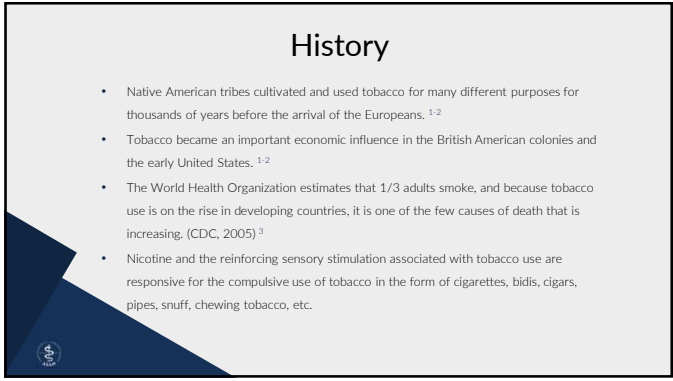


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2



3

Epidemiology of Tobacco

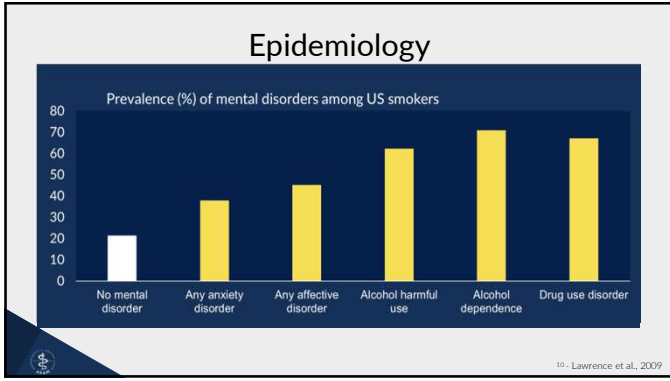
- **Prevalence has declined** in the US from 42% in 1965 to 14% in 2017 ^{4,5}
- Men are more likely to be smokers than women (15.8% vs. 12.2%) ⁶
- >16 million Americans have smoking-related disease
- Accounts for **20%** of coronary-artery disease ⁷

4

Morbidity and Mortality

- Leading cause of preventable death in the United States, accounting for about **440,000 premature deaths annually** ⁸
 - 150K from CV disease
 - 150K from cancer
 - 150K from non-malignant pulmonary disease
- Lost years of life: ⁹
 - adult men: 13.2 yrs
 - adult women: 14.5 yrs

5



6

Compounds in Tobacco Smoke

An estimated 4,800 compounds in tobacco smoke, including 11 proven human carcinogens ¹¹

<p style="text-align: center; background-color: #003366; color: white; padding: 2px;">Gases ¹²</p> <ul style="list-style-type: none"> • Carbon monoxide • Hydrogen cyanide • Ammonia • Benzene • Formaldehyde 	<p style="text-align: center; background-color: #003366; color: white; padding: 2px;">Particles ¹²</p> <ul style="list-style-type: none"> • Nicotine • Nitrosamines • Lead • Cadmium • Polonium-120
--	--

Nicotine is the addictive component of tobacco products, but it does NOT cause the ill health effects of tobacco use.

7

Health Consequences

- Smokers die **10 years earlier** than non-smokers on average
- **Cancer:** oral cavity, pharynx, larynx, bladder, esophagus, cervix, kidney, lung, pancreas, stomach, liver, bowel, acute myeloid leukemia ¹³
- **Cardiovascular disease, DM type ¹⁴**
- **COPD, Asthma ¹⁵**
- Osteoporosis, cataracts and macular degeneration, early menopause, erectile dysfunction, gastric and duodenal ulcer disease, skin aging, periodontal disease ¹⁶

8

Tobacco Associated Problems

- Barrier to Recovery
- Financial Hardships
- More Employment Difficulties
- More Housing Difficulties
- Poorer Mental Health
- More Relapse to Drugs and Alcohol
- Social Stigma
- Poorer Appearance
- More Fires in Home

9

Public Health Interventions ¹⁷

- Anti-smoking advertisements
- Increasing taxes
- Age-restrictions
- Tobacco-free laws and policies
- Support for cessation

