

# Vaped: The Current Status of E-Cigarettes

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# Objectives

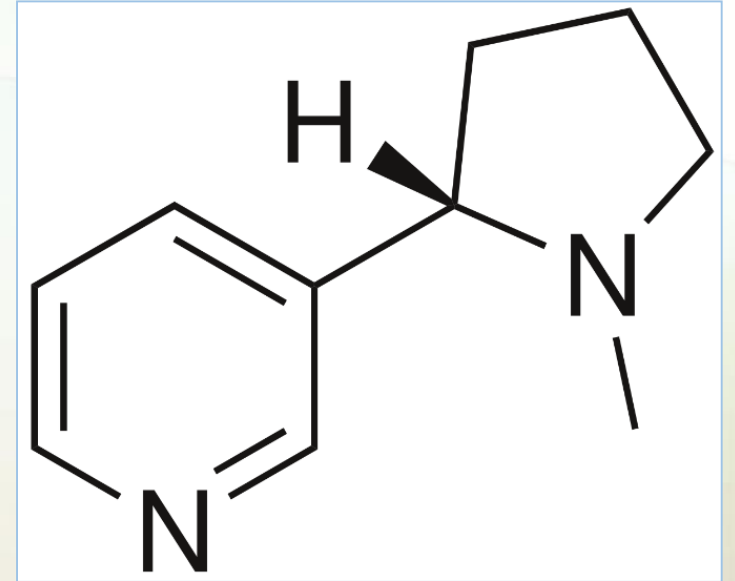
- Review the history of e-cigarettes and their mechanism of action
- Contrast traditional cigarettes with e-cigarettes
- Identify health & safety issues associated with e-cigarettes
- Explore recent regulations against e-cigarettes
- Discuss e-cigarette's role in smoking cessation

# E-Cigarettes: A Brief History

Reviewing the history of e-cigarettes and how they function

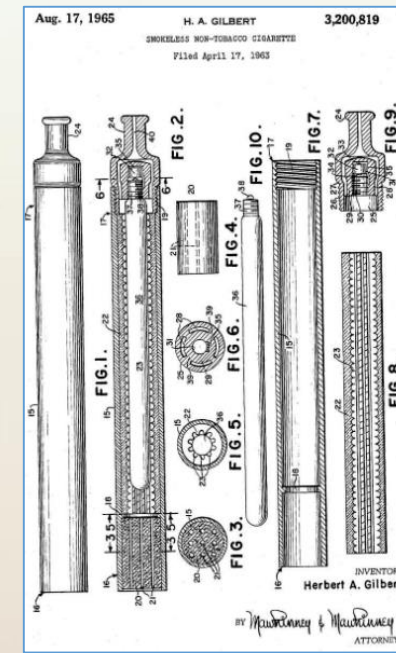
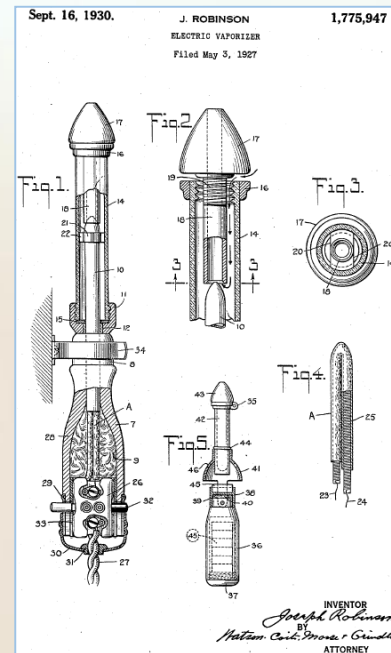
# Why Smoke?

- Nicotine!
  - Binds to receptors in:
    - Autonomic ganglia
    - Adrenal medulla
    - Neuromuscular junction
    - Brain
  - Lower doses:
    - Stimulant effect in locus ceruleus predominant
  - Higher doses:
    - Reward effect in limbic system predominant



