

Cigarettes to Juuls, It's Time to Quit

ANAND POPURI DO
PULMONARY AND CRITICAL CARE MEDICINE

Objectives

- ▶ Examine smoking from a historical perspective
- ▶ Discuss the health risk of tobacco/nicotine use
- ▶ Explore the evolution of nicotine use with Vaporized Nicotine
- ▶ Compare the unknown risks and benefits of Vaporized Nicotine
- ▶ Discuss the essential keys to Smoking Cessation
- ▶ Review recommended therapy of Smoking Cessation

Smoking through history

- ▶ Smoking has been depicted as early as the 9th century
- ▶ The 1st European to discover smoking tobacco was Christopher Columbus
- ▶ Smoking became widespread globally in the 1700s
- ▶ A series of medical reports in the 1950s eventually confirmed tobacco's link to lung cancer and other smoking related lung disease
- ▶ The development of cigarette rollers in the 1800s
- ▶ Smoking increased dramatically during the world wars due to free distribution to soldiers



The Turning Point

- ▶ In the 1950s
 - ▶ 5 large retrospective trials showed a link between smoking and lung cancer
 - ▶ These studies were discredited by tobacco companies as they were retrospective studies
 - ▶ Smokers tended to overestimate the amount they smoked
 - ▶ Nonsmokers downplayed they amount of cigarettes they smoked
 - ▶ A prospective study was needed

The Turning Point

- ▶ E. Cuyler Hammond Ph.D and Daniel Horn Ph.D started a cohort study in January of 1952.
 - ▶ 22,000 Volunteers helped to recruit of men ages 50 to 69 across ten states.
 - ▶ 188,000 men were recruited and followed through 1955
 - ▶ They asked if they smoked, how often and how much.
 - ▶ Volunteers would follow patients to mark if they were alive or dead
 - ▶ Prelim findings were published on August 7th 1954
 - ▶ Men with a history of regular smoking history had a markedly higher death rate
 - ▶ Secondary to heart disease and cancer

The Turning Point

- ▶ “Deaths from cancer were definitely associated with regular cigarette smoking.”
- ▶ “The death rate from lung cancer was much higher among men with a history of regular cigarette smoking than among men who never smoked regularly.”
- ▶ This data was presented at the American Medical Association in June of 1954
 - ▶ While the evidence was convincing, it was rejected by AMA leadership as correlation only
- ▶ 1964- US Surgeon General officially recognizes cigarettes as having an adverse effect on health

The Japanese Smoking Paradox

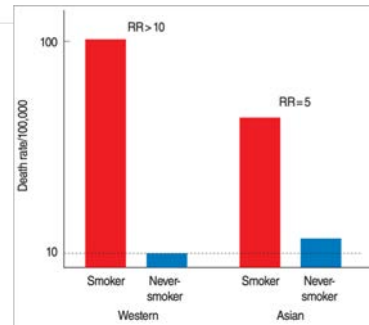
The effect of smoking on lung cancer: ethnic differences and the smoking paradox

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- ▶ Relative risk of death in Asians is less than those in Western populations
- ▶ Major increases in cigarette use per capita lags Western populations by 30-40 years (Lag bias)
- ▶ Asians begin smoking at an older age
- ▶ Asians smoke cigarettes with less nicotine and tar
- ▶ Lung cancer mortality is HIGHER in nonsmokers from Asia compared to Westerners



