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Pharmacotherapy For Tobacco Treatment

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MARYLAND TCRC Tobacco Control Resource Center

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No disclosures

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Why we should prioritize tobacco treatment to all individuals who smoke

Vulnerable populations carry a disproportionate burden of tobacco-related disease

- High smoking rates
- Limited access to effective, guideline-recommended cessation services
- Lack of support for stopping

Benefit in stopping regardless of age:

- Stop at age 35: individual gain of cessation = 6.1 to 8.5 years of life
- Stop at age 65: individual gain of cessation = 1.4 to 3.7 years of life

Several trials suggest benefit of providing cessation treatment to all individuals who smoke regardless of motivation to stop smoking

Jha, P., et al., *21st-century hazards of smoking and benefits of cessation in the United States.* N Engl J Med, 2013. **368**(4): p. 341-50
Cahill, K., et al., *Nicotine receptor partial agonists for smoking cessation.* Cochrane Database Syst Rev, 2016(5): p. CD006103.
Woloshin, S., et al.,*The risk of death by age, sex, and smoking status in the United States: putting health risks in context.* J Natl Cancer Inst, 2008. **100**(12): p. 845-53
Chen, D. and L.T. Wu, *Smoking cessation interventions for adults aged 50 or older: A systematic review and meta-analysis.* Drug Alcohol Depend, 2015. **154**: p. 14-24

Why is it so hard to stop smoking?

- *"I think nicotine is the most addictive substance. I don't want my legacy to be dying from cigarettes, but I don't know if I can stop."*

- *"When I left jail, cigarettes was the first thing on my mind. Didn't even care about getting home from jail safely."*

Understanding Nicotine Addiction

Exogenous nicotine activates neurons of the VTA to create a powerful but incorrect, safety signal.

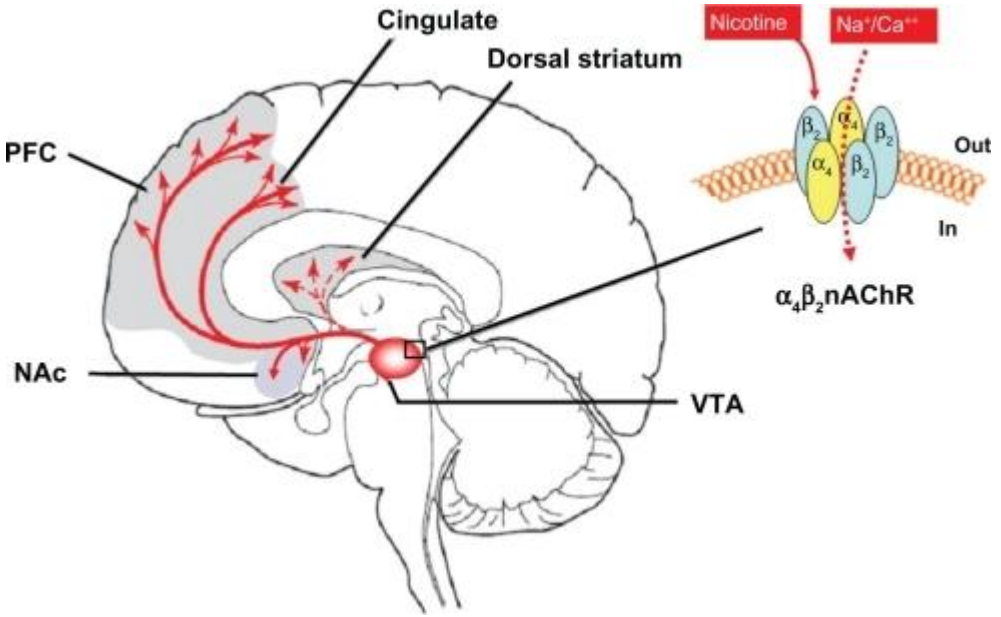
Thus, when patients face the possibility of abstinence, they face the equivalent of a threat to survival.

Nicotine also promotes long-term learned associations that becomes persistent over time, placing patients with tobacco dependence at lifelong risk for relapse.

These effects, coupled with the rapidity with which nicotine reaches the brain, contribute to the significant addictive potential of the cigarette.

Even with smoking-related disease, patients are often conflicted between their desire to quit smoking and the desire to avoid the threat of abstinence.

Mesolimbic DA projection pathway (Xi, 2010)



Nicotine activates α4β2 nAChRs located on dopamine (DA) neurons in the VTA and increases VTA DA neuron activity as well as DA release in the nucleus accumbens (Nac), dorsal striatum, and prefrontal cortex (PFC).

