

# Alternative Nicotine Delivery Systems: How Much Threat? How Much Opportunity? How Do We Know?

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# OBJECTIVES:

At the end of this presentation, learners will be able to:

- Discuss alternative nicotine delivery systems, using fact-based information, with adult and child/adolescent patients.
- Critically evaluate the emerging literature on alternative nicotine delivery systems.
- Understand evidence underlying various policy options on alternative nicotine delivery systems.

# TAILORING THIS TALK FOR YOU

WHAT QUESTIONS DO YOU GET ASKED ABOUT  
NICOTINE PRODUCTS?

WHAT QUESTIONS ABOUT NICOTINE PRODUCTS  
ARE HARDEST FOR YOU?

# ACKNOWLEDGEMENTS

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- Alan Blum MD, University of Alabama
- WAFP Staff!!!





# DISCLOSURES:

No conflicts of interest!

\*\*\* Off-Label Use \*\*\*

- Most of the products we will discuss today are not FDA-approved.
- Some of the products we will discuss today are unregulated or incompletely regulated.
- Extended use of FDA-approved nicotine delivery products constitutes off-label use.



# “ALTERNATIVE NICOTINE DELIVERY SYSTEMS” -- WHAT’S INCLUDED?

- Every nicotine delivery system other than cigarettes
  - Combustibles: Cigars, Pipes
  - Smokeless Tobacco -- Chew/Spit, Snuff, Snus
  - Heat, Not Burn – Hookah (maybe), iQOS
  - Non-Pharma Extracted Nicotine: E-cigs/Aerosols
  - Pharma Nicotine Products – Patch, Gum, Lozenge, Inhaler, Spray

# CLINICAL (AND POLICY) QUESTIONS:

- Do alternative nicotine delivery systems encourage youth to start smoking, or enable them to stop smoking, or both?
- Do alternative nicotine delivery systems encourage/enable adults to start, resume, or stop smoking?
- To what extent are alternative nicotine delivery systems intrinsically dangerous?

# HOW DID I GET INVOLVED?

- Flexible Internship in FP-oriented program
- MPH at Johns Hopkins – strong program in Epidemiology
- Public Health residency at New Jersey State Department of Health
- Early career focused on Communicable Disease epidemiology
- Active anti-smoking work started 1990 in Phoenix/Maricopa County
- Co-chaired AAPHP Tobacco Task Force in mid-1990s
- Special Representative of AAPHP to AMA, 1997
- AAPHP President 2000-2002
- Policy work (including tobacco/nicotine policy)
- AAPHP's AMA Delegate and RPL chair 2016-present

# WHAT HAVE I LEARNED IN 29 YEARS?

- Initiation of nicotine products is all about “culture” and symbolism.
- People continue voluntarily using nicotine because of culture.
- Culture and symbolism are changeable!
  - Marketing – almost no detail is an accident!
  - Word of mouth
  - Health & medical messages
  - Generational rebellion
  - Other
- Nicotine modulates many CNS functions – esp. attention & mood.
- Nicotine use can become involuntary -- “addiction” or “use disorder”.
- Different products have different propensity to addiction.
- Nearly all the harm is from the non-nicotine constituents of product.

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- Nicotine modulates many CNS functions – esp. attention & mood.
  - Users report improved focus compared with recollections of prior times.
  - People with schizophrenia and bipolar illness often feel better when using.
  - Withdrawal is very unpleasant; irritability and dysphoria can last for weeks.
  - Cravings and dreams take a long time to abate after quitting.
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- Nicotine modulates many CNS functions – esp. attention & mood.
- Nicotine use can become involuntary -- “addiction” or “use disorder”.
  - Cigarette use almost always becomes involuntary over time.
- Different products have different propensity to addiction.
  - Anybody have a patient who wanted to quit pipe smoking and couldn’t?
  - 20<sup>th</sup> century: Cigarettes were engineered for addiction.
  - Cigars and early e-cigarettes: Few reports of addiction in never-users of cigarettes.
  - JUUL uses nicotine salts, associated with many reports of addiction.
- Nearly all the harm is from the non-nicotine constituents of product.

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- Initiation of nicotine products is all about “culture” and symbolism.
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- Culture is changeable!
- Nicotine modulates many CNS functions – esp. attention & mood.
- Nicotine use can become involuntary -- “addiction” or “use disorder”.
- Different products have different propensity to addiction.
- **Nearly all the harm is from the non-nicotine constituents of product.**
  - Inflammatory and atherosclerotic effects, platelet activation – CV disease/MI.
  - Cancer initiation, promotion, immune modulation --> cancer, cancer, cancer!
  - Other disease/harms are most plausibly linked to effects of nicotine delivery vehicles.
  - Pure nicotine effects: Vasoconstriction and transient hypoperfusion (exacerbated by CO); exacerbation of pre-existing Buerger’s Disease; modulation of dopamine response? other?
  - Scant nicotine benefits: Parkinson’s, ulcerative colitis, maybe schizophrenia/bipolar.



# WHAT ELSE HAVE I LEARNED?

- Harm Reduction is always opposed in the beginning
  - “Teaching adolescents about condoms encourages sex.”
  - “Supplying clean needles helps people use more drugs.”
- Substance abuse harm reduction is especially fraught
  - “To a politician, ‘drug abuse’ is ‘a drug I don’t use, used by someone I don’t like’.”
- Can Harm Reduction save lives in nicotine policy?

# LEVELS/QUALITY OF EVIDENCE

- Public Health & Preventive Medicine specialists have formal training on the evaluation of medical evidence.
- The next four slides may be the shortest possible “refresher course” on evaluating medical evidence for FPs.
- AAFP and its publications use the Strength Of Recommendation Taxonomy (SORT), based on work by Ebell et al (AFP 2004-02-01, p. 548-556).

-- <https://www.aafp.org/afp/2004/0201/p548.html>, echoed in current guidance at <https://www.aafp.org/dam/AAFP/documents/journals/afp/sortdef07.pdf> . Both accessed 2019-04-18.