10

Pharmacology of Nicotine

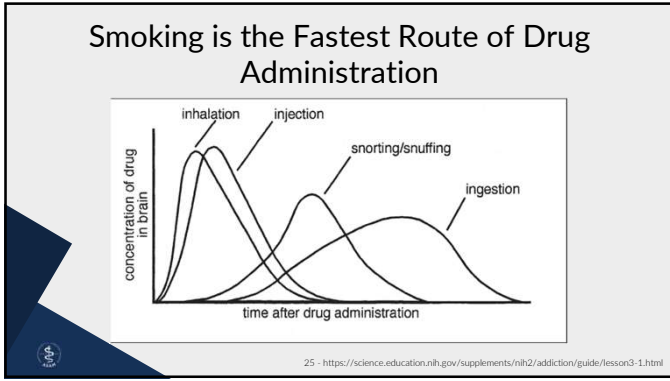
- Naturally occurring alkaloid ³
- Triggers the release of a variety of neuroactive hormones
- Acts as a nicotinic acetylcholine receptor (nAChR) agonist ³
- **Stimulant-like effect** in the CNS: enhances concentration, alertness, arousal ³
- Increase of dopamine in brain's reward circuitry ¹⁸
- Enters the CNS in rapidly after inhalation ¹⁹
- Rapid effect on CNS contributes to reinforcement and dependence

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Routes of Use

- Nicotine and reinforcing sensory stimulation associated are responsible for the compulsive use of tobacco ²⁰⁻²³
- Method of administration modifies the addictive potential associated with use ²⁴
- Compulsive use increases with rapid administration: smoking/vaping >> dermal patch, chewing

12



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Nicotine

- Reaches the brain 20 seconds after inhalation + gradually increases occupancy of the nAChRs over minutes ¹⁹
- Smoking 1 cigarette leads to significant occupancy of alpha4beta2 containing nAChRs for >3 hrs ¹⁹
- The initial relatively rapid rate of rise of nicotine occurs within minutes, though levels of nicotine-bound receptors continue to rise slowly/are maintained for hours ¹⁹
- Rapid onset = allows smokers to control nicotine intake (by # of puffs, intensity of puffs, depth of inhalation)

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Pharmacology of Nicotine

- Half-life is 2 hours ^{25,26}
- Accumulation in various tissues throughout the body during the day ²⁷
- Continue to be release from tissues for 6-8 hours after smoking ceases during sleep ^{25,26}
- **Metabolized in the liver** via cytochrome P450 enzymes ²⁶
- Major metabolite is cotinine ²⁶
- Crosses placenta and is found in breast milk ²⁷

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Pharmacology

- Undergoes 1st pass metabolism²⁶
- Oral bioavailability is 45%²⁶
- Poorly absorbed from stomach 2/2 acidity of gastric fluid, but well absorbed in small intestine 2/2 alkaline environment²⁶
- Renal clearance accounts for 2% to 35% (about 10%) of total nicotine clearance²⁸
- Nicotine obtained via tobacco reaches high initial concentrations in arterial blood and lungs
 - Nicotine is then distributed to brain, storage adipose, muscle tissue from arterial blood
 - Avg steady-state concentration in body tissue is 2.6x that of the blood²⁶

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Pharmacology

- Once absorbed in bloodstream, nicotine has a volume of distribution of about 180 liters, with less than 5% of it binding to plasma proteins²⁶
- Crosses placenta freely
- Found in the amniotic fluid and in the umbilical cord blood of neonates
- Found in breast milk at concentrations approximately 2x those found in blood

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Sex and Race on Metabolism

- Women metabolize nicotine faster than men, 2/2 estrogen effect on CYP2A6²⁹
 - Even faster during pregnancy
- Related to CYP2A6 gene variants, African Americans obtain on average 30% more nicotine per cigarette, and they clear nicotine and cotinine more slowly than Caucasians.³⁰
- Chinese American have a lower nicotine intake per cigarette, and slower metabolism (vs. Caucasians or Hispanics) 2/2 having a higher prevalence of CYP2A6 alleles (associated with slow metabolism)^{31, 32}
 - Suggest why Chinese American smokers have lower rates of lung cancer than either African Americans or Caucasians^{31, 32}

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Biochemical Assessment

- Blood, salivary, and plasma cotinine can be used ^{33, 34}
- others include expired breath CO, blood carboxyhemoglobin, + plasma/salivary thiocyanate concentrations
- 16-hr ½ life of cotinine makes it useful as a plasma and salivary marker of nicotine intake ³⁵
- The gold standard for estimating daily nicotine intake from tobacco use is the sum of nicotine and its metabolites in urine. ³⁶
- Measurement of the minor tobacco alkaloids anabasine and anatabine in urine can be used as a biomarker of tobacco use in individuals who are using nicotine medications. ³⁷