Leone FT, Evers-Casey S. Developing a Rational Approach to Tobacco Use Treatment in Pulmonary Practice: A Review of the Biological Basis of Nicotine Addiction. Clin Pulm Med. 2012;19(2):53-61.
Subramaniyan M, Dani JA. Dopaminergic and cholinergic learning mechanisms in nicotine addiction. Ann N Y Acad Sci. 2015;1349:46-63.
Xi Z-X. Preclinical pharmacology, efficacy, and safety of varenicline in smoking cessation and clinical utility in high risk patients. *Drug, healthcare and patient safety*. 2010;2:39-48.

Tobacco use disorder is a chronic disease that requires treatment

In 2015, 68% of adults who currently smoked (22.7 million) reported they were interested in quitting smoking.

In 2018, 7.5% of adults who smoked (2.9 million) successfully stop smoking in the past year

Combined use of pharmacotherapy and behavioral support increases stop rates (RR 1.82 [95% CI, 1.7 to 2.0].

In 2015, 31% of adults who smoke (7.6 million) reported using counseling or medication when trying to stop.

- 6.8% (1.7 million) reported using counseling
- 29.0% (7.1 million) reported using medication
- 4.7% (1.1 million) reported using both counseling and medication when trying to stop

Chen, D. and L.T. Wu, Smoking cessation interventions for adults aged 50 or older: A systematic review and meta-analysis. Drug Alcohol Depend, 2015. 154: p. 14-24
Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting Smoking Among Adults - United States, 2000-2015. MMWR Morb Mortal Wkly Rep. 2017 Jan 6;65(52):1457-1464.
Creamer MR, Wang TW, Babb S, et al. Tobacco Product Use and Cessation Indicators Among Adults – United States, 2018. MMWR Morb Mortal Wkly Rep 2019;68:1013–1019
S. Department of Health and Human Services. Smoking Cessation. A Report of the Surgeon General. Atlanta, GA:, 2020
Patnode CD et al. Behavioral Counseling and Pharmacotherapy Interventions for Tobacco Cessation in Adults, Including Pregnant Women: A Review of Reviews for the USPSTF. AHRQ 2015

U.S. Preventive Services Task Force (USPSTF) Recommendations

Population	Recommendation	Grade
Adults (not pregnant)	The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and U.S. Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco.	A
Pregnant women	The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco.	A
Pregnant women	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women.	I
All adults (pregnant)	The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women. The USPSTF recommends that clinicians direct patients who smoke tobacco to other cessation interventions with established effectiveness and safety (previously stated).	I
School-Aged Children and Adolescents	The USPSTF recommends that primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents..	B

https://www.uspreventiveservicestaskforce.org/uspstf/document/ClinicalSummaryFinal/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions

Opt-out approaches

Involves screening all patients for tobacco use, advising all who smoke to stop, and offering treatment to all smoke.

Screening can be prompted by notifications in the electronic health record

Healthcare workers then advise stopping offer and deliver treatment, and/or connect individuals to treatment (tobacco treatment specialists, quitline)

Opt-out approaches yield greater cessation rates compared to opt-in, where intervention is offered only to those who are motivated to quit.

Fu SS et al. Proactive tobacco treatment and population-level cessation: A pragmatic randomized clinical trial. JAMA Intern Med. 2014;174:671-7.
Haas J et al. Proactive tobacco cessation outreach to smokers of low socioeconomic status: A randomized clinical trial. JAMA Intern Med.175:218-26.
Herbst N et al. Effectiveness of an opt-out electronic helath record-based tobacco treatment consult service at an urban safety net hospital. Chest. 2020;158:1734-41.
Cartmell K et al. Effect of an evidence-based inpatient tobacco dependence treatment service on 1-year postdischarge health care costs. Medical Care. 2018;56:883-9.
Cartmell K et al. Effect of an evidence-based inpatient tobacco dependence treatment service on 30-, 90-, and 180-day hospital readmission rates. Medical Care. 2018;56:358-63.

Assessing factors that influence relapse risk

Assessing factors that influence relapse:

- Medication adherence
- Level of social support
- Presence of household individuals/peers who smoke
- Retained tobacco or tobacco use paraphernalia
- Insurance or financial insecurity

Strategies to improve long-term outcomes

- Non-confrontational conversations about adherence and possible moderators of relapse
- When controller medications are discontinued, reliever medications can be continued if needed to help acute cravings during the transition.