# GOOD QUALITY Patient-Oriented Evidence: Treatment/Prevention/Screening

- Level 1: One high-quality Randomized Controlled Trial (RCT) (allocation concealed, blinded if possible, intention-to-treat analysis, adequate statistical power, >80% follow-up), OR
- Level 1: Systematic review/meta-analysis of RCTs with consistent findings, OR
- Level 1: All-or-none study [with differences so dramatic that large numbers aren't needed and large study is precluded (examples, without irony: antibiotics for meningitis and surgery for appendicitis)].

-- <https://www.aafp.org/afp/2004/0201/p548.html>, accessed 2019-04-18.

# LIMITED QUALITY Patient-Oriented Evidence: Rx/Prev/Screening

- Level 2: Lower-quality clinical trial OR
- Level 2: Cohort study [ascertain exposure, then follow exposed and unexposed over time] OR
- Level 2: Case-control study [ascertain disease, then trace diseased and non-diseased back in time] OR
- Level 2: Systematic review/meta-analysis of lower quality clinical trials or of studies with inconsistent findings.

-- <https://www.aafp.org/dam/AAFP/documents/journals/afp/sortdef07.pdf>, accessed 2019-04-18.

# OTHER Evidence: Rx/Prev/Screening

- Level 3: Consensus guidelines OR
- Level 3: Extrapolations from bench research OR
- Level 3: Usual practice OR
- Level 3: Opinion OR
- Level 3: Evidence limited to intermediate or physiologic outcomes OR
- Level 3: Case series

- -- <https://www.aafp.org/dam/AAFP/documents/journals/afp/sortdef07.pdf>, accessed 2019-04-18.

# WHY THE DIFFERENT LEVELS OF EVIDENCE?

- **CONFOUNDING VARIABLES**

- If two variables are associated, B can cause A;
- Or A can cause B;
- Or some third factor, “C”, can cause both A and B.
- Example: Post-menopausal estrogen was initially thought to prevent heart disease....
- Good RCTs control for confounding variables, to the extent that these potential confounders are known.

- **EXPECTATIONS ARE POWERFUL!**

- Placebo/Nocebo effects
- Researcher expectations

- **DROPPING OUT ISN'T RANDOM**

- **POPULATIONS DIFFER**

- **THINGS CHANGE**

# TOBACCO HISTORY

- Native only to Western Hemisphere.
- Ritual and ceremonial use, at least in some parts of North America.
- Bartolome de Las Casas, early 1500s: “Spaniards ... were unable to cease using it.”
- Introduced to Spain and Portugal by 1533.
- Usage spread across Europe, with mixed reactions:
  - Francis II of France credited snuff with curing his headaches (1559-1560).
  - James I of England: “loathsome ... hateful ... harmful ...stinking” (1604)
- Nicotiana & nicotine named for Jean Nicot ~1559.

-- [https://en.wikipedia.org/wiki/History\\_of\\_tobacco](https://en.wikipedia.org/wiki/History_of_tobacco), accessed 2019-04-18.





# EARLY REPORTS OF EFFECTS....

- Relaxation
- Concentration
- Anti-Fatigue
- Pleasure



Photo: Frederick William Fairholt, "Raleigh's First Pipe in England"



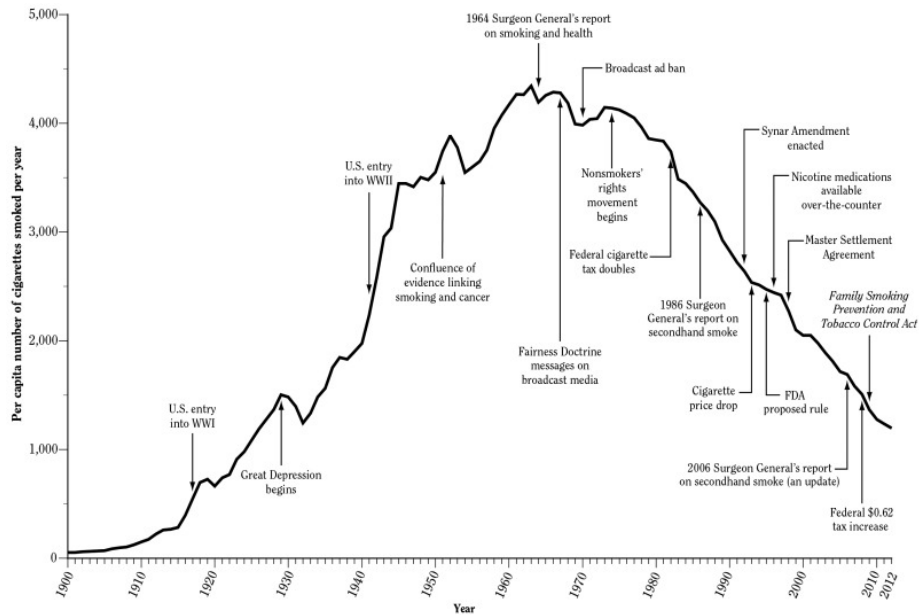
# REPORTS OF HARM

- James I, A Counterblaste to Tobacco (1604):
  - “[a] custome loathsome to the eye, hatefull to the Nose, harmefull to the braine, dangerous to the Lungs, and in the blacke stinking fume thereof, nearest resembling the horrible Stigian smoke of the pit that is bottomeless.”
- Lung cancer: Almost unknown before cigarettes --
  - “In 1919, lung cancer was such a rare disease that Ochsner’s entire junior medical school class was asked to witness the autopsy of a man who had died from it. The professor, Dr. George Dock, believed that no one in the class would ever see another such case. Seventeen years later [1936], after having been a surgeon for more than a decade Ochsner did see his next case of lung cancer – nine cases, in fact, in a period of just six months. Because all the patients were men who had taken up the newly mass-advertised practice of smoking while serving as soldiers in World War I, [Ochsner] had the temerity to suggest that cigarette smoking was responsible.” -- Alan Blum, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3145444/>, accessed 2019-04-23.
- Surgeon General’s Report on Smoking and Cancer (Luther Terry MD, 1964).
- Later Surgeon General reports on non-cancer morbidity/mortality; hazards of environmental tobacco smoke; “smokeless”; etc., etc.