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Drug Interactions from Tobacco Smoke

- Affects the pharmacokinetics or pharmacodynamic mechanisms
- absorption, distribution, metabolism, or elimination
- potentially causing altered response or toxicity
- Accelerates metabolism of many drugs, esp. those metabolize by CYP1A2 ³⁸
- Might increase CYP2E1 and inhibit CYP2A6 enzymatic activity ³⁸
- When smokes discontinue abruptly (i.e., when hospitalized) doses of such meds may need to be lowered to avoid toxicity ³⁸

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Drug Interactions from Tobacco Smoke

Drugs that may have a decreased effect due to induction of CYP1A2 by tobacco smoke: ³⁹

- Caffeine
- Clozapine
- Olanzapine
- Haloperidol
- Chlorpromazine
- Fluvoxamine
- Theophylline

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Quitting Smoking Effects on CYP1A2

- Risk for medication toxicity
- May ↑ levels acutely
- Consider dose adjustment
- Clozapine toxicity
- Seizures
- Reduce caffeine intake

- **Nicotine** (or NRT) **Does Not** Change Medication Levels
- Nicotine metabolized by **CYP2A6**

22

Pharmacodynamic Interactions: OCPs

- Alter the expected response or action of a drug
- Combined OCPs (estrogen + progestin) w/ smoking is very important
- Increased risk of serious cardiovascular effects (stroke, MI, thromboembolism)⁴⁰
- Recommended that OCPs are **contraindicated** in women > 35 yrs old AND are a heavy smoker (>15cigs/day)⁴⁰

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Pharmacodynamic Interactions

- Appear to enhance the procoagulant effect of **estrogens**⁴¹
- Results in less sedation from benzodiazepines and less analgesia from some opioids⁴²
- Impairs the therapeutic effects of histamine H2 -receptor antagonists used in treating **peptic ulcers**⁴²
- Cutaneous vasoconstriction by nicotine can slow the rate of absorption of subcutaneously administered **insulin**⁴³

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Pharmacologic Actions: CNS ^{44, 45}

- Acts on sympathetic system: increase BP, HR, cardiac output, and cutaneous vasoconstriction
- Causes muscle relaxation via simulation of Renshaw cells, via inhibition of motor neurons
- Higher doses: produces ganglionic stimulation -> releases adrenal catecholamines
- Very high doses cause hypotension, slowing of HR

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Psychoactive Effects

- Causes arousal, relaxation, enhancement of mood/attention/rxn time ⁴⁶⁻⁴⁸
- Results in relief of withdrawal sx of dependent smokers, rather than direct-enhancing effects ⁴⁶⁻⁴⁸
- Smokers may need regular doses of nicotine to feel normal rather than to enhance their capabilities/cognitive effects
- Psychoactive effects dependent on route, speed of administration, environmental factors
- Subjective effects depend on pre-drug state, level of genetics, history, expectancy ^{49,50}

26

Genetic Predisposition

- GWAS: single nucleotide polymorphisms on... ⁵¹
- **CHRNA5-CHRNA3-CHRNA4** subunit cluster on chromosome 15q25
 - associated w/ # of cigs/day, serum cotinine levels, lung cancer, peripheral artery disease, chronic lung dz
- **CYP2A6**, primary enzyme responsible for the oxidation of nicotine and cotinine. ⁵²⁻⁵³
 - Reduced function variants of the gene are associated with smoking fewer cigarettes per day and a lower risk of lung cancer
- **Cell adhesion and ECM molecules** ⁵⁴
 - neural plasticity and learning are key determinants of individual differences in vulnerability to drug addictions
- Twin studies: ⁵⁵⁻⁵⁶
 - monozygotic twins are more similar than dizygotic twins w/ smoking behavior
 - ½ of the total variance (28% to 84%) in smoking behavior are due to genetic effects
 - There is genetic influence on nicotine withdrawal symptoms as well

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Psychiatric Comorbidities

- **37%** of those w/ a mental illness are smokers vs. **20%** of smokers who do not carry a mental illness.⁵⁷
- Those with Sz, depression, ADHD have **higher prevalence** of cig smoking compared with general population

