

Nicotine and Nicotine Use Disorder



Wednesday, August 24, 2022

2022 State of the Art Addiction Medicine Conference

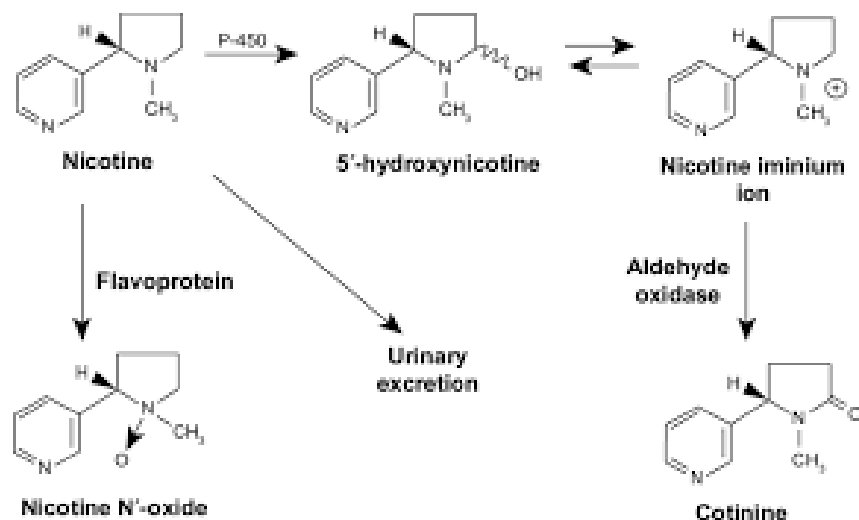
California Society of Addiction Medicine

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Special thanks to Mason Turner, MD, for prior slide deck iteration

Nicotine



CONFLICT OF INTEREST DISCLOSURE

I, Daniel Cox, MD have nothing to disclose, and I will not be discussing “off label” use of drugs or devices in this presentation.

Learning Objectives

1. Understand how best to use nicotine replacement therapies to support patients in quitting tobacco and e-cigarettes.
2. Describe global trends in nicotine use in order to inform culturally appropriate treatment.
3. Apply the 5-A's principles of health education to encourage patients to quit smoking.

Addiction		Target Percentage
01	Alcohol	15-20%
02	Sedatives	7-10%
03	Stimulants	7-10%
04	Opioids	10-15%
05	Cannabinoids	7-10%
06	Nicotine	15-20%
07	Hallucinogens	.5-3%
08	Dissociatives	.5-3%
09	Inhalants	.5-3%
10	Anabolic steroids	.5-3%
11	Other substances	1-3%
12	Nonsubstance addiction	1-3%
13	General/All substances combined	1-5%





1. Neurobiology of nicotine addiction
2. Nicotine metabolism via CYP2A6 + pharmacokinetics
3. Nicotine cholinergic receptor subunits
4. Psychoactive effects of nicotine
5. Role of nicotine metabolism as determinant of tobacco use and dependence
6. Pharmacotherapy for smoking cessation
 - a. Doses of NRT used for number of cigarettes smoked/day
 - b. Mechanism of action for smoking cessation drugs, including receptors and neurotransmitters
 - c. Combination pharmacotherapy
 - d. Adverse effects and contraindications
 - e. Comparative efficacy

NEED TO KNOW

7. Cotinine: Levels for light, moderate, heavy smoking
8. 5 A's for screening and counseling of tobacco use: "Ask, Advise, Assess, Assist, Arrange"
9. Efficacy of telephone quit lines
10. Fagerström test for nicotine dependence
11. Effect of nicotine on metabolism
12. E-Cigarettes/Vaping

Vignette for Q1:

A 24 year old, gay-identified, married Latino male is currently in treatment for alcohol use disorder and is 4 months abstinent from all substances other than smoking cigarettes. He requests consultation with you regarding how to quit smoking. He currently consumes 30 hand-rolled cigarettes per day, using an organic, high-nicotine containing tobacco. Although you initially recommend varenicline, he is resistant to using any medications to help him quit. He notes that his husband is a heavy smoker as well.