# NICOTINE DELIVERY VEHICLES

- Through most of 19<sup>th</sup> century: Pipes, cigars, snuff, chewing.
- In some cultures: Water pipes (hookahs).
- Starting 1847: Slow hand-operated cigarette-making machines
- Starting 1880s: Rapid cigarette-making machines (Bonsack, USA).
  - <https://en.wikipedia.org/wiki/Cigarette>, accessed 2019-04-23.
- Alkaline smoke is more irritating, but has free (nonprotonated) nicotine, which is absorbed faster and appears more addictive.
- Cigarette chemistry is acidic (less irritating than alkaline), with nonprotonated nicotine in an aerosol component.
  - ASAM Principles of Addiction Medicine, 2014 edition, Chapter 12.
- Cigarettes were marketed for sustained use, “engineered for addiction”.
  - <http://www.evolvecigarette.com/the-modern-cigarette-engineered-for-addiction/>, accessed 2019-04-23.

# CULTURE CHANGED, CONSUMPTION DECLINED



Graph from Surgeon General's Report, The Health Consequences of Smoking—50 Years of Progress (2014)

- 1964 was when per capita consumption peaked
- Some quit fairly easily, some had difficulty
- Impact of Public Health measures, cultural change
- SAMMEC software still estimates ~480K annual deaths in USA

# CIGARETTE INDUSTRY BEHAVIOR

- Free samples to military personnel (especially World War I)
- Positioning cigarettes as humanitarian
- Philanthropy and education
- Engineering for addiction – and lying about it
- Exploiting scientific doubt
- Manufacturing scientific doubt
- In-house “research” – findings distorted or cherry-picked
- Buying political influence
- Marketing product differences as beneficial, or as less harmful
- Marketing to powerful, partly subconscious human urges
- Special marketing to women, youth, minorities
- Negotiating with health advocates
- Acquisition of, then divestment of, food and other consumer-product companies
- Now legally adjudged racketeers, culturally adjudged villains
- Public disgust generalized from cigarette companies to “Big Tobacco”

# TOBACCO CONTROL EVOLVES

- Initial efforts volunteer & self-funded
- Initially labeled by AMA and others as extremist
- Smokefree advocates struggled for each gain
- Pharma industry takes a stake in 1980s/1990s
- Liability litigation begins
- Attorneys General Medicaid litigation, 1990s
- Health groups involved to help settle AG litigation
- Negotiation & relationships with cigarette industry
- Intersection of government & Pharma funding
- FDA's current regulatory framework

# MENTHOL

- Local anesthetic – masks harshness, reduces irritant-based cough
- Flavoring agent, masks bitter flavor of nicotine
- Marketed especially to African-Americans
- Specially allowed under current Federal law
- Scientific advisory groups have recommended removing menthol from cigarettes

# NICOTINE PRODUCT DIFFERENCES

- All tobacco products have some toxicity
- Even pharma nicotine products have trace contaminants
- Combustion multiplies harmful contaminants
- All tissues are susceptible, but lungs are most susceptible to harm
- The case against cigarettes has robust, direct epidemiologic evidence
- Other combustible products: Some direct evidence of harm
- Non-combustible products
  - Evidence may be indirect
  - Anecdotes and images predominate
- Do product differences open a way for harm reduction?
  - Harm reduction saves lives with other addiction & injury issues....
  - ... but, with nicotine, will we be fooled again by “Big Tobacco”?
  - Will benefits to established addicts be overwhelmed by addicting new users?

# “SURGEON GENERAL’S WARNINGS”

- “Surgeon General’s warnings” are Congressional mandates
  - Surgeon General has limited or no input on the warnings’ content
  - What does “Not a safe alternative to cigarettes” mean?
  - If it’s not a safe alternative, is it just as harmful as cigarettes?
  - Does that mean, “You might as well smoke?”
- 
- Many messages have unintended consequences
  - Are we, and our patients, ready for messages about relative risk?
  - If so, what messages are accurate -- and appropriate for whom?



# MEDICATIONS FOR NICOTINE ADDICTION

- Cigarette smokers typically “quit” several times before they stay quit.
- More than half of U.S. former smokers say they quit without meds.
  - <https://news.gallup.com/poll/163763/smokers-quit-tried-multiple-times.aspx>, accessed 2019-04-23.
- Nicotine gum, patches, lozenges, inhaler, nasal spray.
- Bupropion; varenicline; nortriptyline; clonidine.
- Standard for most drug approval = Better than placebo at 6 months.
- Sustained quit rates are typically 10% or so with approved meds.
  - Etter & Stapleton, Tobacco Control 2006 Aug; 15(4):280-285
  - Varenicline may be somewhat better: Ebbert et al, Patient Preference and Adherence 2010; 4:355-362
  - But nihilists have evidence too! “Using ... a balanced comparison, there was no evidence that use of varenicline..., bupropion..., or nicotine replacement... increased the probability of 30 days or more smoking abstinence at one-year follow-up.” Leas et al, J Nat Cancer Inst 2018 June; 110(6):581-587
- Market size in USA about \$2B/year; globally >\$7B
  - <https://www.grandviewresearch.com/industry-analysis/smoking-cessation-and-nicotine-de-addiction-products-market> , accessed 2019-05-10
- How long should nicotine-addiction meds be used? “As long as it takes.”
  - ASAM Principles of Addiction Medicine, 2014, Chapter 53.