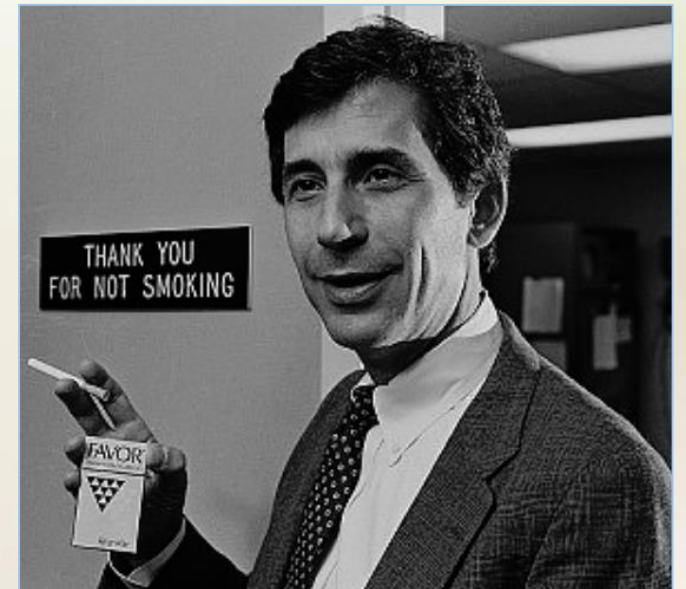
# A Brief History of E-Cigarettes

- First record of any electronic vaporizer was for a patent filed in 1927, granted in 1930—Doubtful a prototype was manufactured
- 1965: Patent for the first device resembling a modern cigarette, featured in December 1965 *Popular Mechanics*



# A Brief History of E-Cigarettes

- 1979: Norman Jacobson, MD, along with his patient, (John) Phil Ray, an early pioneer of personal computers:
  - First formal research into nicotine delivery
  - Their delivery device was not actually electronic, but relied on evaporated nicotine
  - Source of the term “vape”



# A Brief History of E-Cigarettes

- 2003: Chinese pharmacist Hon Lik
  - First commercially successful electronic cigarette
- 8/22/2006: First “e-cigarette” in US market
- April 2009: US court ruled that the FDA could not regulate e-cigarettes as “drug delivery devices” as they made no therapeutic claims
  - (*Smoking Everywhere, Inc. v. FDA*)





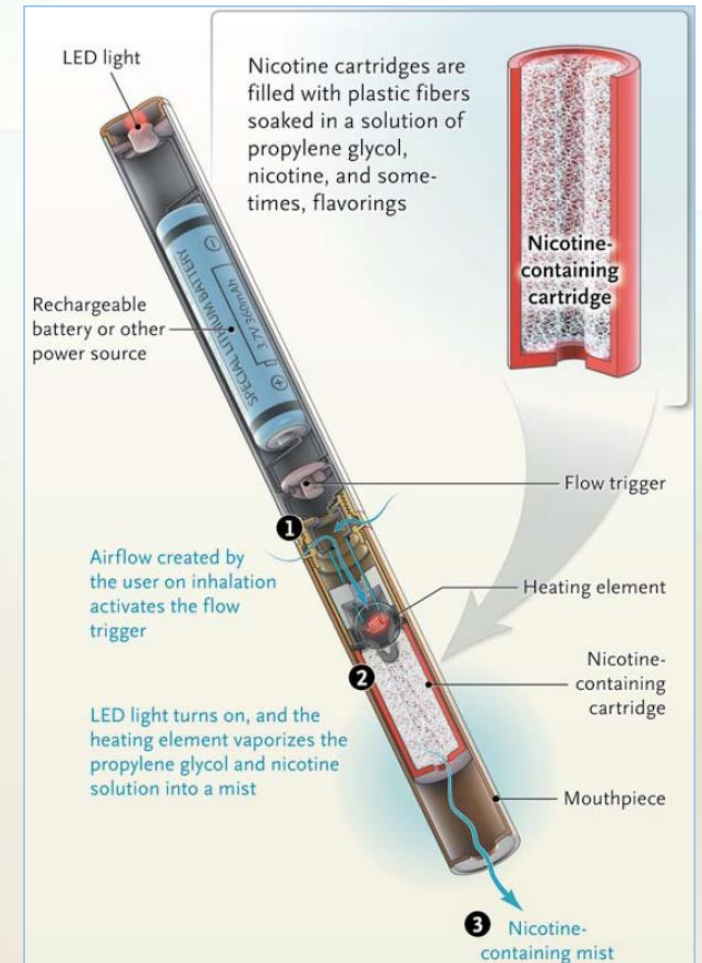
# How Do E-Cigarettes Work?