Chang EHE et al. Treating Nicotine Dependence and Preventing Smoking Relapse in Cancer Patients. Expert Rev Qual Life Cancer Care. 2017;2(1):23–39.
Robinson JD et al. Evaluating the temporal relationships between withdrawal symptoms and smoking relapse. Psychol Addict Behav J Soc Psychol Addict Behav. 2019 Mar;33(2):105–16.
American College of Chest Physicians. Smoking and Tobacco Use [Internet]. 2021 Available from: https://foundation.chestnet.org/lung-health-a-z/smoking-and-tobacco-use

Pharmacotherapy

THERE ARE 6 FDA-APPROVED MEDICATIONS TO TREAT TOBACCO DEPENDENCE

- 4 forms of nicotine replacement
- Varenicline (Chantix)
- Bupropion SR (Wellbutrin)

Addressing Knowledge Gaps in Medications

- *"No one has ever talked to me about Chantix. Never tried the gum or lozenge. If they offered me the patch when I leave, I would use it."*

- *"I'd like to talk to someone. Quitting cold turkey sucks. Unless you have help, you'll just pick it up again."*

Nicotine Replacement Therapy

MOI: AGONIST AT NICOTINIC-CHOLINERGIC RECEPTORS

Addressing mistrust and misinformation

- *"You can't smoke and have the patch at the same time. I heard that's real bad for you."*

This is not unexpected given that until 2013, labels on NRT packaging indicated that people should stop NRT with any smoking to avoid nicotine intoxication and were warned against the combined use of NRT products.

Nicotine Delivery

NICOTINE DELIVERY DEVICE - TOBACCO	Nicotine In Product	Approximate Amount of Nicotine Delivered to User	Comments
Marlboro Red	13 mg	1 to 3 mg	Also delivers a wide range of carcinogens and other toxins.
Marlboro Light	13 mg	1 to 3 mg	
Cigars	10 to 440 mg	Highly variable	
Moist Snuff	4 to 12 mg/gm	Varies depending on pH & other characteristics	
Bidis		1.8 to 5.6 mg	

Nicotine Delivered by Nicotine Replacement Products

NICOTINE DELIVERY DEVICE – NICOTINE REPLACEMENT	Nicotine In Product	Approximate Amount of Nicotine Delivered to User	Comments
Nicotine Lozenge	4 mg	Up to 3.2mg	
Nicotine gum	2 mg/piece	Up to 0.8 mg	Only delivers nicotine to the consumer
Nicotine gum	4 mg/piece	Up to 1.2 mg	
Nicotine patch (Habitrol)	17 mg	7 mg/24 hrs	
Nicotine patch (Habitrol)	35 mg	14 mg/24 hrs	
Nicotine patch (Habitrol)	52 mg	21 mg/24 hrs	
Nicotine nasal spray	10 mg/ml	0.5 mg/1 spray	
Nicotrol® inhaler	10 mg/cartridge	Up to 4 mg/ cartridge	

Ferrence, R ad Slade J APHA Washington DC, 2000 Nicotine and Public Health

The Fagerstrom Test for Nicotine Dependence (helps to dose NRT)

		0 Points	1 Point	2 Points	3 Points
1.	**How soon after you wake do you smoke your first cigarette?**	**After 60 mins**	**31-60 mins**	**6-30 mins**	**Within 5 mins**
2.	Do you find it difficult to refrain from smoking in places where it is forbidden?	No	Yes		
3.	Which cigarette would you hate most to give up?	All others	First one in the morning		
4.	How many cigarettes do you smoke a day?	10 or less	11-20	21-30	31 or more
5.	Do you smoke more frequently during the first hours after waking than the rest of the day?	No	Yes		
6.	Do you smoke if you are so ill that you are in bed most of the day?	No	Yes		

Heatherton TF et al. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict.* 1991;86(9):1119–1127.
Fagerström K. Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine Tob Res.* 2012;14(1):75–78.

The Fagerstrom Test for Nicotine Dependence

Value	Description
0 to 2	Very low level of dependence on nicotine.
3 to 4	Low level of dependence on nicotine.
5	Medium level of dependence on nicotine.
6 to 7	High level of dependence on nicotine.
8 to 10	Very High level of dependence on nicotine.

Heatherton TF et al. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict.* 1991;86(9):1119–1127.
Fagerström K. Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine Tob Res.* 2012;14(1):75–78.