Sz: 70-88% are smokers⁵⁸

- Diminished sensory gating to repeated stimuli, smoking can relieve negative sx (blunted affect, emotional withdrawal, lack of spontaneity)
- Smokers experience fewer side effects from antipsychotics (2/2 stimulating effects of nicotine), which might contribute to greater prevalence of smoking in ppl w/ Sz

ADHD: 40% are smokers⁵⁹

- Associated with early initiation of regular cigarette smoking, even after controlling for confounding variables such as socioeconomic status, IQ, and psychiatric comorbidity
- transdermal patches improve the attentional symptoms of ADHD

28

Best Measure of Nicotine Dependence Severity

Heaviness of Smoking Index

- AM (upon awakening) Time to First Cigarette (TTFC)⁴⁶
 - < 30 minutes = moderate
 - < 5 minutes = severe
- **Implications for Treatment Outcome**
- **Need for Medications**
- **Implications for Dose**

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Tobacco Tolerance

- Causes effects of individual cigarettes tend to lessen throughout the day.
- Overnight abstinence allows considerable, but not complete, re-sensitization of nicotinic receptors to non-desensitized states
- Populations of nAChR subtypes that begin to change as other molecular mechanisms involving neuroadaptations come into play after days and weeks of tobacco use^{47,48}

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Tobacco Cravings

- Powerfully conditioned cues = cravings become associated with everyday events, become linked with mood
- High rates of relapse: ⁴⁹
 - Population surveys find that up to 75% of adults who smoke want to stop, but only 1/3 try to stop, and only 3% of those do without aids
 - 50% of individuals w/ past hx of MI, COPD, and other sequelae of smoking, revert to cig smoking days or weeks after leaving the hospital

31

Which of the following is a symptom of tobacco withdrawal?

- A. Irritability
- B. Hypersomnia
- C. Elated Mood
- D. Decreased Appetite

32

Tobacco Withdrawal

- Nicotine use is continued to avoid the negative sx associated with withdrawal (known as negative reinforcement)
- Majority of withdrawal sx are distressing, but not life-threatening
- Acute withdrawal sxs reach max. Intensity 24 - 48 hrs after cessation and then gradually diminish over weeks ⁵⁰⁻⁵¹
- Extrahypothalamic corticotropin-releasing factor (CRF-1) contributes to negative affect during withdrawal ⁵²
- CRF released in central amygdala following nicotine withdrawal -> produces anxiety behavior
- Pharmacological blockade of CRF1 receptors inhibits the anxiogenic effects in withdrawal


33

Tobacco Withdrawal Symptoms ⁵³

Emerge hours after last cigarette

Can last up to (4) weeks


- Depressed mood
- Insomnia
- Irritability, frustration or anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased appetite or weight gain



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MAO and Nicotine Dependence


- Cig smoking is associated w/ inhibition of monoamine oxidase A + B ⁵⁴⁻⁵⁶
- Not caused by nicotine itself, but the condensation products of acetaldehyde with biogenic amines, such as benzoquinones, 2-naphthylamine, harman, + others
- MAOs = metabolize catecholamines, including dopamine
- Rat studies: ⁵⁷
 - Pre-tx with MAO-I makes nicotine more rewarding and increases the likelihood and rate of acquisition of nicotine self-administration
 - Important consideration: anti-depressants also inhibit MAOs, therefore smoking-induced inhibition of MAO might contribute to the perceived benefit of smoking by some depressed patients



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Systemic Toxicities

- **Tobacco smoke** = carries volatile and particulate phases that contain substances that are primarily responsible for the human morbidity and mortality ⁵⁸
- Volatile = 500 compounds (nitrogen, CO, carbon dioxide, ammonia, hydrogen cyanide, and benzene)
- Particulates = >3,500 (alkaloids normicotine, anabasine, anatabine, myosmine, nicotyrine, and nicotine)
- **Tar:** contains many carcinogens, including polynuclear aromatic hydrocarbons, N-nitrosamines, and aromatic amines ⁵⁸



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Toxicities: Pulmonary

- Causes imbalance between proteolytic and antiproteolytic forces in the lung⁵⁹
- Heightens airway responsiveness
- High rates of COPD in tobacco smokers linked to:⁵⁹
 - Exposure to tar, nitrogen oxides, hydrogen cyanide, and volatile aldehydes
 - These exposures results in oxidative stress and generation of superoxide radicals and hydrogen peroxide and lung damage
- Smokers with DNA damage from polynuclear aromatic hydrocarbons in the WBCs are 3x more likely to be dz with lung cancer than smokers with lower concentrations⁶⁰

