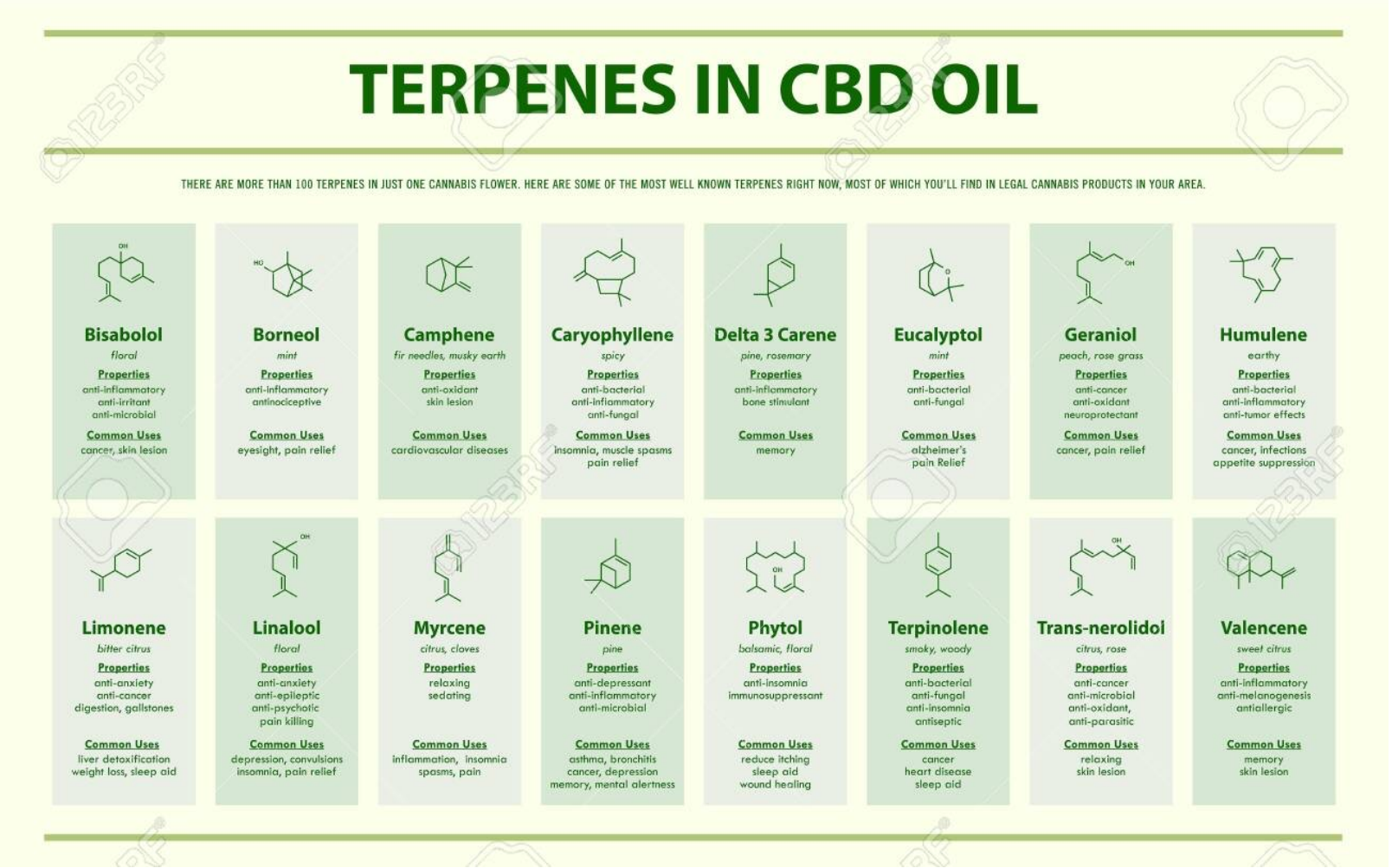
www.analyticalcannabis.com/articles/cbd-vs-thc-what-are-the-main-differences-297486.

Other Cannabinoids



Dos Santos. *J Braz Chem Soc*. 2018;30.10.21577/0103-5053.20180152.