Heaviness of smoking index

TABLE 1 **Heaviness of Smoking Index: 2 Questions to Assess a Smoker's Degree of Nicotine Dependence**

How many cigarettes do you smoke?

0: 10 or fewer

1: 11-20

2: 21-30

3: ≥31

How soon after waking up do you smoke your first cigarette of the day?

0: After 60 minutes

1: 31-60 minutes

2: 6-30 minutes

3: within 5 minutes

- 0-2 = low nicotine dependence
- 3-4 = moderate nicotine dependence
- 5-6 = high nicotine dependence

Heatherton TF et al. Measuring the heaviness of smoking: using self reported time to the first cigarette of the day and number of cigarettes smoked per day. Br J Addict. 1989;84:791–9.

Nicotine Delivery Systems: 5 Available forms

NICOTINE TRANSDERMAL PATCH	FDA-RECOMMENDED DOSING	DOSING MODIFICATIONS AND TIPS
MOI: • Agonist at nicotinic-cholinergic receptors. • Blood levels of nicotine peak around 2 hours after applying the patch, but provides the longest and most constant rate of delivery **Precautions:** • Recent MI (within 2 weeks), serious arrhythmias, unstable angina • Adolescents <18 • Pregnancy (D) and breastfeeding	**Dosage:** 21mg/day x 4–6 weeks ≤10 cigs/day: 14 mg/day x 6 weeks 7 mg/day x 2 weeks Duration: 8–10 weeks **Adverse Events:** Local skin reactions, HAs, sleep disturbances	**Pre-treatment:** **Consider pre-cessation treatment with nicotine patch prior to quit date** **Dosage Modification:** Consider 21 mg for all Can continue up to 24 months >40 cigs/day: consider 42 mg/day **Combination + Extended Therapy:** **Strongly consider >13 weeks transdermal patch + ad lib short acting NRT [Odds ratio of quitting 3.6 (2.5-5.2)]** **Tips to Increase Clinical Utility:** Rotate patch site every 24 hours Consider removing at bedtime if insomnia

Kathuria H, Leone FT, Neptune E. Treatment of Tobacco Dependence: Current State of the Art, *Current Opinion in Pulmonary Medicine, 2018*

NICOTINE LOZENGES	FDA-RECOMMENDED DOSING	DOSING MODIFICATIONS AND TIPS
MOI: Nicotinic-cholinergic receptors agonist **Peak levels at 20 mins** **Precautions:** Similar to Above	**Dosage:** Duration: up to 12 weeks **1st cig <30 min after waking: 4mg** **1st cig >30 min after waking: 2mg** Weeks 1–6: 1 lozenge q 1–2 hrs Weeks 7–9: 1 lozenge q 2–4 hrs Weeks 10–12: 1 lozenge q 4–8 hrs MAX=20 lozenges/day **Adverse Events**: Nausea, hiccups, cough, heartburn, headache, insomnia	**Combination + Extended Therapy:** **Consider >13 weeks transdermal patch + ad lib lozenges consider 4 mg for all** **Tips to Increase Clinical Utility:** Park between cheek and gum and rotate to different areas in mouth. Do not chew or swallow No food/beverages 15 mins before use
NICOTINE GUM	**FDA-RECOMMENDED DOSING**	**DOSING MODIFICATIONS AND TIPS**
MOI: Nicotinic-cholinergic receptors agonist **Peak levels at 20 mins** **Precautions:** Similar to above	**Dosage:** Duration: up to 12 weeks **1st cig <30 min after waking: 4mg** **1st cig >30 min after waking: 2mg** Weeks 1–6: 1 piece q 1–2 hours Weeks 7–9: 1 piece q 2–4 hours Weeks 10–12: 1 piece q 4–8 hours MAX=24 pieces/day **Adverse Events:** Hiccups, dyspepsia, nausea and lightheaded (if incorrect chewing)	**Combination + Extended Therapy :** **Consider >13 weeks transdermal patch + ad lib gum 4 mg for all** **Tips to Increase Clinical Utility:** Park between cheek and gum when peppery taste appears; resume chewing when sensation goes away; Repeat chew/park steps Park in different areas of mouth No food/beverages 15 mins before use