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Toxicities: Cardiovascular

- **Increased risk** of CV toxicity⁶¹
- Related to exposure to oxidant chemicals and CO, + hydrogen cyanide, carbon disulfide, cadmium, and zinc
- CO reduces oxygen delivery to the heart
- Oxidant chemicals are primarily responsible for endothelial dysfunction, platelet activation, thrombosis, and coronary vasoconstriction

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Other Effects and Toxicities

- **For women:**⁶²
 - lower levels of estrogen
 - earlier menopause
 - increased risk of osteoporosis
 - alkaloids in tobacco smoke decrease estrogen formation by inhibiting an aromatase enzyme in granulosa cells or placental tissue
- **Skin changes:**⁶³
 - yellow staining of fingers
 - precancerous and squamous cell carcinomas on the lips and oral mucosa
 - vasospasm and obliteration of small skin vessels
 - enhanced facial skin wrinkling

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Predictors of Abstinence ⁶⁴⁻⁶⁶

- Lower level of dependence
- Higher socioeconomic status: education, insured
- Older age
- Male gender
- No behavioral health comorbidity
- Fewer smokers in social networks
- Quit in first 7 days / # days quit
- Use of cessation treatment

40

Why is it so hard to quit?

- Smoking a drug is highly addicting
- **Treatment options are limited**
 - Few medication types
 - Limited (brief) counseling support
 - No levels of care
- **Utilization of treatment is poor**
 - Most don't use counseling
 - Medications-too low dose, not enough time

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Brief Intervention
2As and R (Ask, Advise, and Refer)

- Do you use Tobacco?
- How much? What kinds?
- Document tobacco use at visits
- How do you feel about quitting?
- Can I give your name to someone to get more information?

42

**Why Not Quit For One Day?
Or Six Hours?**

- Save money
- Try free NRT
- Feel better
- Master a new skill
- Try other coping
- Not go outside in bad weather

You can be tobacco-free for one day!

Join the Great American Smokeout.
November 21st

IQ Quit with AHEC. **Tobacco Free Florida.com**
www.ahcetobacco.com

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Quitline
1-800-QUIT-NOW

- Telephone counseling
- Toll-free / state funded
- Assessment
- 4 follow-up calls
- Good for transportation issues
- Scheduled calls from tobacco specialist
- Success rate in smoking cessation
- Many languages, free NRT

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Pharmacologic Treatments

- First line (FDA-approved): ⁶⁷
 - Nicotine replacement therapy (NRT)
 - Bupropion
 - Varenicline
- Second line (not FDA-approved): ⁶⁷
 - Nortriptyline

Counseling + Medications = Best Treatment Plan

45

Which of the following is TRUE of nicotine replacement therapies (NRT)?

- A. Most people who use NRT become long term users of it
- B. These medications produce serum nicotine levels, which are higher than that of a smoked cigarette
- C. Most people use NRT incorrectly or at too low a dose
- D. Medicaid insurance never pays for coverage over the counter products like nicotine patch or gum

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Nicotine Medications ⁶⁸

- Use high enough dose
- Scheduled better than PRN
- Use long enough time period
- Can be combined with bupropion
- Can be combined with each other
- Have almost no contraindications
- Have no drug-drug interactions
- Safe enough to be OTC

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Oral Nicotine Spray ^{69,70}

- Approved Sept 2019; OTC (Canada & Europe)
- Faster absorption
- 1-2 to two sprays (140/ container; each 1mg nic). Max 4/ hour, 64/ day (most 10-14/ day)
- No evidence product abuse
- Real world and efficacy trials 2X placebo
- Contains tiny amount ethanol. At 64 doses/d, <one tsp (~ 5ml) of wine with 12% alcohol)
- Side effects: hiccups, headache, nausea, mouth/throat irritation, dyspepsia, dizziness

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Combination Therapies ^{71,72}

- Improve abstinence rates
- Decrease withdrawal
- Well tolerated

	OR
Patch + gum or spray	1.9 (1.3-2.7)
Patch + bupropion	1.3 (1.0-1.85)