# CIGARETTE COMPANIES' DILEMMA

- Legally (and morally, some argue) required to maximize profit
- Cigarettes still profitable in USA and worldwide
- Technology and culture are changing
- Cigarette companies can market existing cigarettes in poor countries
- Unsure how much longer cigarettes will be viable in rich countries
- Cigarette companies have lost cultural influence in rich countries
- Cigarette companies may or may not control technological change, especially in rich countries

# EASTMAN KODAK



- Kodak was “best in the world” in photographic film
- They thought they only needed to innovate/excel in photographic film, not in other technologies
- Reorganized, drastically downsized after bankruptcy in 2012-2013
- Taught in business schools as an example of what dominant companies and industries should NOT do

# CHANGING CIGARETTE TECHNOLOGY

- Filters
  - Visibly removed some black stuff from the smoke
  - Most consumers thought they were reduced risk
  - Epidemiologic data showed that risk stayed basically the same
- Air Holes
  - With smoking machines, the smoke was diluted
  - Official “tar and nicotine” ratings declined dramatically
  - Human users covered the holes with fingers &/or lips
  - Again, risk stayed basically the same
- With this history, anti-smoking activists mistrust industry-driven technological change as a harm reduction idea!

# CURRENT FDA LAW

- “Family Smoking Prevention and Tobacco Control Act”
- Negotiated between Altria & “Campaign for Tobacco-Free Kids” in 2006
- Health groups’ stated intention: “strong regulation”
- Altria’s apparent intention: Discourage innovation
- Cigarettes “grandfathered”, but cigarette marketing restricted
- Regulation is product-by-product, not category-by-category
- New products must show long-term Public Health benefit before they can be introduced to the market
- How do you prove “real world” benefit for a pre-market product?
- Alan Blum labeled this bill “The Marlboro Protection Act”
- Passed and signed in 2009

# BEYOND CIGARETTES

- Smokeless tobacco
- Hookah – water pipes come to USA
- iQOS – “Heat, not burn”
- Electronic cigarettes

# SMOKELESS TOBACCO

- Not a combusted product
- Cancer risk varies by product, but generally lower than cigarettes
  - Confounder: High concordance between Hx of smokeless and Hx of smoking
- Swedish experience with snus is positive, w/ Europe's lowest smoking rates

# HOOKAH

- Flavored tobacco is heated, often with charcoal
- Smoke is drawn through water before inhaling
- Marketed as less toxic – but the water absorbs few contaminants
- Esthetic appeal – hookah pipes can be intricate and beautiful
- Social appeal – hookah is often smoked in groups
- Oxygen-deprived combustion, so very high CO





# iQOS



- Proprietary “heat, not burn” technology from Altria/PM
- Altria claims this to be less hazardous than smoking
- Do “reduced contaminant levels” translate to lower risk?
- Independent research suggests modest decreases in risk
- How would such a product change tobacco use patterns?
  - It depends mostly on how it fits into – and how it changes – tobacco culture
  - That’s not a technological issue!