- Simply put: Aerosolizing delivery devices with disposable cartridges
  - “E-cigarettes” have more in common with multi-dose inhalers & nebulizers than cigarettes
- General composition:
  - Battery (often rechargeable) or other power source
  - Flow-pressure switch
  - Heating element
  - Cartridge of nicotine +/- flavoring in humectant
  - Mouthpiece



# Types of E-Cigarettes

- Three general categories:
  - Disposable
  - Refillable
  - Variable voltage



# Disposable E-Cigarettes

- Many look like traditional cigarettes
  - Some have glowing LED to mimic smoldering embers
- Some are rechargeable
- Short battery life
- Poorer performance
- Advantage is small size



# Refillable E-Cigarettes

- Allows for easy refill of liquid
  - Cheaper than replaceable cartridge
- Longer battery life
- Improved performance
- Higher start-up cost, but cheaper than disposables
- Can plug into USB ports to recharge



# Variable Voltage E-Cigarettes

- Can adjust power of vapor for more intense smoke
- Uses larger batteries for more power
- Difficult to use for first-time users
  - Typically for long-term or advanced users



# Best-In-Class Brands from 2019



Best performance:  
V2 EX Starter Kit



Best value:  
Halo G6



Best vape juice:  
JUUL

# Clinical Concerns

Cases and conundrums associated with e-cigarette use

# Clinical Concerns with E-Cigarettes

- Cancer
- Cardiovascular disease
- Nicotine toxicity
- EVALI
- Formaldehyde exposure
- Respiratory disease
- Thermal injury



# Mimicking Cancer

- Case report of multiple pulmonary and hepatic nodules
  - PET positive
  - Biopsy: Multinucleated giant cells
  - Resolved with e-cigarette cessation

# Cardiovascular Disease

- Cross-sectional study of 449,092 participants:
  - 58,789 (13.1%) used regular cigarettes
  - 15,863 (3.5%) used e-cigarettes
  - 12,908 (2.9%) used e-cigarettes in conjunction with regular cigarettes
  - 44,852 (10%) had cardiovascular disease
- No statistical increase in cardiovascular disease with e-cigarette use alone
  - 36% increased odds of cardiovascular disease with dual use compared to regular cigarettes alone (OR 1.36; 95% CI 1.18-1.56)

# Nicotine Poisoning

- Infants and children highly susceptible
  - Highly concentrated liquid nicotine solutions
- Poison control
  - Reports of nicotine exposure/toxicity tripled between 2012 & 2013
- Nicotine toxidrome:
  - Low exposure: Stimulant effects (tachycardia), N/V
  - Moderate: Ataxia, seizures
  - High: Neuromuscular block, respiratory failure, death
    - Note: As dose exposure increases, nicotinic specificity decreases, acquiring muscarinic effects (e.g. “SLUDGE”)

# Not Just in Children...

- Adults can have “abnormal exposures too”
  - Nicotine solutions confused with ophthalmic solution
  - Subcutaneous absorption

# Nicotine Is Not Alone

- Other flavorings & diluents have their own associated toxicities
  - Wintergreen: Methyl salicylate → “Aspirin overdose”
  - Sweet: Diacetyl → “Popcorn lung”
  - Cherry: Benzaldehyde → Irritant/bronchospastic
  - Propylene glycol → Formaldehyde
  - Glycerin → Lipoid pneumonia

# Additional Irritants & Carcinogens

- Toluene
- Acetone
- Glycerin
- Metals:
  - Cadmium
  - Copper
  - Nickel
  - Lead
  - Silver

# EVALI

- EVALI: E-cigarette/Vaping product use-Associated Lung Injury
- Can present on CT imaging as 4 patterns:
  - Acute eosinophilic pneumonia
  - Diffuse alveolar damage
  - Organizing pneumonia
  - Lipoid pneumonia



# Lipoid pneumonia

- Foreign body reaction to lipophilic molecules
  - Glycerin-based oils from e-cigarette vapor
- HRCT:
  - Diffuse ground-glass opacities
  - Subpleural cysts
- Pathology
  - Lipid-filled macrophages
  - “Cholesterol clefts”
- Treatment: STOP SMOKING E-CIGARETTES

# The Toll of EVALI

- Sharp increase in cases with peak September 2019
- Cases declined and dwindled by the end of February 2020:
- Overall statistics
  - >2800 hospitalizations
  - 68 deaths
  - 15% patients <18 years old
- After analysis and testing including bronchoalveolar lavage, the overwhelming cases were found to be secondary to vitamin E
  - CDC has since stopped collecting data since end of February 2020