Vignette 1 (continued):

He asks you about switching to light cigarettes as a means of quitting smoking. “That just makes sense to me. I’ll keep smoking the same amount of cigarettes, but since they are light cigarettes with less nicotine, it will help me reduce my use. Then, I’ll just stop from there over the next couple of months. Maybe reduce 1-2 cigarettes every week or something? Plus, using light cigarettes will keep me from missing having a cigarette in my mouth.”

Q1. Which of the following statements about light cigarettes is most supported by scientific evidence?

- A. If the patient is unable to quit, the fact that he initially tried light cigarettes will allow him to use a lower dose of nicotine replacement therapy if that is later indicated.
- B. Using light cigarettes to quit helps to address the behavioral aspects of smoking while delivering less nicotine.
- C. Smoking light cigarettes will not help. Smokers adjust their nicotine level by adjusting puffing habits.
- D. The patient is right: Reduction in the total amount of nicotine smoked on a daily basis allows the patient to gradually withdraw from nicotine, facilitating the quitting process.

Answer: C. Smoking light cigarettes will not help. Smokers adjust their nicotine level by adjusting puffing habits.

Much evidence has refuted decades-old claims that light or ultra-light cigarettes help to improve the chances of success with smoking cessation among heavy smokers.

While it is true that patients who smoke primarily light cigarettes will potentially require lower doses of nicotine replacement therapy, in this patient with heavy tobacco use, he will probably adjust his puffing habits (puff volume, number of puffs, intensity of puffing, and depth of inhalation) and potentially, increase the number of cigarettes smoked to maintain his baseline nicotine level.

Reference:

Benowitz NL, Henningfield JE Reducing the nicotine content to make cigarettes less addictive *Tobacco Control* 2013;**22**:i14-i17.



Q2. After attempting to smoke light cigarettes for one month to quit smoking and finding that his use of cigarettes increased to 3 packs per day, the patient asks about which nicotine replacement therapies might work for him. Which of the following statements is the most accurate regarding long-term efficacy of these therapies?

- A. Nicotine patch has been found to be superior to the nicotine gum.
- B. Nicotine gum has been found to be superior to the nicotine patch.
- C. Cognitive-behavioral therapy (CBT) alone has been found to be as effective as CBT plus nicotine replacement therapy.
- D. All types of nicotine replacement are equally effective.

D: All types of nicotine replacement are equally effective.

No difference in long-term abstinence rates has been found among the different types of nicotine replacement therapies; all are twice as likely to produce abstinence compared to placebo and are as effective as CBT.

In the short-term, nicotine gum is most effective in combination with other therapies, but in the long-term, there is no difference when used as a single agent. Combination of patch and more immediate acting NRT is more effective than NRT monotherapy. Also, most studies have shown that combining CBT with nicotine replacement treatment is more effective than either treatment used alone.

In this patient, who is likely consuming up to 60mg or more of nicotine per day, a **higher dose of NRT will be required** to prevent cravings and address smoking-related behaviors. The choice of nicotine replacement should be based on patient acceptability and tolerance of the various delivery methods.

Tobacco Use and Dependence Guideline Panel. Treating Tobacco Use and Dependence: 2008 Update. Rockville (MD): US Department of Health and Human Services; 2008 May. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK63952/>

Anczak JD, Nogler RA. Tobacco cessation in primary care: maximizing intervention strategies. Clinical Medicine and Research. 2003. 1; 3:201-216



Q3. The patient successfully quits smoking using a combination of nicotine replacement therapy with patches and CBT focused on quitting smoking. He asks you “What is my chance of being off cigarettes at one year?”

Which of the following is the most accurate statement?

- A. Rates of recurrent use are high, with 40% of smokers returning to use in the first year.
- B. The highest rates of abstinence are achieved in the first year, during which almost 75% of smokers will achieve abstinence. Rates of longer-term abstinence continue to steadily increase.
- C. Return to use is extremely common in the first 3-6 months after a quit attempt, but the rates of recurrent use drop significantly after 6 months.
- D. Former cigarette smokers who remain abstinent for at least two years return to use at a rate of 2% - 4 % each year within the second through sixth years, but this risk decreases to less than 1% annually after 10 years of abstinence.

D. Former cigarette smokers who remain abstinent for at least two years have a risk of recurrent use of 2% - 4% each year within the second through sixth years, but this risk decreases to less than 1% annually after 10 years of abstinence.

Return to use is a major problem with nicotine use disorders, particularly in the first two years after a quit attempt and in spite of treatment.