Nicotine E-volution



E-Cigarettes

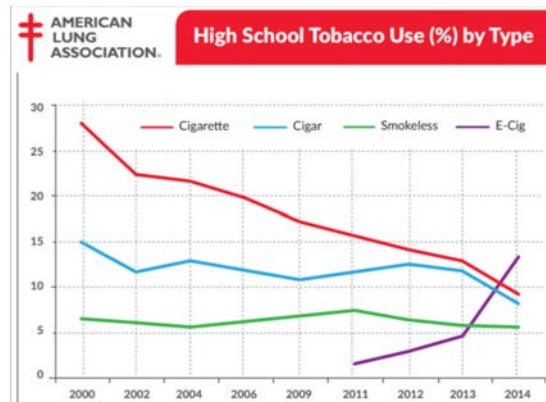


- ▶ Introduced in 2004
- ▶ This is NOT a nicotine inhaler (which is FDA approved for smoking cessation)
- ▶ E-cigarettes consists of a power source, electronic heating element and liquid nicotine cartridge containing a stabilizing compound such as propylene glycol or vegetable glycerin
- ▶ When activated by the user, a heating element atomizes the liquid resulting a vapor and visible plume
 - ▶ Various amounts of nicotine and flavoring additives can be added

E-Cigarettes

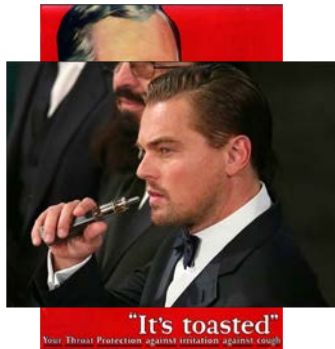


- ▶ More than 1.78 Million middle school and high school children tried e-cigarettes in 2011-2012
- ▶ The # of middle schoolers and high school students who used e-cigarettes tripled since 2011
- ▶ Many of these teens have never smoked conventional cigarettes
- ▶ Are we seeing a re-NORMALization and a re-GLAMORIZATION of smoking?



E-cigarettes, E-cigs, E-Hookahs, Vape Pens, Vapes, Tank Systems

- ▶ Are we seeing a re-NORMALization and a re-GLAMORization of smoking?



E-cigarettes- Risks

- ▶ Constituents of e-Cigarette Vapor
 - ▶ Nicotine levels vary amongst cartridges and e-cig suppliers
 - ▶ Serum levels of nicotine vary based on brand of e-cig and user
 - ▶ A study of 16 different e-cigs demonstrated that the total level of nicotine in 15 puffs of vapor generated by an automatic smoking machine varied from 0.5 to 15.4 mg
 - ▶ The typical level from a conventional cigarette ranges from 1.54 to 2.6 mg
 - ▶ Conventional cigarettes contain more than 7,000 compounds with at least 70 recognized carcinogens including formaldehyde, benzene, nitrosamines, free radicals, toxic gases, heavy metals
 - ▶ Nitrosamines, cadmium, nickel, lead, and diethylene glycol can be found in e-cigarettes but vary based on supplier.

E-cigarettes- Risks

Toxin	Conventional cigarette ($\mu\text{g}/\text{cigarette}$ in mainstream smoke)	Electronic cigarette (μg per 15 puffs)	Average ratio (conventional: electronic)
Carbonyl compounds			
formaldehyde	1.6-52	0.20-5.61	9
acetaldehyde	52-140	0.11-1.36	450
acrolein	2.4-62	0.07-4.19	15
Toluene	8.3-70	0.02-0.63	120
Nitrosamines			
N'-nitrosonomocotine	0.005-0.19	0.00008-0.00043	380
NNK	0.012-0.11	0.00011-0.00283	40

- ▶ This data demonstrates that vapor generated from e-cigs contain potentially harmful compounds although at a much lower level than conventional cigarettes
- ▶ This data suggests that e-cigarettes may be a safer alternative to conventional cigarettes

E-cigarettes on Lung Function

- ▶ A recent study with 30 health smokers after 5 minutes of e-cigarette use
 - ▶ Resulted in increased total respiratory impedance, respiratory flow resistance and overall peripheral airway resistance
 - ▶ There was 2 % reduction in FEV1/FVC and 30ml fall in FEV1
 - ▶ E-cigarettes generate smaller acute effects on lung function than conventional cigarettes
 - ▶ Similar to cancer risk, there is no published data describing the long term lung function or cardiovascular effects of e-cigarettes