Some Other Noncannabinoids



The "Entourage Effect" – Real or Imagined?*

- At least 1 researcher** has suggested that the therapeutic effects of cannabis aren't due to CBD or THC alone, but all the other molecules (cannabinoids, terpenes, etc) plus the CBD and/or THC
  - Net effect is that there are manufacturers claiming "full spectrum CBD" oil is "superior"
    - ie, everything but THC or CBD
  - At this point, we really don't know. BUT…
    - We know presumptive testing for cannabis may be positive for trace amounts of THC (which accumulates over time) and other cannabinoids such as cannabinol (CBN)
      - Acting on presumptive testing may result in false accusations of cannabis use
      - Since control over products supplied is limited, they may contain substantially higher THC than advertised

*Russo. *Front Plant Sci*. 2019;9:1969. **Ben-Shavat. *Eur J Pharmacol*. 1998;353(1):23-31.

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?

Regulatory Framework – A Real Mess

- Cannabis and ALL compounds derived therefrom are ILLEGAL
  - Schedule 1 at the federal level (in the US)
- Hemp is defined as 'cannabis' containing less than 0.3% THC by dry weight (legal)
  - CBD from 'hemp' is legal (Hemp Farm Bill 2018*)
- Cannabis containing more than 0.3% THC is marijuana (illegal)
  - CBD from marijuana – still illegal
- Cannabis or any of its products cannot cross international borders
  - (Even if the product is legal in both countries, ie, CBD products can't cross from US to Canada - US)

*www.fda.gov/news-events/congressional-testimony/hemp-production-and-2018-farm-bill-07252019.

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

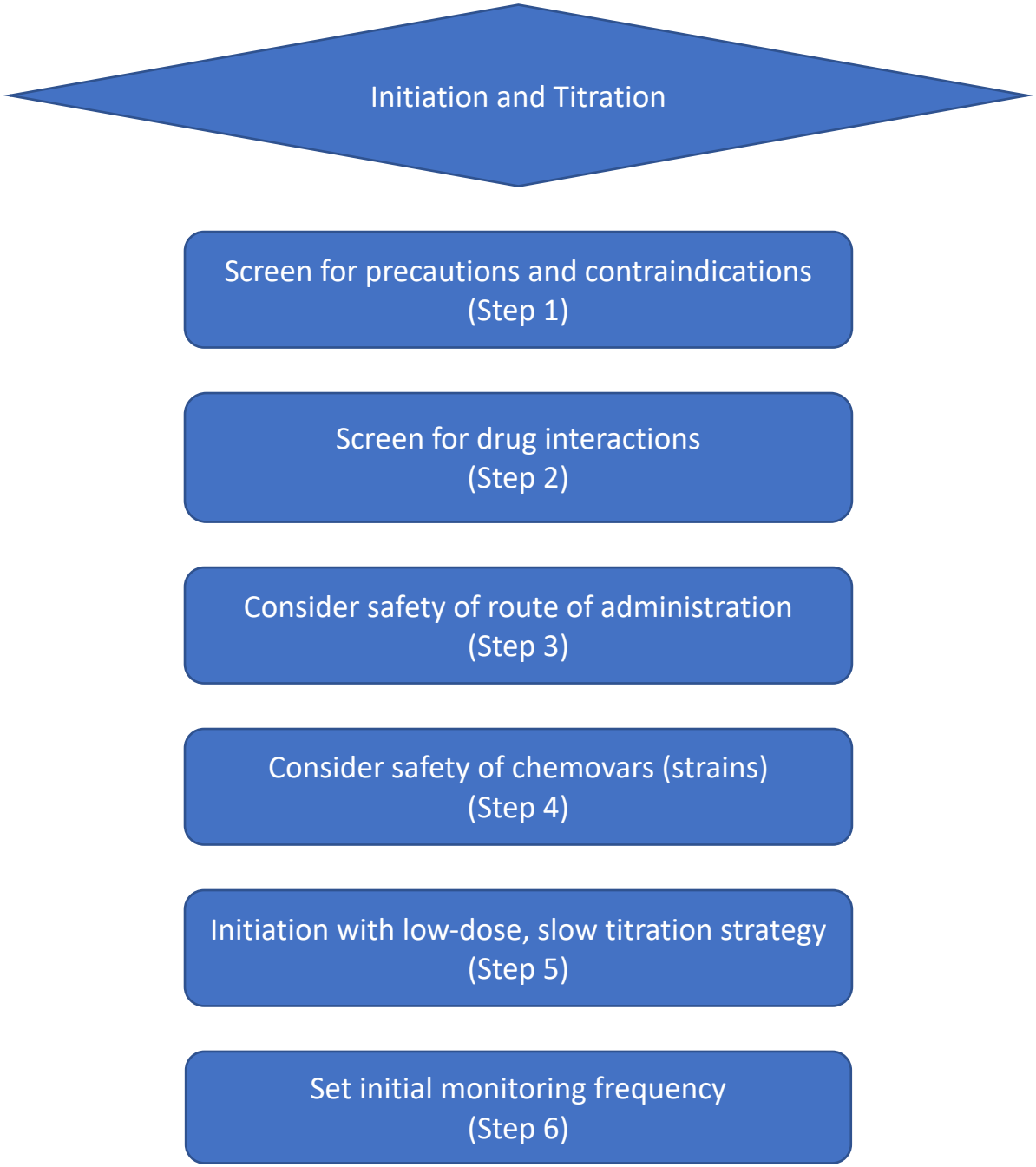
So Who Wins?