Up to 90%, not 40%, of patients will return to use annually in the first two years, but once **two** years of abstinence is achieved, this rate diminishes substantially and decreases to less than 1% annually after 10 year of abstinence.

Efforts to enhance abstinence can be achieved through supportive psychotherapy and techniques for preventing return to use.

Vignette for Q4:

You see the patient in follow-up about six months after he quits smoking and following cessation of nicotine replacement therapy. While he has not resumed smoking cigarettes, he has started to use e-cigarettes, noting, “Doc, I tried to get off the patches, and I just couldn’t handle the cravings. So I found a solution. All my friends say vaping is totally harmless and at least I’m not smoking cigarettes. What do you think?”



Q4. Regarding the use of e-cigarettes/vaping, which of the following is not true?

- A. Most people who use e-cigarettes to stop smoking tobacco cigarettes are successful and do not use tobacco cigarettes at the same time they are vaping.
- B. Levels of nicotine vaping amongst high school students rose dramatically from 2017 to 2019, peaking historically, before declining significantly during the COVID pandemic.
- C. E-Cigarettes are equally as addictive as tobacco cigarettes.
- D. Many users of e-cigarettes have greater nicotine exposure than when they were smoking tobacco cigarettes.

A. Most people who use e-cigarettes to stop smoking tobacco cigarettes are successful and do not use tobacco cigarettes at the same time they are vaping. **NOT TRUE**

- Most people who vape to quit smoking tobacco cigarettes end up using both products simultaneously, which renders their use in smoking cessation questionable. A 2022 meta-analysis deemed efficacy estimates of e-cigarettes for tobacco cessation to be uncertain/imprecise despite some positive RCTs and some signal for efficacy. Estimates of relative harm are even less well-known.
- Although e-cigarettes have been associated with a number of different pulmonary and cardiac issues, regular tobacco cigarettes contain over 7000 chemicals and cause a greater burden of disease.
- Because of the ease of increasing nicotine with use of e-cigarettes, many users end up using more nicotine when they switch.
- Decreases in vaping amongst HS students during the COVID pandemic likely reflected constraints in supply chains for e-devices as well as changes in school and social structure related to the pandemic.
- The other distractor is true.

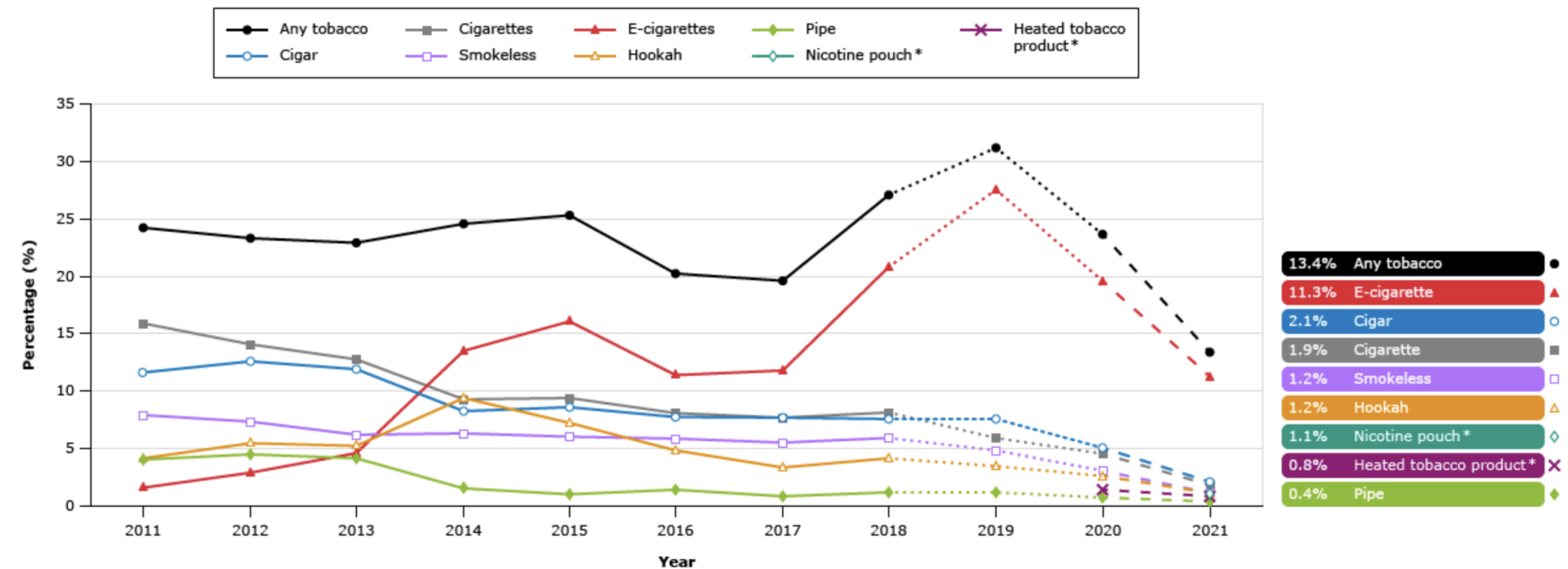
<https://www.hopkinsmedicine.org/health/wellness-and-prevention/5-truths-you-need-to-know-about-vaping>