NICOTINE NASAL SPRAY	FDA-RECOMMENDED DOSING	DOSING MODIFICATIONS AND TIPS
MOI: Nicotinic-cholinergic receptor agonist **Peak at 5-10 min** **Precautions:** Similar to other NRT Chronic Nasal Disorders Severe reactive airway disease	**Dosage (**Prescription only) 8–40 doses/day (One dose = 2 sprays) • Initially use 1–2 doses/hour and at least 8 doses/day • MAX= 5 doses/hour or 40 doses Duration 3-6 months **Adverse Events:** Nasal/throat irritation, rhinitis, sneezing, cough, and headache	**Combination + Extended Therapy:** **Consider >13 weeks transdermal patch + ad lib nasal spray** **Tips to Increase Clinical Utility:** Do not sniff, swallow, or inhale through the nose as the spray is being administered

Kathuria H, Leone FT, Neptune E. Treatment of Tobacco Dependence: Current State of the Art, *Current Opinion in Pulmonary Medicine, 2018*

Bupropion

RE-UPTAKE INHIBITOR OF DOPAMINE AND/OR NOREPINEPHRINE; UNCLEAR IN SMOKING CESSATION

BUPROPION SR (ZYBAN)	FDA-RECOMMENDED DOSING	DOSING MODIFICATIONS AND TIPS
MOI: Dopamine/norepinephrine-reuptake inhibitor **Precautions:** • Concomitant therapy with medications/conditions that lower the seizure threshold • Hepatic impairment • Adolescents • Pregnancy (C) and breastfeeding **Contraindications:** • Seizure disorder or abrupt discontinuation of alcohol or sedatives/benzodiazepines • Bulimia or anorexia nervosa • MAO inhibitors in preceding 14 days or concurrent use of reversible MAO inhibitors	**Dosage:** • Begin therapy 1-2 weeks prior to quit date 150 mg qAM x3 days, then 150 mg BID (Max 300 mg/day) • Duration: 7–12 weeks, with maintenance up to 6 months in selected patients • Decrease dose with hepatic or renal disease **Adverse events:** Insomnia, difficulty concentrating; seizures; rare neuropsychiatric events **(Boxed Warning for serious mental health side effects from drug label was removed in December 2016)**	**Combination Therapy:** **Strongly consider transdermal nicotine patch + Bupropion** [Odds ratio of Quitting: 2.5 (1.9-3.4)] **Extended Duration:** For patients who successfully quit after 12 weeks, consider an additional 12-week course. **Tips to Increase Clinical Utility:** Avoid taking at bedtime to minimize insomnia

Kathuria H, Leone FT, Neptune E. Treatment of Tobacco Dependence: Current State of the Art, *Current Opinion in Pulmonary Medicine, 2018*

Varenicline

MOA: PARTIAL AGONIST OF ALPHA-4-BETA-2 NICOTINIC ACETYLCHOLINE RECEPTOR; PREVENTS NICOTINE BINDING TO RECEPTORS

VARENICLINE	FDA-RECOMMENDED DOSING	DOSING MODIFICATIONS AND TIPS
MOI: • Partial agonist of alpha-4-beta-2 nicotinic acetylcholine • Prevents nicotine binding to receptors **Precautions:** • Severe renal impairment (dosage adjustment needed) • Adolescents • Pregnancy (C) and breastfeeding	**Dosage:** Begin 1 week prior to quit date Days 1-3: 0.5 mg qAM; Days 4-7: 0.5 mg BID Weeks 2-12: 1 mg BID **Decrease dose in renal disease** CrCl <30: initial 0.5 mg, max dose 0.5 mg BID HD: max 0.5 mg daily Duration: 12 weeks **Adverse effects:** Nausea, headache and insomnia; rare neuropsychiatric events **(Boxed Warning for serious mental health side effects from drug label was removed 12/2016)**	**Pre-treatment for smokers not ready to quit:** **Consider flexible quit date during days 8-35 of treatment OR reducing smoking over a 12-week period of treatment prior to quitting** **Increased abstinence:** RR 2.00, 95% CI 1.70–2.35; ARR 173 more per 1,000 **Combination Therapy with patch + varenicline:** **Consider initiating nicotine patch + varenicline** **Increased abstinence:** RR 1.36, 95% CI 1.07–1.72; ARR 105 more per 1,000 **Extended Duration:** **Consider additional 12-weeks after quitting** **Increased abstinence:** RR 1.22, 95% CI 1.07–1.39; ARR 53 more per 1,000 **Dosage Modification** If adverse effects, consider lowering to 1 mg/day **Tips to Increase Utility: Take after food & with H20**

Kathuria H, Leone FT, Neptune E. Treatment of Tobacco Dependence: Current State of the Art, *Current Opinion in Pulmonary Medicine*