Should we use E-cigarettes for Smoking Cessation

- ▶ 40 active smokers (15 cigarettes/day or more) with no interest in quitting were observed in a 6 month observational study.
 - ▶ Given e-cigarettes and supplies. They had 4 follow ups
 - ▶ They were told e-cigarettes are a healthier alternative to conventional cigarettes
 - ▶ 33% of participants had a 50% reduction in conventional cigarette use
 - ▶ Median number of cigarettes dropped from 25 to 5
 - ▶ On a 2 year follow up, (23 patients followed up), 28% continued to have a greater than 50% reduction in cigarettes, 13% had cigarette abstinence

Should we use E-cigarettes for Smoking Cessation

- ▶ The largest study investigating e-cigarettes vs nicotine patches included 657 smokers
 - ▶ Intervention 1 - 16mg nicotine e-cigarette
 - ▶ Intervention 2 - placebo e-cigarette
 - ▶ Intervention 3 - 21mg nicotine patch
- ▶ There was no significant difference in 6 month verified abstinence with all interventions equally ineffective in promoting cessation
- ▶ E-cigarette and placebo use resulted in similar cessation rates
- ▶ With the findings from this study, there is no data supporting e-cigarettes as a more effective tool than available FDA-approved nicotine replacement therapies for smoking cessation.
 - ▶ In addition we have not established the health risk from e-cigarette use

Smoking Cessation

- ▶ Approximately 70% of smokers say that they want to quit, and over 50% of smokers report that they tried to quit in the past year.
- ▶ Only 3-6% of smokers who make an unaided quit attempt are still abstinent one year later.
- ▶ Only 32% of smokers who try to quit seek help and even fewer use the most effective treatments.
- ▶ With optimal treatment, one-year abstinence rates after a single quit attempt can exceed 50%.

Smoking Cessation Management

- ▶ Clinician intervention increases the likelihood that the patient will successfully stop smoking
 - ▶ Your role: document smoking status, offer advice to quit, evaluate interest, offer tools and follow up
 - ▶ The 5A approach
 - ▶ Ask about tobacco use
 - ▶ Advise quitting
 - ▶ Assess readiness to quit
 - ▶ Assist smokers ready to quit
 - ▶ Arrange follow up
- ▶ Randomized trials of proactive outreach programs that offer smoking cessation interventions to smokers have been shown to increase smoking cessation rates

The 5-A approach

- ▶ Ask
 - ▶ Do you smoke?
 - ▶ Did you ever smoke?
 - ▶ Non-daily smokers or social smokers may not identify themselves as "smokers"

The 5-A approach

- ▶ Advise
 - ▶ There is clear evidence that a brief clinician advice to quit increases abstinence rates
 - ▶ Although complete smoking cessation is always preferable, reducing the number of cigarettes smoked daily has been advocated as a possible alternative to complete cessation by patients who are unable to quit smoking.

The 5-A approach

- ▶ Assess
- ▶ The clinician should assess the patient's willingness to quit.
 - ▶ Pre-contemplation (not ready to quit)
 - ▶ Contemplation (considering a quit attempt)
 - ▶ Preparation (actively planning a quit attempt)
 - ▶ Action (actively involved in a quit attempt)
 - ▶ Maintenance (achieved smoking cessation)

The 5-A approach

- ▶ Assist
 - ▶ "Let's set a quit date"
 - ▶ Abrupt cessation tends to be more effective than gradual reduction prior to quitting
 - ▶ Most smokers are not aware of all available cessation tools
 - ▶ Behavioral Counseling
 - ▶ Nicotine Replacement therapy (NRT)
 - ▶ Varenicline (Chantix)
 - ▶ Bupropion (Wellbutrin)
 - ▶ Acupuncture
 - ▶ Hypnotherapy