Johnston, et al. Monitoring the Future, National Survey Results on Drug Use, 1975-2021. 2021 Overview. Key Findings on Adolescent Drug Use.

Thomas KH, et al. Comparative clinical effectiveness and safety of tobacco cessation pharmacotherapies and electronic cigarettes: a systematic review and network meta-analysis of randomized controlled trials. *Addiction*. 2022 Apr;117(4):861-876.



Current tobacco product use among high school students (NYTS, 2011-2021)



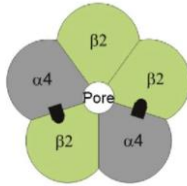
Dashed and dotted lines represent changes in survey methodology and may affect the comparability of results with prior years. In 2019, data collection included a new electronic mode of survey administration as well as presentation of tobacco images; in 2020, data collection was terminated early due to the COVID-19 pandemic; and in 2021, many students participated in distance learning so survey questionnaires were administered both remotely and in school settings.

Q5. The $\alpha_4\beta_2$ nicotinic acetylcholine receptor (nAChR) is the site of action of nicotine. Which of the following statements is *false*?

- A. In the central nervous system (CNS), these receptors are pentameric ion channel complexes found in the dopamine (DA) neurons which connect the ventral tegmental area (VTA) to the nucleus accumbens (NAcc)
- B. There are four α subunits.
- C. There are three β subunits.
- D. Activation of nAChR leads to $\text{Na}^+/\text{Ca}^{2+}$ ion channel fluxes.

B. There are four α subunits. **NOT TRUE**

- In nicotine use disorders, the primary site of action of nicotine is the **$\alpha_4\beta_2$ nicotinic acetylcholine receptor**, and the endogenous transmitter acting on nAChRs is acetylcholine. These CNS receptors are **pentameric** ion channel complexes, which are composed of **two** α_4 and **three** β_2 subunits.
- Note that the subscript numbers (**$\alpha_4\beta_2$**) in the receptor name do **not** refer to the number of each subunit present but rather the subtype of alpha and beta units present in that specific type of nicotinic ACh receptor. Structurally, all nAChRs are homo- or heteropentamers composed of various combinations of alpha (subtypes α_{1-10}) and beta (subtypes β_{1-4}) subunits.
- Activation of nAChRs leads to opening of $\text{Na}^+/\text{Ca}^{2+}$ ion channel, influx of these cations, and thus neuronal depolarization/firing.
- nAChRs are located presynaptically on several neurotransmitter-secreting neuron types in the CNS, including mesolimbic DA neurons that project from the ventral tegmental area to the nucleus accumbens. nAChR activation on mesolimbic DA neurons leads to DA secretion in the nucleus accumbens.



CSAM

Q6. An investigator at the FDA publishes an update on patterns of menthol cigarette use in the United States. All of the following are true except:

- A. Menthol cigarette use declined over the past decade in youth and young adults, mirroring declines in cigarette use across all demographics.
- B. Adolescent menthol smokers show significantly higher levels of nicotine dependence, tolerance and emotional attachment to cigarettes, compared to non-menthol smoking peers.
- C. Among daily smokers, menthol cigarette smokers have a lower odds of quitting as compared to non-menthol smokers.
- D. The tobacco industry has targeted Blacks with marketing for menthol cigarettes for decades, leading to a strong preference for menthol cigarettes amongst Black smokers relative to non-Black smokers.