# Vitamin E and “Vape Lung”

- Vitamin E acetate was a popular additive to e-cigarettes, especially THC oil
- Thought to impede pulmonary surfactant’s ability to maintain surface tension
- Other consideration is production of ketene, a toxic irritant
- “Dabbing”: Vaping with THC (as highly concentrated butane hash oil)
- “Dripping”: Reassembling the device in order to drip the solution directly on the heated coils to increase intensity

# Self-Embalming with E-Cigarettes

- Common diluent is propylene glycol
- Formaldehyde is a degradation product of propylene glycol
  - Group 1 carcinogen
- Higher voltage systems (~5V) increase formaldehyde production
  - Very little detected in lower voltage systems (~3.3V)
- Studies vary between less or more formaldehyde in high voltage e-cigarettes vs. cigarettes

# Asthma

- 2016 Florida Youth Tobacco survey with asthma diagnosis
  - Investigated asthma exacerbations in presence of nicotine
    - First-hand: Cigarettes, cigars, hookah, e-cigarettes
    - Second-hand: Smoke from cigarettes, cigars, hookah; Vapor from e-cigarettes
  - Overall 21% reported asthma exacerbation (out of  $N = 11,830$ )
  - Focusing on secondhand exposure:

Exposure		Reported exacerbation	Adjusted odds ratio
Secondhand smoke exposure (cigarettes)	Yes	23.7% ( $N = 1410$ )	1.19 (1.05-1.35); ( $p < 0.5$ )
	No	18.8% ( $N = 1163$ )	1.00
Secondhand vapor exposure (e-cigarettes)	Yes	24.2% ( $N = 989$ )	1.27 (1.11-1.47); ( $p < 0.5$ )
	No	19.5% ( $N = 1560$ )	1.00

# Thirdhand Smoke Exposure

- Researchers examined deposition of particulate matter from various e-cigarettes in a controlled setting
- Nicotine residue measured compared to baseline
  - Floor: 47x ( $p < 0.05$ )
  - Window: 6x ( $p < 0.05$ )
- Various brands emit different amounts of nicotine