The 5-A approach

- ▶ Arrange – Follow-up
 - ▶ Monitor response to smoking cessation therapy
 - ▶ Follow up can be in a face-to-face encounter or a telephone encounter
 - ▶ Follow up should be scheduled within 1-2 weeks of patient's quit date to provide reinforcement
- ▶ After quitting, 72% of smokers are not abstinent at 3 months
 - ▶ Repeated smoking cessation attempts is essential




PHARMACOTHERAPY
SHOULD BE **COMBINED**
WITH BEHAVIORAL
THERAPY AS THE
COMBINATION
PRODUCE HIGHER
QUIT RATES

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CANCER A-Z STAY HEALTHY TREATMENT & SUPPORT OUR RESEARCH GET INVOLVED OUR PARTNERS ABOUT US


GET HELP QUITTING SMOKING

Quitting smoking is not easy, but you can do it. To have the best chance of quitting and remaining smoke-free, you need to know what you're up against, what your options are, and where to go for help.




Benefits of Quitting

The sooner you quit, the more you can reduce your chances of getting cancer and other diseases.




Helping a Smoker Quit

Do's and Don'ts, general hints for friends and family.



How to Quit Smoking or Smokeless Tobacco

It's hard to quit smoking, but you can do it.



Enroll in the Quit for Life[®] program

While quitting can be tough, planning ahead can boost your chances for success.

<https://www.cancer.org/healthy/stay-away-from-tobacco/great-american-smokeout.html>

Combination Nicotine Replacement Therapy (NRT)

- OTC products = patch, lozenge, and gum
- Prescription products = nasal spray and oral inhaler
- The long-acting, slow-onset nicotine patch is the primary NRT to control baseline nicotine withdrawal symptoms.
- Adding a short-acting NRT helps to control cravings and withdrawal symptoms during the day on an as-needed basis.
 - Choice of short-acting product (lozenge, gum, inhaler, nasal spray) depends upon patient preference and comorbidities

Patch + short-acting NRT

Efficacy

- NRT is superior to placebo, increasing quit rates approximately two-fold
- Few trials compare one product to another
 - One randomized trial found no difference in efficacy between the patch, gum, inhaler, and nasal spray
- Combination NRT is more effective than single-product therapies

Dosing

- Initial dosing of NRT is based on the number of cigarettes smoked daily
- Dose is gradually tapered as nicotine withdrawal symptoms subside
- NRT use is generally recommended for two to three months after smoking cessation though use for a longer period of time is acceptable in patients with a high risk of relapse

Nicotine Patch

- Simplest to use
- Provides the most continuous nicotine delivery of all NRT products
- Requires several hours to reach peak levels
- Dosing (apply each morning to a non-hairy skin site)
 - Smoke >10 cigarettes/day → Use highest dose (21 mg/day) for 6 weeks, followed by 14 mg/day for two weeks, and finish with 7 mg/day for two weeks
 - Smokers who weigh <45 kg or smoke ≤10 cigarettes/day → begin with 14 mg/day for six weeks, followed by 7 mg/day for two weeks
- Can be left on or removed overnight

Adjunctive NRT

- Used in combination with the patch
- Require repeated use
- Lead to more variable nicotine levels
- Require more instruction for correct use
- OTC = gum, lozenges
- Rx = inhaler, nasal spray

Adjunctive NRT

► **Gum**

- Nicotine absorbed through the oral mucosa; peak blood nicotine levels 20 minutes after starting to chew
- Dosing
 - 25 or more cigarettes/day → 4 mg dose
 - Lighter smoker → 2 mg dose
- Frequency = smokers should chew the gum whenever they have an urge to smoke. Can chew one piece of gum every 1 to 2 hours for 6 weeks, with a gradual reduction over a second six weeks, for a total duration of 3 months.
- Acidic beverages should be avoided before and during gum use (reduces absorption)
- "Chew and park" for 30 minutes