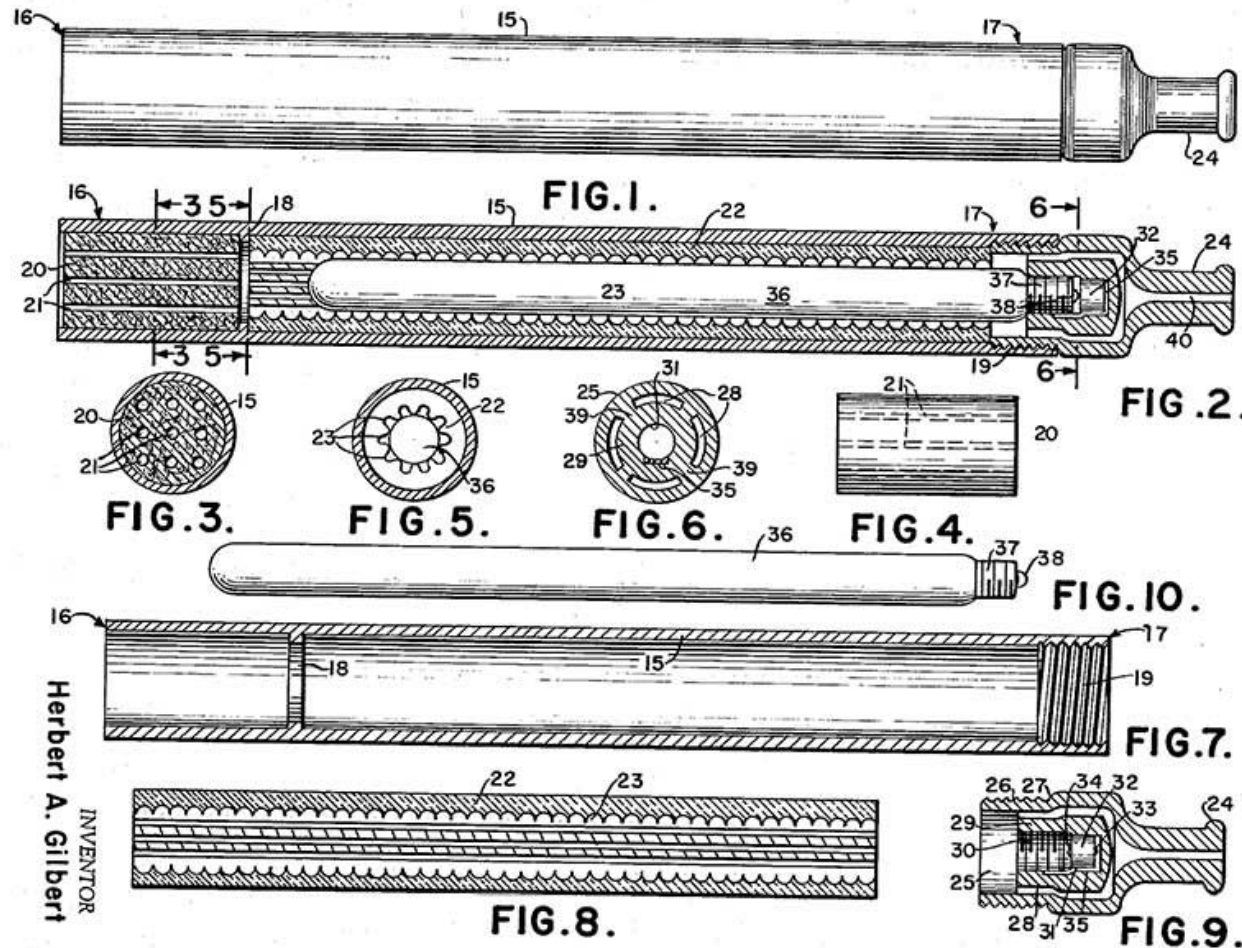
# ELECTRONIC CIGARETTES: GENERAL

- Nicotine solution is heated and aerosolized
- Humectants mostly propylene glycol (PG) and vegetable glycerin (VG)
- Humectants are “generally recognized as safe” for oral ingestion
  - Long-term respiratory effects are unknown
- PG and VG have different boiling points, particle size, distribution
- Nicotine is absorbed through mucous membranes
- Inventors intended e-cigarettes for smoking cessation & harm reduction
- Almost any substance, almost any concentration
  - Intended for nicotine, but substance abusers are creative!
- Initially, no regulatory framework

# ELECTRONIC CIGARETTES: QUESTIONS FROM A PUBLIC HEALTH PERSPECTIVE

- Do e-cigs make smokers more likely to quit, or less?
- How toxic are e-cigs to users in the short run? In the long run? Compared to what?
  - Compared to combustible cigarettes, for smokers considering switching to e-cigs or for e-cig users considering switching to smoking
  - Compared to non-use of any drug-delivery product, for current non-smokers
  - First-hand effects on users, second-hand effects via shared air, third-hand effects via surfaces
- Do e-cigs result in more youth uptake of nicotine, or less?
- Does the chemical form of nicotine matter to Youth? Adults? Both?
- Do flavorings facilitate quitting? Youth uptake? Both? Neither?
- Do e-cigs result in an increase in use of other drugs? If so, in whom?
- What Public Health outcome is most important here?
- What Public Health messaging will best facilitate that outcome?
- How can we get the most reliable research on which to base policy?
- **Honest Public Health professionals disagree about every single one of these questions!**
- Strength Of Recommendation Taxonomy, and similar frameworks, can help us classify levels of evidence

Herbert Gilbert's "Smokeless Non-Tobacco Cigarette", April 1963  
U.S. Patent #3,200,819; Smithsonian, December 2018.  
Flavors, but no nicotine. Never commercially produced.



# HON LIK

- Pharmacist, trained in traditional Chinese medicine/pharmacy
- Smoker whose father died of lung cancer in 2004
- Affiliated with Liaoning Academy of Traditional Chinese Medicine
  - [https://en.wikipedia.org/wiki/Hon\\_Lik](https://en.wikipedia.org/wiki/Hon_Lik), accessed 2019-04-26.
- “I tried nicotine patches but I didn't care for the idea of slow diffusion of the drug into the organism. I missed the effect of the sudden impact, the act of smoking, the sensation of smoking. So I started thinking of a way to create vapor containing nicotine, similar to cigarette smoke but not as harmful for the organism.”
- Patent application: “[T]he user still feel smoking and experiencing the excitement”. Application March 2004; patent was granted February 2006.
- Ultrasound to create nicotine aerosol; later “resistance heat”
- Apparently others have received most of the profits, but Lik is doing OK
  - [https://www.sciencesetavenir.fr/sante/i-was-sure-that-the-electronic-cigarette-would-be-welcomed-with-open-arms\\_26020](https://www.sciencesetavenir.fr/sante/i-was-sure-that-the-electronic-cigarette-would-be-welcomed-with-open-arms_26020). A 2013 interview, accessed 2019-04-26.

# TYPES OF ELECTRONIC CIGARETTES

- Three major types
  - Disposables, mostly “cig-alikes”
  - Tanks and mods
  - Rechargeables
- Initial products used mostly protonated nicotine
- JUUL uses nicotine salts
- Marketed variably
  - Partly because health claims are forbidden
  - Partly because there aren’t many enforceable e-cig marketing rules in USA

# ELECTRONIC CIGARETTE REGULATION

- FDA attempted to classify e-cigs as “drug delivery devices” requiring clinical trials
- Courts forced FDA to regulate e-cigs as new tobacco products under the 2009 Act, not as drug delivery devices
- The 2009 Act was written to discourage new tobacco products
- FDA interpretation under Obama Administration:
  - Need an application (>\$250,000 estimated preparation cost) for every dose/flavor/device combination
  - Once approved, if ever approved, can’t change the device or supplies
  - Many assumed this would concentrate e-cig manufacture in a few wealthy companies, most likely the existing cigarette companies
  - This prospect troubled some observers more than others
- FDA interpretation under Trump Administration:
  - FDA head had e-cig industry experience
  - Delayed implementation of the new rules
  - Alarmed by increased youth vaping rates in 2017-2018
  - Angry posturing by FDA head and by the US Surgeon General, some voluntary change, not much regulatory change
- Upshot: No enforceable e-cig-specific manufacturing (or marketing?) standards at all



# ELECTRONIC CIGARETTES: SOME STAKEHOLDER PERSPECTIVES

- E-cig developers' stated intentions: Help smokers transition off cigarettes
- Reality is WAY more complicated than that. Examples:
- For FDA, "This product helps people quit smoking" is a medical claim
  - Requires product-specific clinical trials before claims can be approved
  - Trials can be paid for if patents protect the specific product tested
- For cigarette companies, massive cessation/switching would be an existential threat – but "dual use" could relieve cessation pressure
- Pharma companies prefer cessation methods that feature their products
- Advocacy groups and professional associations receive Pharma money
- E-cig ads: "This is cool" vs. "Make the switch".
  - Both of these are culture messages!
  - Semi-forbidden words: "quit", "addiction", and "health"
  - <https://www.apnews.com/7bf104d1814d447094255a7327b0c5c5>
    - Posted 2019-05-09