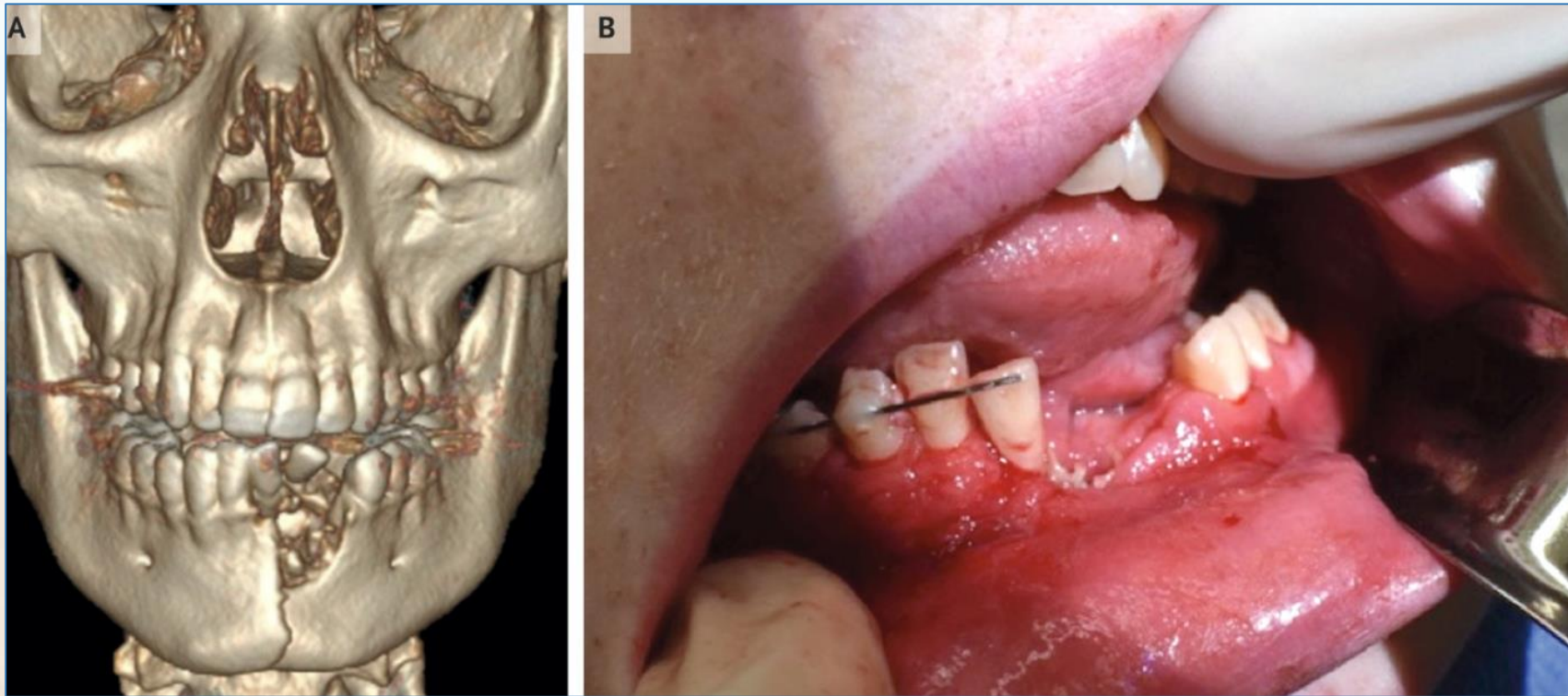
# Explosion Injuries

- “Thermal runaway”
  - Internal battery overheating creates fire or explosion
- Injury mechanisms:
  - Flame burns
  - Chemical burns
  - Blast injuries
- Injury locations:
  - Face
  - Hands
  - Thigh/groin

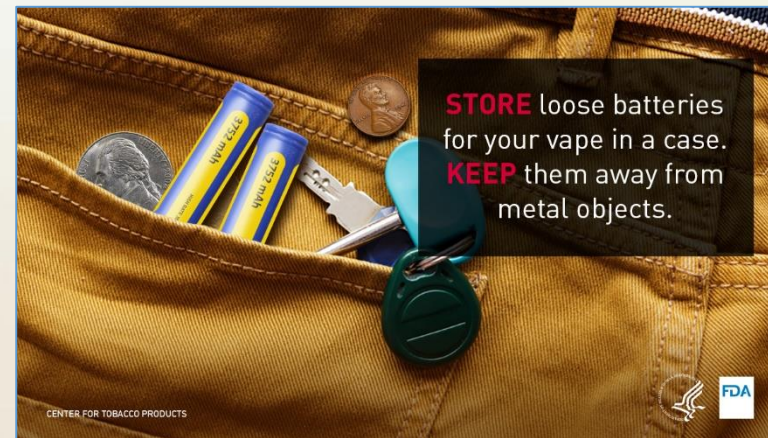


# Explosion Injuries

- This 17-year old had an e-cigarette explode in his mouth...



# FDA's Tips to Prevent Explosions



# Enticing a Generation

Youth use and government's response



# Youth Tobacco Use 2018

- In 2018, tobacco use in US high school:
  - Any tobacco/nicotine-containing product: 27.1%
    - E-cigarettes: 20.8%
    - Cigarettes: 8.1%
    - Cigars: 7.6%
    - Smokeless tobacco: 5.9%
    - Hookah: 4.1%
    - Pipe tobacco: 1.1%

# Vaping Beyond the “Intended Use”

- “Dabbing”: Vaping with THC (as highly concentrated butane hash oil)
- “Dripping”: Reassembling the device in order to drip the solution directly on the heated coils to increase intensity

# Seducing the Youth

- Cool/luxurious names
- Flavorings appealing to a younger demographic
- Sleek/chic form/style of the device

# Stylish Names (from Halo)

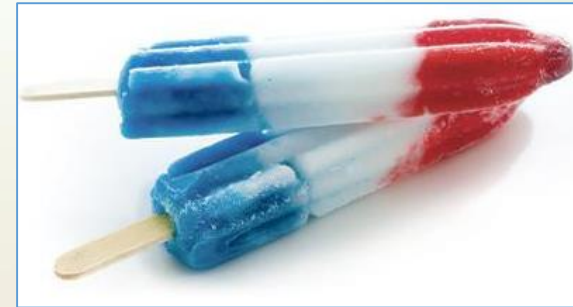
- Prime 15 = Nutty Tobacco
- Sub Zero = XStrength Menthol
- Torque 56 = Robust Tobacco
- Tribeca = Smooth Tobacco
- Turkish Tobacco = Robust Tobacco
- Twisted Turnover = Gourmet Pastry
- Voodoo = Sugar & Spice Tobacco