Adjunctive NRT

► **Lozenge**

- Pharmacokinetics similar to gum; easier to use correctly
- Dosing
 - Smokers who smoke within 30 minutes of awakening → 4 mg dose
 - All other smokers → 2 mg dose
- Frequency = 1 lozenge every 1-2 hours for six weeks, with a gradual reduction in the number of lozenges used per day over a second six weeks. The max dose is 5 lozenges every 6 hrs or 20 per day.
- Placed in the mouth and allowed to dissolve for 30 minutes

Adjunctive NRT

► Inhaler

- Addresses the physical dependence and the behavioral/sensory aspect of smoking
- Pharmacokinetics similar to gum; produces plasma nicotine levels that are roughly 1/3 of cigarettes
- Nicotine vapor is released and deposited primarily in the oropharynx and absorbed through the oral mucosa. Does not reach the lungs to an appreciable extent.
- Frequency = 6 to 12 cartridges per day for the first 6 to 12 weeks, followed by gradual reduction of dose over the next 6 to 12 weeks.
- Localized irritation of the mouth or throat is common, particularly during the early stages of use

Adjunctive NRT

► Nasal Spray

- Delivers an aqueous solution of nicotine to the nasal mucosa.
- Produces a more rapid rise in plasma nicotine concentration than orally-absorbed products. Peak effect of nicotine occurs 10 minutes after use.
- Frequency = 1 or 2 sprays per hour are recommended for about 3 months. The maximum dose is 10 sprays per hour or 80 total sprays per day.
- Limited by side effects including nasal (81-94%) and throat irritation, rhinitis, sneezing, and tearing.

Varenicline (Chantix)

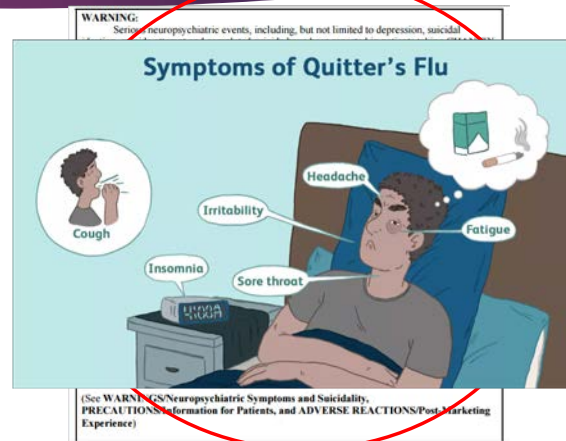
- Partial agonist at the alpha-4 beta-2 subunit of the nicotinic acetylcholine receptor
 - This receptor appears to produce the reinforcing effects of nicotine and leads to nicotine dependence
- Hypothesized to aid smoking cessation in two ways
 - Partial stimulation of the alpha-4 beta-2 nicotinic receptor reducing the symptoms of nicotine withdrawal
 - Binds with high affinity to the alpha-4 beta-2 receptor subunit which blocks the nicotine in tobacco smoke from binding to the receptor, thereby reducing the rewarding aspects of cigarette smoking
- Efficacy—meta analysis found compared with placebo, varenicline was more effective for smoking cessation (RR 2.27, 95% CI 2.02-2.55)

Varenicline (Chantix)

- Dosing
 - 0.5 mg QD for three days, then 0.5 mg BID for four days, then 1 mg BID for the remainder of a 12-week course
 - No advantage to higher doses
 - Titration minimizes nausea (also minimized if taken with food and a full glass of water)
- Smokers are instructed to quit one week after starting varenicline
- Does not undergo liver metabolism; few drug-drug interactions
- Excreted almost entirely by the kidney; requires dose reduction in moderate renal insufficiency
- Longer preload period may increase success
- Some patients may benefit from an additional 12-week course

Varenicline (Chantix)