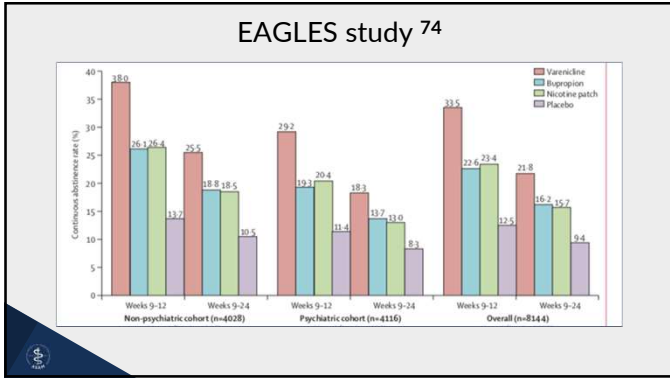
49

Varenicline: A selective $\alpha 4\beta 2$ nicotinic receptor partial agonist

Partial Agonist ⁷³
 Partially stimulates receptor
 Some dopamine release
 Prevents withdrawal

Antagonist
 Blocks nicotine binding

50

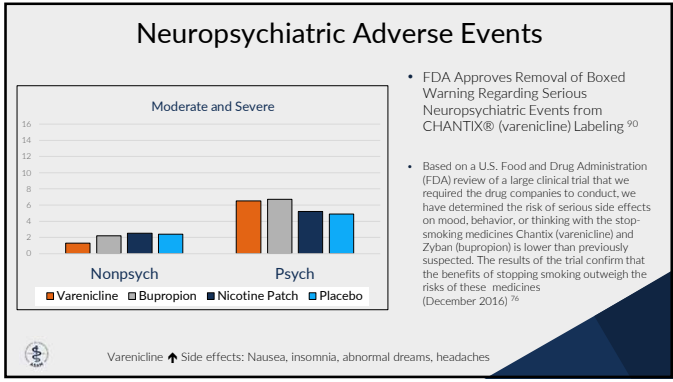


51

Results from 2013 Cochrane Review ⁷⁵

Medication	Versus Placebo OR (95% Credible Interval)	Versus other medication OR (95% Credible Interval)
NRT	1.84 (1.71-1.99)	Combination outperformed single formulations
Bupropion	1.82 (1.60-2.06)	NRT: 0.99 (0.86-1.13)
Varenicline	2.88 (2.40-3.47)	Nicotine patches: 1.51 (1.22-1.87) Nicotine gums: 1.72 (1.38-2.13) Other NRT: 1.42 (1.12-1.79) Combination NRT: 1.06 (0.75-1.48)

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53

- ### Summary of Treatment
- All tobacco users should be offered treatment to try to stop
 - Counseling + Medications = Best treatment plan
 - Better outcomes
 - Education to use medication effectively
 - Combinations of NRT or Varenicline as first line
 - Longer durations (6 mos) effective for relapse prevention

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Gender Issues

- In any given quit-attempt, women are less likely to successfully quit smoking than men ⁷⁷
- Negative affect/ depression/ socioeconomic issues/ less likely meds
- Women in placebo group less likely than men to quit
- Varenicline was more effective than TNP for women (OR=1.51; 95%CI=0.12,2.05; p=0.007) but not men (OR=0.92; 95%CI=0.65,1.31; p=0.64). ⁷⁸
- The advantage of varenicline over bupropion SR and TN is greater for women than men
- Clinical trials and epidemiologic studies

55

Combination Therapy Of Varenicline and Bupropion

- Meta Analysis: 4 RCTs with 1230 smokers.
- Compared with varenicline, combination treatment with varenicline and bupropion could significantly improve the abstinence rate at the end of treatment (RR 1.153, 95% CI 1.019 to 1.305, P = 0.024). ⁷⁹

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Combination Therapy Of Varenicline and Bupropion

- The benefit existed at 6 months follow-up (RR 1.231, 95% CI 1.017 to 1.490, P = 0.033), and was mainly concentrated in highly dependent smokers (RR 1.631, 95% CI 1.290 to 2.061, P < 0.001) and heavy smokers (RR 1.515, 95% CI 1.226 to 1.873, P < 0.001) ⁷⁹
- For safety outcomes, the combination treatment was associated with more anxiety (RR 1.717, 95% CI 1.176 to 2.505, P = 0.005) and insomnia (RR 1.268, 95% CI 1.076 to 1.494, P = 0.005) symptoms vs varenicline monotherapy. ⁷⁹