A. Menthol cigarette use declined over the past decade in youth and young adults, mirroring declines in other nicotine products across all demographics.

NOT TRUE

- A nationally representative study found that, among youth and young adults, non-menthol cigarette prevalence declined from 2004 to 2020. By contrast, menthol cigarette prevalence remained constant among youth and increased among young adults over this period. Menthol makes up a large portion of the cigarette market in the U.S.: 37% in 2020, up from 26% in 2000.
- Menthol reduces the harshness of cigarette smoke due to its characteristic cooling effects on the mouth and throat. It also suppresses the coughing reflex, which makes inhaling smoke from cigarettes more tolerable. Multiple mechanisms may play a role in the addictive potential of menthol. Menthol fundamentally alters nicotine receptors, masks the adverse sensory properties of tobacco products (which ultimately may enhance nicotine intake and drive relapse), and alters nicotine metabolism, increasing its bioavailability.

A. Menthol cigarette use declined over the past decade in youth and young adults, mirroring declines in other nicotine products across all demographics.

NOT TRUE

- A recent study found that, among daily smokers, menthol cigarette smokers have a 24% lower odds of quitting as compared to non-menthol smokers.
- The tobacco industry has targeted Black communities and other vulnerable populations with marketing for menthol cigarettes through community event sponsorship, targeted advertising, youthful imagery, price discounting and intense marketing in the retail environment. This inequitable promotion of tobacco products contributes to health disparities within the United States, which are exacerbated by unequal access to medical care and treatment for tobacco dependence.
- From 1980-2018, Blacks represented 15% of extra new smokers, 41% of excess premature deaths and 50% of excess life-years lost related to tobacco use, despite only accounting for 12% of the population.

Delnevo CD, et al. Assessment of Menthol and Nonmenthol Cigarette Consumption in the US, 2000 to 2018. JAMA Netw Open. 2020;3(8):e2013601. doi: 10.1001/jamanetworkopen.2020.13601.

Mills, S, et al., The Relationship between Menthol Cigarette Use, Smoking Cessation and Relapse: Findings from Waves 1 to 4 of the Population Assessment of Tobacco and Health Study, Nicotine & Tobacco Research, published online October 16, 2020

Ribisl, KM, et al., "Disparities in tobacco marketing and product availability at the point of sale: results of a national study," Preventive Medicine, April 2017.

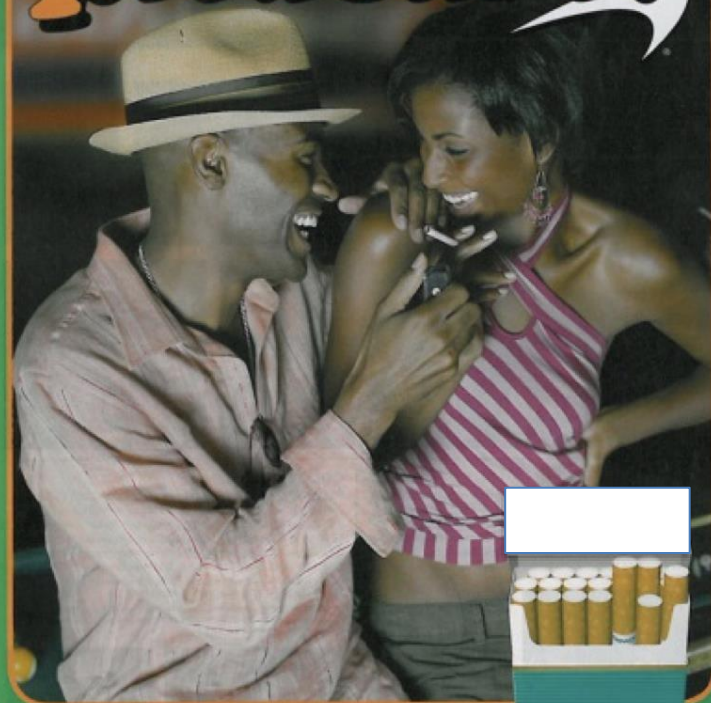
TPSAC, FDA, Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations, July 21, 2011

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM269697.pdf>.