# Children's Candy...or Vape Flavors?

- Berry Rush
- Blue Razz
- Custard Craze
- Jaw Dropper
- Kookie Krunch
- Lemon Glaze
- Melon Lush
- Strawberry Crush
- Tropic Freeze
- Banana Split
- Cotton Candy
- “Kool-Laid”
- “Sweet Tart”
- Hawaiian Punch
- Rocket Pop
- Gummy Bears
- “Fruity Loops”
- Skittles



# The Cool JUUL® “Pod Mod”

- JUUL® device
- USB charging dock
- JUULpod
  - Snap pod on the top to “customize your experience”
  - “Listed ingredients”
    - Flavors (natural & artificial)
    - Nicotine *salts* (3% & 5% formulations)
    - Propylene glycol/glycerine (30%/60% mix)
    - Benzoic acid
  - Each pod is ~200 puffs



# Fashionable JUULry

- Nielsen data January 2018: JUUL® 49.8% of e-cigarette market
- Wells Fargo data June 2018: JUUL® 65% sales, \$650M in 6 months
- Highly popular in schools:
  - “Addicted to my JUUL” was quoted often in social media
  - Easily concealable given USB appearance
    - Some schools banned USB drives altogether due to this
  - Sophisticated, modern design (such as a smart phone)
  - Customizable adhesives “skins”

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- Alluring descriptors of flavors: “creme,” “fruit medley,” “cool mint”
  - NOTE: Flavors are banned in cigarettes but not smokeless, hookah, cigars, e-cigarettes

# Erasing Gains in Youth Smoking

- CDC data 2018:
  - Nicotine product use:
    - 4.04 MILLION high school students (27.1%)
    - 840,000 middle school students (7.2%)
  - E-cigarettes most common source now in high school students
    - 3.05 MILLION (20.8%)
    - Increase of 77.8% from 2017 (previously 11.7%)
  - Overall no change in other product use (e.g. cigarettes)
- Where do the kids smoke?
  - Bathrooms
  - Classrooms!?!

# E-Cigarettes a “Gateway Drug?”

- Colorado in 2017 had highest use of e-cigarettes in minors
  - E-cigarette use twice national average in high school students

	All students (N = 45,385)	No E-cigarette use (N = 31,991)	E-cigarette use (N = 13,394)
Binge drinking	16%	6.1%	43%
Illegal Rx opioid use	12.4%	7.1%	26%
Marijuana use	19.4%	7.6%	50.1%
Cocaine use	5%	1.4%	14.2%
Sex ≥ 1 partner past 3 months	22.9%	14.6%	45.1%
Heroin use	1.5%	0.5%	3.7%
Methamphetamine use	2%	0.6%	5%



# The FDA Awakens

- Recall in April 2009, e-cigarettes were not “drug delivery devices” as deemed by the court (*Smoking Everywhere, Inc. v. FDA*)
- However, Tobacco Control Act was enacted on June 22, 2009
  - Amended Food, Drug & Cosmetic (FD&C) Act to provide FDA authority to regulate tobacco products
  - “Tobacco product”
    - “...any product made or derived from tobacco that is intended for human consumption, including any component, part, or accessory of a tobacco product (except for raw materials other than tobacco used in manufacturing a component, part, or accessory of a tobacco product).”
  - If a “tobacco product” is used as a drug, then jurisdiction falls under the drug and devices authority



# The FDA Strikes Back

- 2016: FDA finalized rule extending the Center for Tobacco Products (CTP) regulatory authority over *all* tobacco products
  - Includes electronic nicotine delivery systems (ENDS)
  - August 8, 2016: Illegal to sell ENDS to people under age 18
- However, manufacturers were touting e-cigarettes for therapeutic purposes (i.e. a smoking cessation product)
  - These devices are regulated by the Center for Drug Evaluation and Research (CDER)

# Revenge of the FDA

- May 2018: FDA sends 17 warning letters regarding e-liquids with kid-friendly sounding names (e.g. candy, cookies, etc.)
- September 2018: FDA once again sends 12 warning letters for the same
- 11/15/2018: FDA Commissioner Scott Gottlieb, M.D.
  - Moves to restrict all *flavored* ENDS products to be sold in age-restricted, in person locations
  - Exceptions are tobacco, mint, and menthol
    - As they are less popular with minors rather than adults
  - This would effectively ban selling e-cigarettes at gas stations, convenience stores, etc.
  - Target date for enactment: August 8, 2021

# 21 & Done

- December 20, 2019:
  - President Trump signed legislation amending the Food, Drug, and Cosmetic Act to raise the minimum age of sale of tobacco products from 18 to 21, which includes:
    - Cigarettes
    - Cigars
    - ENDS (including e-cigarettes and e-liquids)
    - Smokless tobacco
    - Hookah tobacco
    - Pipe tobacco