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Medication Interaction Tobacco Treatments ⁷⁹

Nicotine	CYP ₂ A6	None
Bupropion	CYP ₂ B6 CYP ₂ D6 inhibitor	Many
Varenicline	Excreted in urine	None

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Special Population: Pregnancy

In 2016, 7.2% of US women who gave birth smoked cigarettes during pregnancy. ⁸⁰

Smoking in pregnancy ↑ risks of:

- Spontaneous pregnancy loss
- Placenta abruption
- Ectopic pregnancy
- Placenta previa
- Preterm rupture of membranes
- Low birth weight
- Sudden infant death syndrome
- Low milk volume production and shorter duration of lactation

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Special Population: Pregnancy ⁸⁰

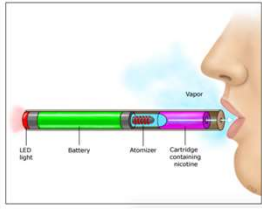
- More likely to quit smoking in pregnancy
- Initiate intervention before conception
- Continue interventions during prenatal care visits
- Counseling is the first-line of treatment
- NRT or bupropion are acceptable second-line options (data lacking but supported by experts committees)
- Limited information regarding safety of varenicline

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Special Population: Adolescents

- Early intervention is important
- **Counseling is the first-line** of treatment
- If counseling fails **NRT is an acceptable** options
- Insufficient data regarding bupropion and varenicline

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E-Cigarettes

- Battery-operated device
- Heats liquid containing nicotine
- Creates vapor that is inhaled
- Entered US market in 2006 ⁸¹

Image from Rigotti N, et al. E cigarette chapter. Update 2019.

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Chemicals in Electronic Cigarettes ^{82,83}

- Propylene glycol, ethylene glycol and glycerin
- Nicotine
- Flavors (sweeteners)
- Most chemicals found **at or below 1% of levels in tobacco smoke**, and far below safety limits for occupational exposure.
 - Metals (cadmium, chromium, lead, manganese and nickel)
 - Formaldehyde
 - Other carcinogens
 - Solvents
 - Tobacco alkaloids

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Vaping and Youth

- Vaping = nicotine, marijuana, just flavoring since 2017
- Increased dramatically in 2018 84
 - **Nicotine vaping largest ↑ ever recorded for any substance in the 44 years of MTF (2017-2018)**
 - 30% of 12th graders vaping nicotine (↑ 11%)
 - Marijuana vaping increased (1-3%) among 8, 10, 12th graders 4%, 12% and 13%
 - Just flavoring increased among 8, 10, 12th graders
 - 15%, 25% and 26%

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Association of Electronic Cigarette Use With Subsequent Initiation of Tobacco Cigarettes in US Youths

- Prospective cohort (6123=N), mean age 13.4
- Cigarette use at wave 3 was higher among prior e-cigarette users (20.5%) vs no prior tobacco (3.8%). 85
- Prior e-cigarette use was associated with more than 4 times the odds of ever cigarette use (odds ratio, 4.09; 95%CI, 2.97-5.63) and nearly 3 times the odds of current cigarette use (odds ratio, 2.75; 95%CI, 1.60-4.73) vs no prior tobacco use.
- Supports that e-cigarette use is associated with increased risk for cigarette initiation and use, particularly among low-risk youths.

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E-cigarette or Vaping Associated Lung Injury (EVALI) ⁸⁶


- Lung injury cases associated with e-cigarette, or vaping, to CDC
- **Vitamin E acetate** - bronchoalveolar lavage (BAL) fluid samples
- Thickening agent in THC-containing e-cigarette
- **Most (86%) involved THC products**; some (11%) nicotine alone
- 70% of patients are male; 79% are < 35 years old



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E-Cigarettes


- More frequently used by Americans than other FDA-approved treatments for smoking cessation
- Safer than combustible products, but long-term effects are unknown
- Controversial whether e-cigarette should be used as a first line of treatment, although this is common in UK



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Select the one TRUE statement about nicotine dependence.

- A. Smokers that report smoking within 30 minutes of waking are moderately nicotine dependent and may need medications to succeed in quitting
- B. Smokers who use less than 10 cigarettes per day are not nicotine dependent
- C. Users of electronic cigarettes almost never become addicted to nicotine
- D. Treatment for tobacco dependence should not be initiated until the primary mental disorder is in remission and all symptoms have abated



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