Mendez, D and Le, TT, "Consequences of a match made in hell: the harm caused by menthol smoking to the African American population over 1980-2018," Tobacco Control, published online September 16, 2021.

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**SURGEON GENERAL'S WARNING: Smoking
By Pregnant Women May Result in Fetal
Injury, Premature Birth, And Low Birth Weight.**

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Q7. A 60-year-old Caucasian male presents to your primary care office, complaining of a recurrent cough and chest pain. He has a 50 pack/year history of smoking and has not had routine preventive medical care except for occasional visits to his physician for acute illness. In addition to performing routine health screening, what is the most appropriate initial approach to addressing his smoking?

- A. Given his advanced age and respiratory complaints, immediately prescribe either nicotine replacement therapy or varenicline today.
- B. As part of the medical work-up for his complaints, order a chest CT scan today and schedule a follow-up visit in one week to discuss smoking cessation once you have the results.
- C. Inquire about the patient's tobacco use history and if he has tried to quit smoking before, then indicate to the patient that you are quite worried about his health, that his current symptoms may be related to his smoking, and that he should stop smoking cigarettes.
- D. Contact the patient's family to express your concern for the patient's inability to quit smoking.

C. Inquire about the patient's tobacco use history and if he has tried to quit smoking before, then indicate to the patient that you are quite worried about his health, that his current symptoms may be related to his smoking, and that he should stop smoking cigarettes.

While recommending that the patient start nicotine replacement therapy or prescribing varenicline are appropriate interventions to help him quit smoking, the best initial approach (after asking about his smoking) is to advise the patient of the health risks of his behavior and that he should quit smoking.

An assessment for readiness for quitting can follow, with assistance by prescription of appropriate interventions following that assessment.

Arranging follow-up is the final step in the 5 A's recommended for smoking cessation by the Public Health Service guidelines.

Continued...

Ordering a chest CT is an appropriate next step in the medical work-up for his condition, but the physician should address the patient's smoking during this office visit, before he departs, given his lack of preventive care in the past (i.e., this may be the only time you have a chance to address his smoking).

Contacting the patient's family is not an appropriate next step unless specifically requested by the patient and only with the appropriate authorization in place.

- **Promoting Smoking Cessation.** MICHELE M. LARZELERE, PhD, and DAVE E. WILLIAMS, MD, *Louisiana State University School of Medicine, New Orleans, Louisiana*
- Lung CA Screening CDC: https://www.cdc.gov/cancer/lung/basic_info/screening.htm
- Also this YouTube video goes through the 5 A's <https://www.youtube.com/watch?v=iYCMluD6djc>



Q8. After you advise the patient about the health effects of cigarettes and recommend that he quit smoking, the patient agrees that he is interested in smoking cessation to improve his health. He reveals that he has not succeeded with numerous attempts to quit using patches, gum, lozenges, naturopathic remedies and “just quitting cold turkey.” You tell the patient that several non-nicotine pharmacotherapy agents can assist in smoking cessation. Which of the following drugs has been shown to produce the highest continuous abstinence rate among smokers motivated to quit smoking?