# ELECTRONIC CIGARETTES: AN ECOLOGICAL PERSPECTIVE

- Every player in this web influences most of the other players
- FDA regulates Pharma and non-Pharma nicotine
- Federal staff want Pharma goodwill & jobs
- Pharma & Feds fund researchers (and, more recently, activists)
- Congress & FDA tolerate combustible cigarettes
- Cigarette companies fear technological and regulatory obsolescence
- State legislatures need cash, including tobacco settlement funds
- Paid Tobacco Control staff and researchers need funders
- Unpaid activists are largely irrelevant at Congressional level

# GOOD QUALITY Patient-Oriented Evidence: Treatment/Prevention/Screening

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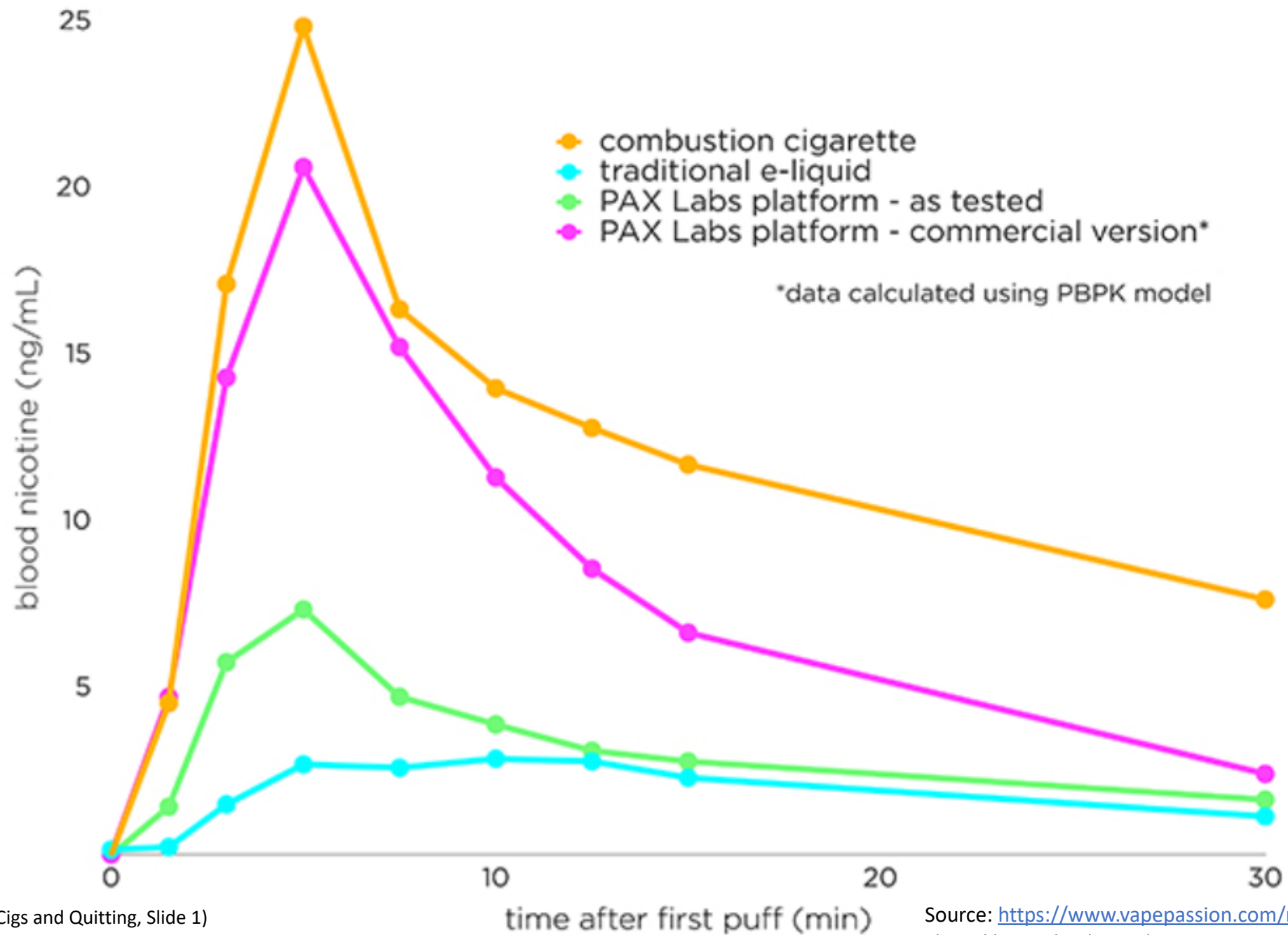
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# CHEMICAL FORM OF NICOTINE

- Protonation of nicotine delays nicotine absorption
- Pipes, cigars, and most e-cig brands use protonated nicotine
- Combustible cigarettes and JUUL use non-protonated nicotine
- Anecdotal data (Level 3) suggest that this is an important factor in addiction



# E-CIGS AND QUITTING:

Do e-cigs make smokers more likely to quit, or less?

- Several randomized trials compared only nicotine vs. non-nicotine e-cigs
  - (Nicotine-containing e-cigs yield better quit rates than non-nicotine in each study)
- One trial compared e-cigs w/ cash payments, to conventional nicotine replacement with & without \$600 cash payments, in smokers selected from employment databases
  - (Cash increased quit rates; insert reference)
- Two trials (Bullen & Hajek) compared nicotine e-cigs vs. pharma nicotine replacement
- Bullen, New Zealand, 2014: Nicotine e-cigs were non-significantly better than patch, BUT small quit rates in all groups meant statistical significance was very low
  - Bullen et al, Lancet 2013 Nov 16; 382(9905):1629-1637
- Hajek, United Kingdom, 2019: Nicotine e-cigs (540 mg dispensed, with encouragement to experiment with brand/dose) were significantly better than patient's choice of pharma product(s) (3 months paid for). One-year abstinence 18.0% vs. 9.9%,  $p < 0.001$ 
  - Voluntary crossovers from pharma to e-cigs 20%, from e-cigs to pharma 3%
  - 78.8% follow-up; Level 1 requires >80%. Was evaluation as blinded as possible?
  - Hajek et al, New Engl J Med 2019 Feb 14;380(7):629-637
- Conclusion: E-cigs increase quitting, in the right context; evidence quality is in the upper ranges of Level 2

# E-CIGS AND QUITTING:

Do e-cigs make smokers more likely to quit, or less?