# Youth E-Cigarette Use in 2021

- Compared to 2018:
  - High-school e-cigarette use in 2018: 20.8%
  - High-school e-cigarette use in 2021: 11.3% (1,720,000)
- Current trends in 2021:
  - Favorite type: Disposable (55.8%), Refillable/prefilled (28.9%), Mod (7.5%)
  - Favorite brands: Puff Bar (26.1%), Vuse (10.8%), SMOK (9.6%), JUUL (5.7%)
  - Flavor preference: Flavored (85.8%), Unflavored (8.4%)
  - Favorite flavors: Fruit (72.3%), Candy/sweet (33%), Mint (30.5%)

# Smoking Cessation

How and Where E-Cigarettes Fit In

# Who Is Motivated to Quit?

- More likely to quit:
  - Older age
  - Hispanic
  - Married
  - Urban residence
  - Commercial insurance
  - Pregnant
  - Medical diagnoses:
- Less likely to quit:
  - Medicaid
  - Low income
  - High BMI
  - Medical diagnoses:
    - Alcohol-related diagnosis
    - COPD
    - PVD

# Cigarettes Vs. E-Cigarettes

- 2012 smokers in Czech Republic approached to discuss smoking
- Out of 1738 who agreed to participate:
  - Never heard of e-cigarettes: 3.3% ( $n = 57$ )
  - Heard of them, but never tried: 46.7% ( $n = 811$ )
  - Tried once: 23.9% ( $n = 416$ )
  - Tried repeatedly: 16.6% ( $n = 289$ )
  - Use regularly: 9.1% ( $n = 158$ )
  - Lied about frequency of use 0.4% ( $n = 7$ )
- 870 (50%) have used once or more



# Pros & Cons

- Why E-Cigarette Users Vape?
  - To decrease regular cigarette use
  - To quit
  - To use in non-smoking places
- Why Cigarette Users Won't Vape?
  - Cost
  - Poor taste
  - Not satisfying
  - Impracticable
  - Embarrassment

# Smoking Cessation: 1 Quit Method

Self-Reported Quit Method Utilized	# (n = 15,943)
Reported only 1 quit method	3,526 (22.1%)
“Cold turkey”	2,040 (12.8%)
Gradual reduction	905 (5.7%)
Nicotine patch and/or gum	159 (1.0%)
Substituted some cigarettes with e-cigarettes	159 (1.0%)
Switched completely to e-cigarettes	136 (0.9%)
FDA-approved prescription (e.g. Chantix <sup>®</sup> , Zyban <sup>®</sup> )	69 (0.4%)
Switched to “mild” cigarettes	33 (0.2%)
Received help from physician or other health professional	16 (0.1%)
Received help from a website (e.g. Smokefree.gov)	6 (<0.1%)
Received help from a telephone quit line	3 (<0.1%)

# Smoking Cessation: Multiple Methods

Self-Reported Quit Method Utilized	# (n = 15,943)
Reported multiple quit methods	12,417 (77.9%)
“Cold turkey”	10,631 (66.7%)
Gradual reduction	9,682 (60.7%)
Substituted some cigarettes with e-cigarettes	5,861 (36.8%)
Nicotine patch and/or gum	4,047 (25.4%)
Switched completely to e-cigarettes	3,721 (23.3%)
Switched to “mild” cigarettes	3,376 (21.2%)
Received help from physician or other health professional	2,963 (18.6%)
FDA-approved prescription (e.g. Chantix®, Zyban®)	2,374 (14.9%)
Received help from a website (e.g. Smokefree.gov)	1,146 (7.2%)
Received help from a telephone quitline	853 (5.4%)

# Smoking Cessation Highlights

- Study highlights:
  - Majority of cessation attempts utilize multiple approaches
  - “Cold turkey” and gradual reduction are the most popular methods
  - E-cigarette use is higher than other nicotine replacement therapies
  - E-cigarette use is higher than FDA-approved medications (e.g. Chantix<sup>®</sup>, Zyban<sup>®</sup>)
  - Many smokers who use e-cigarettes continue to smoke traditional cigarettes