- Case reports had suggested neuropsychiatric effects such as suicidal/self-injurious behavior and/or depression
- In December 2016 the FDA removed the black box warning based on the EAGLES trial.
 - While this was a pivotal trial, it was criticized for perhaps not having enough patient in the 8 arm trial to capture the severe psychiatric side effects the drug
 - Taking a careful psychiatric history prior to prescribing varenicline is recommended
 - It is also recommended that it should be avoided in smokers with current unstable psychiatric status or a recent history of suicidal ideation
 - It could be suggested the the side effects reported in case reports could be the same adverse effect from smoking cessation



Varenicline (Chantix)

- Cardiovascular effects—might increase the risk of CV effects
 - 2011 FDA advisory based on a randomized trial in 714 smokers with stable CVD. Compared to placebo, increase in non-fatal MI and need for coronary revascularization. Differences were not significant.
 - Monitor for new or worsening signs/symptoms
- Other effects
 - Increased risk for accidental injuries, accidents, and falls
 - Nausea, insomnia, abnormal dreams, visual disturbances, syncope, and moderate to severe skin reactions.

Bupropion (Zyban)

- Enhances central nervous system noradrenergic and dopaminergic release.
- Identical to bupropion SR or Wellbutrin SR
- Efficacy—Increases the likelihood of smoking cessation compared to placebo (RR 1.62, 95% CI 1.49-1.76)
- Dosing
 - Started one week before quit date
 - Recommended dose is 150 mg QD for 3 days, then 150mg BID thereafter
 - 150 mg QD is an option for those who cannot tolerate 300mg daily
 - Recommended duration is for at least 12 weeks. A longer duration may prevent relapse in successful quitters

Bupropion (Zyban)

- Neuropsychiatric effects—suicidal/self-injurious behavior and/or depression
 - Higher risk than NRT, but lower than that reported for varenicline
 - All patients should be monitored for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts
- Other effects
 - Lowers the seizure threshold; should not be used in patients with a seizure disorder
 - Common side effects: insomnia, agitation, dry mouth, and headache

Other Medications

- Nortriptyline—considered 2nd line
- Cytisine—plant derivative; partial agonist at the alpha-4 beta-2 nicotinic acetylcholine receptor. Not available in U.S.
- Clonidine—limited efficacy for smoking cessation; not statistically better than placebo
- SSRI/anxiolytics—generally have not been shown to be effective
- Nicotine vaccine—none have demonstrated efficacy versus placebo

Comparative Studies

- ▶ Varenicline vs. combination NRT
 - No differences in biochemically confirmed rates of smoking abstinence among groups.
- ▶ Varenicline vs. nicotine patch
 - Open label studies—no statistically significant difference in abstinence at 24 weeks
 - Cohort study in those who had a choice of available pharmacotherapies found that smoking cessation rate 4 weeks after the quit date was higher for varenicline compared to NRT.
- ▶ Varenicline vs. bupropion
 - RCTs comparing varenicline, bupropion and placebo found
 - 4-week continuous abstinence at the end of drug treatment was higher with varenicline than with bupropion or placebo
 - Continuous abstinence through week 52 higher with varenicline

Combination Therapy

- ▶ Nicotine patch + varenicline
 - Treatment with varenicline + patch had a higher continuous abstinence compared with varenicline + placebo patch at 6 months after the end of drug treatment

- ▶ Bupropion + varenicline
 - Bupropion + varenicline had higher rates of prolonged abstinence at 12 and 26 weeks compared to varenicline monotherapy.

- ▶ Bupropion + NRT
 - Non-significant trend toward higher rates of abstinence with the combination of NRT and bupropion compared to NRT alone.

Conclusion

- ▶ It took centuries to establish the health detriment of smoking
- ▶ We can thank Christopher Columbus sailing the ocean blue for the globalization of tobacco use
- ▶ Electronic cigarettes are a new frontier with an unestablished health risk
- ▶ Remember smoking cessation starts with asking our patients about it
- ▶ Behavioral therapy combined with pharmacotherapy will provide better success rates with smoking cessation

Questions?

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