- Meanwhile, in observational studies, susceptible to confounding:
- Any e-cig use is associated with lower quit rates than no e-cig use
- Daily e-cig use is associated with higher quit rates than no e-cig use
- Concurrent or “dual use” of e-cigs with combustible cigarettes is thought to be about as dangerous as smoking without e-cig use
  - Some, but not all, think there is modest benefit if cigarette use is drastically reduced
  - Is dual use a transitional state, or is it a long-term impediment to quitting?
- Ecologic data show dramatic drops in adult smoking during e-cig era
  - Ecologic data are very susceptible to confounders
  - Inflection points depend on what data set you choose
- Observational/ecological data would only be Level 2, no matter how big the studies were – but they don’t even point in the same direction



# E-CIGARETTE TOXICITY – ACUTE USE

- Glycerin & Propylene Glycol
- Particulate pollution is dangerous; does particle chemistry matter?
- No manufacturing performance standards
- Heavy metals: Found in some studies
- Formaldehyde: You can make an e-cig generate a lot of formaldehyde, but it's unclear whether vapers will actually breathe it
- Cellular and immune problems in laboratory and non-human models
- Some irritant effects, mostly respiratory
- Asthma symptoms improve markedly on switching from smoking to vape
- Evidence quality: Some is Level 2, most is level 3
- Message: Not as good as clean air – but much less hazardous than smoking, at least in the short run

# E-CIGARETTE TOXICITY – CHRONIC USE

- No data on chronic e-cig use, for any population anywhere in the world
- Toxicology data suggest per-user chronic illness burden will probably be lower than cigarettes – but is it a lot lower, or only a little lower?
- Public Health England opines that e-cigs are 95% less dangerous than smoking, based on one “expert opinion” committee
- Others deride the PH England committee’s use of “educated guesswork” (Level 3 evidence quality) and accuse the committee of bias
- Some public health agencies say “e-cigs are no safer than smoking”
  - The obvious corollary is that “cigarettes are no more dangerous than e-cigs”.
  - What happens if current vapers believe that they might as well smoke?

# NICOTINE TOXICITY – PREGNANCY

- Cigarettes → Low birth weight, IUGR, many other fetal problems
- Nicotine during pregnancy is associated with substantial effects on the fetus' subsequent childhood, adolescence, adulthood
- Possible confounders include poverty, mental illness, other psychological stress, use of other substances, etc.
- Nicotine is a vasoconstrictor – does it impair uterine, placental, and/or fetal circulation?
- Strong preference for stopping all nicotine if feasible
- Evidence quality: Level 2 (it's not ethical/feasible to get level 1 evidence)
- E-cigarettes might constitute harm reduction if nothing else will work

# NICOTINE TOXICITY – ADOLESCENCE

- Effects on attention
- Effects on dopamine reward system
- Might predispose to other forms of substance abuse
- California Department of Public Health beginning to tell adolescents that nicotine is “brain poison”.
- Messaging to adolescents is tricky
  - “Forbidden fruit” can be attractive
  - Adolescents may trust peers more than they trust adults
  - Adolescents may not understand messages the same way adults do
  - Adolescents are very sensitive to anything they consider deceptive, patronizing, or unfair
  - Adolescents reject messages that they believe are exaggerated or misleading
  - Adolescents’ brains don’t consider consequences very well
  - Adolescents strongly discount long-term consequences

# E-CIGS AND YOUTH:

Do e-cigs make smokers more likely to start - & to start what?

- Large increase in occasional use of e-cigs, especially 2017 & 2018
- Not so large increase in daily or near-daily use of e-cigs
- Many surveys don't separate occasional from regular use
- Dramatic decrease in youth smoking, nadir in 2017, increase in 2018 (USA)
- Some cohort studies try to control for susceptibility-related variables
- Causal relationships easy to speculate about, difficult to prove
- JUUL seems to have a special role:
  - Nicotine salts – rapidly absorbed. JUUL doesn't market any non-nicotine pods.
  - Youth say most of their vaping is non-nicotine – but JUUL dominates the youth market
  - Some youth report extreme difficulty quitting JUUL
  - JUUL's market dominance began just before the 2017 nadir in youth smoking rates

# E-CIGARETTE FLAVORING

- Non-tobacco flavoring has dominated from the beginning
- Youth and adults both like sweet flavors
- “Unicorn Poop” – REALLY????
- Vaping advocates say sweet flavors deter returning to smoking
- Vaping opponents say adolescents attracted to sweet flavors might not otherwise have vaped and might progress to smoking
- One observational study noted e-cig flavors are associated with lower rates of smoking cessation
- Diacetyl and bronchiolitis obliterans – what’s the evidence?



MENU ▾

ABOUT US ▾

BLOG

CONTACT

KEYSTONE VAPOR

WHOLESALE INFO

ACCOUNT

\$0



## Unicorn Poop

Well... everyone knows Unicorns are made of cupcakes and rainbows! This tastes like blueberry cupcakes with white chocolate frosting and a raspberry on top!