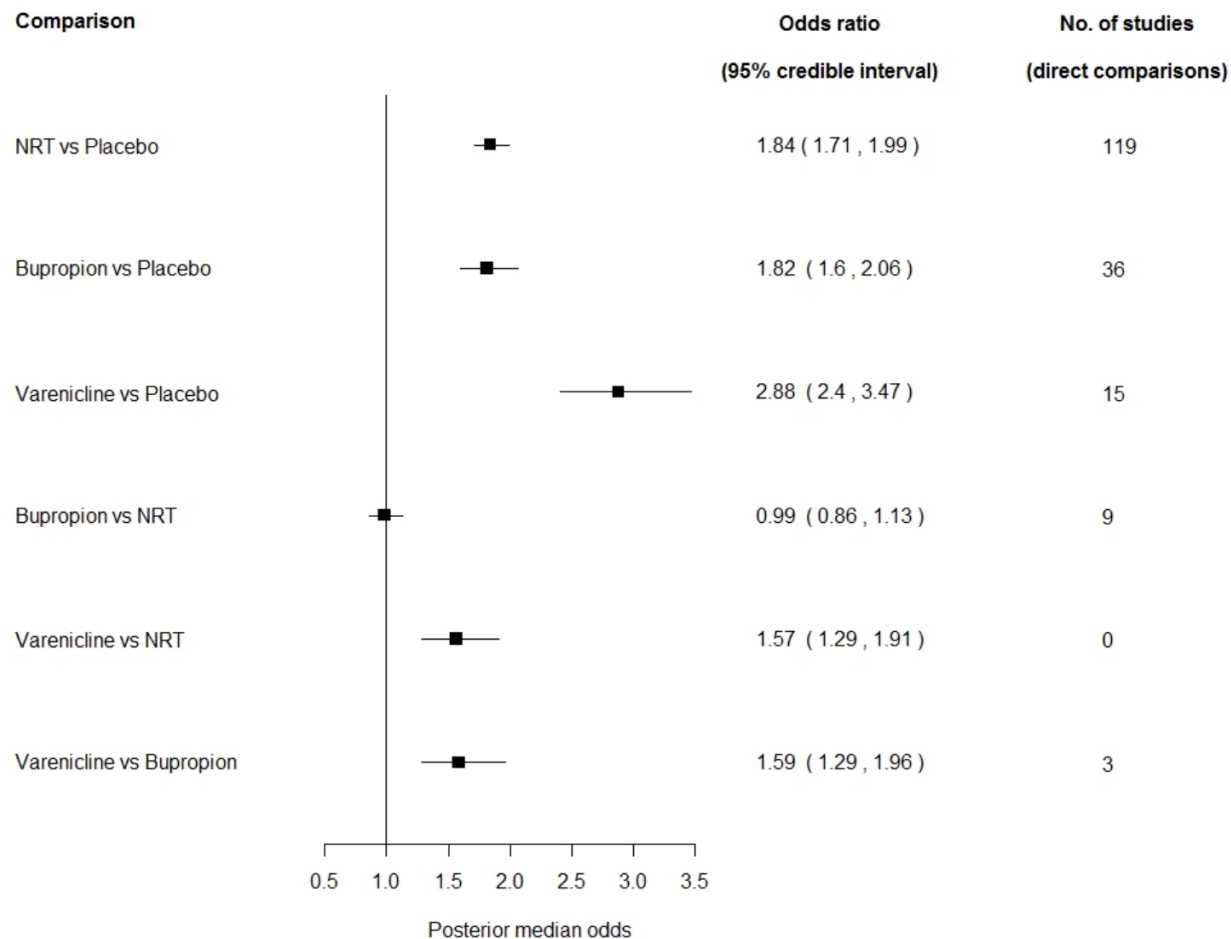
- A. Bupropion
- B. Varenicline
- C. Nicotine patch
- D. Naltrexone

Results from 2013 Cochrane Review

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)

Cahill K. et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane database of systematic reviews. 2013.

Figure 2. Network meta-analysis of smoking cessation with each first-line pharmacotherapy versus placebo and versus each other



B. Varenicline

Varenicline acts as a partial agonist of $\alpha_4\beta_2$ nAChRs and produces the highest rates of abstinence among pharmacotherapy options even including NRTs.

Bupropion, structurally a substituted amphetamine, blocks reuptake of dopamine and norepinephrine, and its high-affinity, noncompetitive nAChR antagonism reduces nicotine reinforcement, withdrawal, and craving.

Naltrexone blocks μ opioid receptors and may reduce pleasurable effects from substances. Its utility in smoking cessation has not been established, however.

Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR, Varenicline Phase 3 Study Group FT. Efficacy of Varenicline, an $\alpha_4\beta_2$ Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomized Controlled Trial. *JAMA*. 2006;296(1):56-63. doi:10.1001/jama.296.1.56

Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, Treadow J, Yu C, Dutro MP, Park PW. Effect of Varenicline on Smoking Cessation Through Smoking Reduction: A Randomized Clinical Trial. *JAMA*. 2015;313(7):687-694. doi:10.1001/jama.2015.280



Q9. Regarding the use of smokeless chewing tobacco and cigars, which of the following statements is *not true* regarding the use of non-cigarette forms of tobacco delivery?

- A. Men are four times more likely to use smokeless tobacco than women.
- B. Evidence has demonstrated that non-cigarette tobacco users who use those products in combination with cigarettes have a more difficult time quitting either.
- C. The use of cigars and pipes is associated with cancers of the lung, stomach, oral cavity, larynx, and esophagus.
- D. E-cigarettes should not be recommended as a secondary strategy for quitting if other interventions fail.