# Enticing Patients to Quit

- 6006 randomized smokers from 54 companies enrolled & randomized
  - Usual care ( $n = 813$ )
    - Information & motivational text messaging
  - Free cessation aids ( $n = 1588$ )
    - Nicotine-replacement therapy/pharmacotherapy, then e-cigarettes if failed
  - Free e-cigarettes ( $n = 1199$ )
    - No requirement for prior nicotine-replacement therapy/pharmacotherapy
  - Free cessation aids + reward incentives ( $n = 1198$ )
    - \$600 after sustained abstinence (6 months)
  - Free cessation aids + redeemable deposit ( $n = 1208$ )
    - \$600 deposited initially, withdrawn if abstinence not maintained (6 months)

# The Most Enticing Factor Is...

- Those achieving sustained 6 months of abstinence:
  - Usual care ( $n = 813$ ): 0.1%
  - Free cessation aids ( $n = 1588$ ): 0.5%
  - Free e-cigarettes ( $n = 1199$ ): 1%
  - Free cessation aids + reward incentives ( $n = 1198$ ): 2%
  - Free cessation aids + redeemable deposit ( $n = 1208$ ): 2.9%

# Free E-Cigarettes Aren't Enough...

- Redeemable rewards superior to free cessation aids ( $P = 0.006$ )
- Redeemable deposits superior to free cessation aids ( $P < 0.001$ )
- Redeemable deposits superior to free e-cigarettes ( $P = 0.008$ )
- Free e-cigarettes not superior to usual care ( $P = 0.020$ )
- Free e-cigarettes not superior to free cessation aids ( $P = 0.043$ )



# Aren't E-Cigarettes Cheaper?

Group	Average cost per participant (US\$)	Cost per successful quit (US\$)
Usual care	\$0.82	\$700.00*
Free cessation aids	\$39.55	\$7,797.52
Free e-cigarettes	\$54.01	\$5,416.33
Rewards	\$72.65	\$3,623.13
Redeemable deposit	\$100.96	\$3,461.47

\* Only 1 participant in “usual care” group successfully quit

- E-cigarettes were not profoundly beneficial towards cessation...
- But COLD HARD CASH is!

# E-Cigarettes Vs. Nicotine Replacement

- Issues with prior study:
  - Employers pressuring employees to quit
    - Ulterior motives to quit...employees may not have been motivated to quit on their own
- What about those who actually want to quit?
  - 886 smokers recruited with goal to quit smoking
    - E-cigarettes: 438 included in final analysis
    - Nicotine-replacement: 446 included in final analysis
  - Nicotine-replacement included any product other than e-cigarettes
    - Patches, gum, lozenges, nasal spray, mouth spray, mouth strips, micro tabs
    - Products could be used in any combination (e.g. long-acting & short-acting)
      - 88% used a combination

# Results

- Abstinence from cigarettes after 1 year:
  - E-cigarettes: 18% ( $N = 79$ )
  - Nicotine-replacement therapy: 9.9% ( $N = 44$ )
- Unintended consequences:
  - Of the 79 e-cigarette users who stopped smoking after 1 year:
    - 80% continued to use e-cigarettes ( $N = 63$ )
- Participants noted:
  - E-cigarettes were less satisfying than cigarettes, but better than NRT
- Issues:
  - Did not compare with bupropion +/- varenicline

# Are E-Cigarettes a Valid Option — Pro

- Non-nicotine FDA-approved medications are limited and may be contraindicated
- Mimics the physical habit of smoking not addressed by PO/buccal/TD routes
- “Safer” than smoking cigarettes
- Economical: does not waste a whole cigarette for a single puff or two

# Are E-Cigarettes a Valid Option — Con

- There are FDA-approved medications
- Long-term health effects of e-cigarettes are unknown
- E-cigarettes have their own side effects & issues
- Smokers may transition completely to e-cigarettes or use in combination chronically

# Counseling Points with E-Cigarettes

- E-cigarettes are not FDA-approved for smoking cessation
- Limited regulatory oversight regarding e-cigarette manufacturing
- No definitive superiority data when compared to FDA-approved medications
- Increased nicotine exposure when concomitant e-cigarette use with cigarettes
- E-cigarettes have their own litany of issues & side effects
- Long-term risks are unknown
- E-cigarettes are not intended for indefinite use



# Conclusion



# End Points

- E-cigarettes are an appealing method of nicotine delivery
- Multiple potential adverse effects beyond traditional cigarettes
- Significantly increased government oversight in the past 3 years
- Gains have been made towards elimination of youth smoking, but significant use remains
- For selected patients, there may be a role for e-cigarettes in smoking cessation, but it is not FDA-approved and has increased risk of additional addiction