- 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 noncombusted 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

Some Potential Cannabinoid Drug Interactions*

• Enzyme	• Interaction and effect	▪ Interaction and effect
• CYP3A4	• **Inducers:** may decrease THC/CBD **Inhibitors:** may increase THC/CBD	▪ Carbamazepine, phenytoin, refampin, St. John's Wort, etc
• CYP2C9	• **Inducers:** may decrease THC not CBD **Inhibitors:** may increase THC not CBD	▪ Amiodarone, fluconazole, fluoxetine, etc
• CYP2C19	• **Inducers:** may decrease CBD/THC **Inhibitors:** may increase CBD/THC	▪ Carbamazepine, rifampin, St. John's wort, etc
• CYP1A1/ 1A2	• **Substrate:** may increase levels of meds metabolized by 2C19. CBD may prevent clopidogrel ;from being activated • **Substrates:** smoking cannabis can stimulate these isoenzymes and increase the metabolism of these medications	▪ Amitriptyline, caffeine, clozapine, etc

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

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 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)
  - Inhaled is the fastest way to inject the 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 use of e-cigarettes to quit smoking may be effective in the short term but lacks evidence to support it as a safe alternative
- At the present time, much of the advertising and a large internet presence are being dedicated toward the youth market potentially making this method of use even more dangerous to nonsmoking youth
- The relatively unregulated nature of this industry is likely to become more heavily regulated, over time – children and adolescent use will likely move to more readily available, traditional tobacco containing products
- Time will tell how “safe” these practices are

References:

- Contact:
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  - dgourlay@cogeco.ca

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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 continued

- Pre-intubation x-ray

Question 1 continued

- 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

Questions 2 and 3

The long-term use of vape technology has been shown to be safer than smoking

1) True
2) **False**

The “entourage effect” includes all of the following EXCEPT:

1) **The tendency of cannabis users to use in groups**
2) Suggests that the therapeutic effects of cannabis is a function of many plant constituents, not simply THC or CBD
3) Is not widely accepted in the scientific community
4) May help explain why purer compounds tend to have less therapeutic effective

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 past 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!

Questions 6 and 7

Both cannabidiol (CBD) and/or tetrahydro cannabinol (THC) are metabolized through the following CYP450 iso enzymes ***except***:

1) 3A4
2) **2D6**
3) 2C9
4) 2C19

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

1) **Vitamin E**
2) Motor oil
3) Niacin
4) Olive oil

Questions 8 and 9

Of the following routes of administration, which has the fastest onset of action?

1) Oral
2) Topical
3) Intravenous
4) **Inhalation**

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

1) True
2) **False**

Question 10

- 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' alternative lung disease algorithm