B. Evidence has demonstrated that non-cigarette tobacco users who use those products in combination with cigarettes have a more difficult time quitting either.

NOT TRUE

Evidence is actually mixed and has not definitively demonstrated comparative successes (or failures) in quitting when non-cigarette tobacco products are used in conjunction with cigarettes (or alone).

Smokeless tobacco is used by 4% of men and 1% of women according to the most recent population estimates.

The use of cigars and pipes is associated with cancers of the lung, stomach, oral cavity, larynx, and esophagus. Smokeless tobacco on the other hand is typically associated with oral, pancreatic and esophageal cancer, but no clear evidence has associated use with stomach cancer.

Finally, at this time, recommending e-cigarettes to quit smoking or use of non-nicotine products is not recommended given a lack of knowledge about safety.



Q10. Which of these is *not* part of the Fagerström test for nicotine dependence?

- A. How soon after you wake up do you smoke your first cigarette?
- B. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in cinema, etc)?
- C. Which cigarette would you hate most to give up?
- D. How often have you attempted to quit smoking?

D. How often have you attempted to quit smoking?

**NOT
PART OF**

Fägerstrom Test for Nicotine Dependence (FTND)

- How soon after you **wake up** do you smoke your 1st cigarette?
 - > 60 min (0)
 - 31-60 min (1)
 - 6-30 min (2)
 - Within 5 min (3)
- Is it difficult to not smoke in places where it is **forbidden** (e.g., church, school, hospital)?
 - No (0)
 - Yes (1)
- Which cigarette would you **hate** most to **give up**/treasure the most?
 - First morning cigarette (1)
 - Any other one (0)
- **How many** cigarettes/day?
 - ≤ 10 (0)
 - 11-20 (1)
 - 21-30 (2)
 - ≥ 31 (3)
- Smoke more **during first few hours** after waking up than the rest of the day?
 - No (0)
 - Yes (1)
- Do you **still smoke if you are sick** (have a cold or the flu, difficulty breathing, in bed all day, etc.)?
 - No (0)
 - Yes (1)

Q11. Which of the following **does not** explain the link between schizophrenia and cigarette smoking?

- A. Smoking changes gene expression for more than 200 genes in the human hippocampus, and differentially normalizes aberrant gene expression in schizophrenia.
- B. Nicotine has been shown to improve cognitive function in schizophrenics.
- C. Nicotine acts through a family of nicotinic receptors with either high or low affinity for nicotine. The loci for several of these receptors have been genetically linked to both smoking and to schizophrenia .
- D. Nicotine has been demonstrated to reduce positive, more than negative, symptoms of schizophrenia.

D. Nicotine has been demonstrated to reduce positive, more than negative, symptoms of schizophrenia. **NOT TRUE**

Nicotine has been shown to improve psychiatric symptoms in persons with schizophrenia. Typically, *negative* symptoms are improved more than *positive* symptoms.

Research has now demonstrated significant genetic links between cigarette smoking/tobacco use disorders and schizophrenia, which may explain the inordinately high incidence of cigarette smoking in that population (80% in persons with schizophrenia versus 25% or less of the general population).

Nicotine is known to improve cognitive deficits in schizophrenia, including those caused by anti-psychotic medications.

Continued...

Notably, when patients are discharged from inpatient psychiatric units, where cigarettes are not available, and resume smoking cigarettes, the efficacy of their medications may go down. Cigarette smoke (but not nicotine per se) increases the activity of CYP 1A2 enzymes, decreasing the concentration of many psychoactive drugs, including clozapine and olanzapine. Some patients may smoke to actually reduce the cognitive side effects of medications such as haloperidol.

Positive Symptoms of Schizophrenia

- Delusions
- Hallucinations (auditory primarily, but sometimes, tactile, olfactory or visual)
- Ideas of reference
- Disorganized speech and behavior
- Paranoia (a type of delusion)

Negative Symptoms of Schizophrenia

- Blunting of affect
- Poverty of speech and thought
- Apathy
- Anhedonia
- Reduced social drive/social interest
- Loss of motivation
- Inattention to social or cognitive input.