\$6.49

Nicotine Level (mg/ml)\*:

0 mg

PG/VG Ratio\*:

Max VG

size

10 ml

Quantity

1

ADD TO CART



Chef's Table

# BRONCHIOLITIS OBLITERANS

- Bronchiolitis obliterans is widely considered to be caused by diacetyl
- Diacetyl flavors many foods and is generally accepted as safe to eat
- In some forms, inhaled diacetyl is associated with bronchiolitis obliterans
  - Popcorn manufacturing facilities – this led to the nickname “popcorn lung”
  - Coffee roasting facilities
- Diacetyl is found at high levels in cigarette smoke
  - Cigarette smoking is not a recognized risk factor for bronchiolitis obliterans
  - Cigarette smoking is a recognized risk factor for other forms of bronchiolitis
- Diacetyl is used as an e-cigarette flavoring
  - Variable levels of diacetyl in vaping aerosols
- One case report of bronchiolitis (not bronchiolitis obliterans, as far as I can tell) associated with e-cigarette use
- Level 3 evidence suggests that bronchiolitis obliterans is at least a theoretical concern



# E-CIGARETTES AS VEHICLES FOR OTHER DRUGS

- Easy to conceal e-cig use if you really want to
- Easy to put other drugs into user-modifiable e-cig systems
- Hard to distinguish nicotine vaping from vaping of other drugs
- Some survey data, especially about cannabis
- Lots of anecdotal reports, especially from educators

# AAPHP TOBACCO POLICIES - 1

- Adopted 2011-12-09, reviewed frequently by AAPHP's policy committee but not revised (most members like it as is)
  - Policy-relevant recommendations are #2-13
- 
- 2. Tobacco use is a major cause of illness and death in the United States.
  - 3. Almost all tobacco-attributable mortality in the USA is due to cigarette smoking.
  - 4. While nicotine is the primary addictive substance in cigarette smoke, other factors substantially enhance the addictiveness of cigarettes. These factors include habituation to the cigarette handling ritual, psychological appeal based on advertising themes, the strength and speed of the nicotine "hit," and other factors. This set of factors make cigarettes the most addictive of tobacco/nicotine products.

<http://www.aapHP.org/tobacco>



# AAPHP TOBACCO POLICIES - 2

- 5. Substances in the cigarette smoke, other than the nicotine, inhaled deep into the lung, cause most of the tobacco-attributable illness and death in the United States.
- 6. Smoke-free tobacco/nicotine products, as available on the American market, while not risk-free, carry substantially less risk of death and may be easier to quit than cigarettes.
- 7. Since susceptibility to tobacco/nicotine addiction is strongest in adolescence and early adulthood, measures to prohibit sale of tobacco/nicotine products without a physician prescription should be maintained and strengthened.

<http://www.aapHP.org/tobacco>



# AAPHP TOBACCO POLICIES - 3

- 8. The healthiest option is to never initiate tobacco/nicotine use.
- 9. For those already using a tobacco/nicotine product, the best option is to quit.
- 10. Harm Reduction: Smokers who have tried, but failed to quit using medical guidance and pharmaceutical products, and smokers unable or uninterested in quitting should consider switching to a less hazardous smoke-free tobacco/nicotine product for as long as they feel the need for such a product. Such products include pharmaceutical Nicotine Replacement Therapy (NRT) products used, off-label, on a long term basis; electronic “e” cigarettes, dissolvables (sticks, strips and orbs), snus, other forms of moist snuff, and chewing tobacco.

<http://www.aapnp.org/tobacco>



# AAPHP TOBACCO POLICIES - 4

- 11. Harm reduction should be considered as an addition to current tobacco control policies and programming and should be done in a way that will minimize initiation of tobacco/nicotine use, maximize quit rates and assure that dual use does not increase potential harm to the user.
- 12. Mandated health related warnings on tobacco/nicotine products should be periodically reviewed to assure that each warning reflects a real-life hazard posed by the product in question and is not misleading in any way.
- 13. AAPHP tobacco policy should be intended to reduce the burden of illness, death and property damage attributable to tobacco products in American society. In pursuit of this goal, AAPHP must consider the needs and risks of current tobacco users, those potentially exposed to tobacco smoke, and those at risk of initiating future use of tobacco/nicotine products.

<http://www.aaphp.org/tobacco>



# AAFP RECOMMENDATIONS

- E-cigs generally: <https://www.aafp.org/about/policies/all/e-cigarettes.html>, appears to be 2015
  - Calls for rigorous research into e-cigs as a quit-smoking strategy
  - Calls for all e-cig marketing to cease until safety, toxicity, efficacy are known
- JUUL: <https://www.aafp.org/patient-care/public-health/tobacco-nicotine/tools/e-cigs.html>, appears to be 2018
  - JUUL is more easily concealed than other nicotine products
  - JUUL uses nicotine salts
  - JUUL has higher levels of nicotine than other e-cigs
- Both sites have links, including links to physician and patient fact sheets on the AAFP JUUL site
- AAFP Public Health Blog: <https://www.aafp.org/news/health-of-the-public.html>

# COUNSELING PATIENTS

- SCHOOL AGE
  - Consider asking if friends smoke, vape, use e-cigs
  - Short term risks matter more to children/adolescents (looks, athletics, cars, money, sex)
  - Be ready to talk about long-term risks, known and unknown
  - Be ready to talk about marketing and peer influences in terms of fairness
- YOUNG ADULTS
  - Often willing to talk about their own behavior
  - Curious about alternative nicotine delivery systems
- SMOKERS AT ANY AGE
  - "Cold turkey" lasts longest – when it works
  - Congratulate effort – "Keep trying!"
  - Don't be afraid to try new quitting "tricks" – behavior, meds, etc.
  - E-cigs should be discussed as a "last resort" for selected patients
- QUITTERS OR SWITCHERS (to other nicotine products)
  - Congratulate switchers, not just quitters
  - Encourage cessation of all nicotine products when ready
  - Discuss responses to stress and to cravings/triggers
  - "Whatever you do, don't go back to smoking!"

# OBJECTIVES (REPRISE):

At the end of this presentation, I hope all of you are more able to:

- Discuss alternative nicotine delivery systems, using fact-based information, with adult and child/adolescent patients.
- Critically evaluate the emerging literature on alternative nicotine delivery systems.
- Understand evidence underlying various policy options on alternative nicotine delivery systems.



# THANK YOU!

Questions/discussion, please....

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