Longitudinal management of tobacco use disorder

- *"No one has ever talked to me about Chantix. Never tried the gum or lozenge. If they offered me the patch when I leave, I would use it."*

- *"I'd like to talk to someone. Quitting cold turkey sucks. Unless you have help, you'll just pick it up again."*

Strategies for treatment should shift away from a singular focus of 'quitting' and toward alignment with the longitudinal control over the compulsion to smoke

Kathuria H, Leone FT, Neptune ER. Treatment of tobacco dependence: current state of the art. Curr Opin Pulm Med. 2018 Jul;24(4):327–34.
Leone FT, Evers-Casey S. Behavioral Interventions in Tobacco Dependence. Prim Care Clin Off Pract. 2009 Sep;36(3):489–507.

Initiating Tobacco Treatment: 2020 ATS Clinical Guideline

	Clinical Question(s)	PICO Question(s)
Initial Medication Choice	Which is the optimal controller medication choice for initiating tobacco dependence treatment?	PICO 1: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with varenicline or nicotine patch? PICO 2: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with bupropion or varenicline?
Potential Modifications	Would combining multiple mechanisms of action improve outcomes?	PICO 3: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with the optimal controller medication (varenicline) plus nicotine replacement therapy or the optimum controller (varenicline) alone?

Varenicline is the optimal controller compared to both nicotine patch and bupropion (both for long-term abstinence and serious adverse events)

Combination varenicline + nicotine patch performed better than varenicline monotherapy; newer studies show no difference between groups

Controller medications are expected to have a delayed onset of effect, acting to reduce the frequency and intensity of the impulse to smoke

Leone FT, Zhang Y, Evers-Casey S, Evins AE, Eakin M, Fathi J, Fennig K, Folan P, Galiatsatos P, Gogineni H, Kantrow S, Kathuria H, Lamphere T, Neptune E, Pacheco MC, Pakhale S, Prezant D, Sachs DPL, Toll B, Upson D, Xiao D, Cruz-Lopes L, Fulone I, Murray RL, O'Brien KK, Pavalagantharajah S, Ross S, Zhang Y, Zhu M, and Farber HJ. Initiating Pharmacologic Treatment of Tobacco Dependence in Adults: An Official ATS Clinical Practice Guideline. *Am J Respir Crit Care Med* 2020; 2020;202(2):e5-e31

Initiating Tobacco Treatment: 2020 ATS Clinical Guideline

	Clinical Question(s)	PICO Question(s)
Important Patient-Level Moderators →	What if patients... • aren't interested in approved therapies? • have a mental health or substance use disorder? • remain ambivalent about not smoking?	PICO 4: For tobacco-dependent adults in whom treatment is being initiated, should treatment be started with an electronic cigarette or the optimal controller medication? PICO 5: In tobacco-dependent adults who are not ready to discontinue tobacco use, should clinicians begin treatment with the optimal cotroller or wait until they are ready to stop tobacco use? PICO 6: In tobacco-dependent adults with co-morbid psychiatric conditions, including substance use disorder, depression, anxiety, schizophrenia, and/or bipolar disorder, in whom treatment is being initiated, should clinicians start with the optimal controller medication identified for patients without psychiatric conditions or use NRT patch?
Maintenance →	What is the optimal duration of pharmacologic treatment?	PICO 7: In tobacco-dependent adults for whom treatment is being initiated with a controller, should they be treated with standard duration (6 to 12 weeks) or extended duration (greater than 12 weeks)?

Guidelines recommend starting varenicline in those not ready to quit

Guidelines recommend varenicline when initiating pharmacotherapy in patients with psychiatric comorbidities.

Varenicline: better abstinence rates with no difference in serious adverse event rates.

Leone FT et al Initiating Pharmacologic Treatment of Tobacco Dependence in Adults: An Official ATS Clinical Practice Guideline. *Am J Respir Crit Care Med* 2020; 2020;202(2):e5-e31

Initiating Pharmacotherapy for Tobacco Dependence: Varenicline

14 RCT directly comparing efficacy of varenicline to nicotine patch

- Varenicline increased 7-day point prevalence abstinence at 6-month f/up
- (RR 1.20, 95% CI 1.09–1.32; ARR 40 more per 1,000, 95%CI 18 to 65 more)

7 RCT comparing varenicline to bupropion

- Varenicline increased 7-day point prevalence abstinence at 6-month f/up
- (RR 1.30, 95% CI 1.19-1.42; ARR 77 more per 1,000, 95% CI 40 to 108 more)

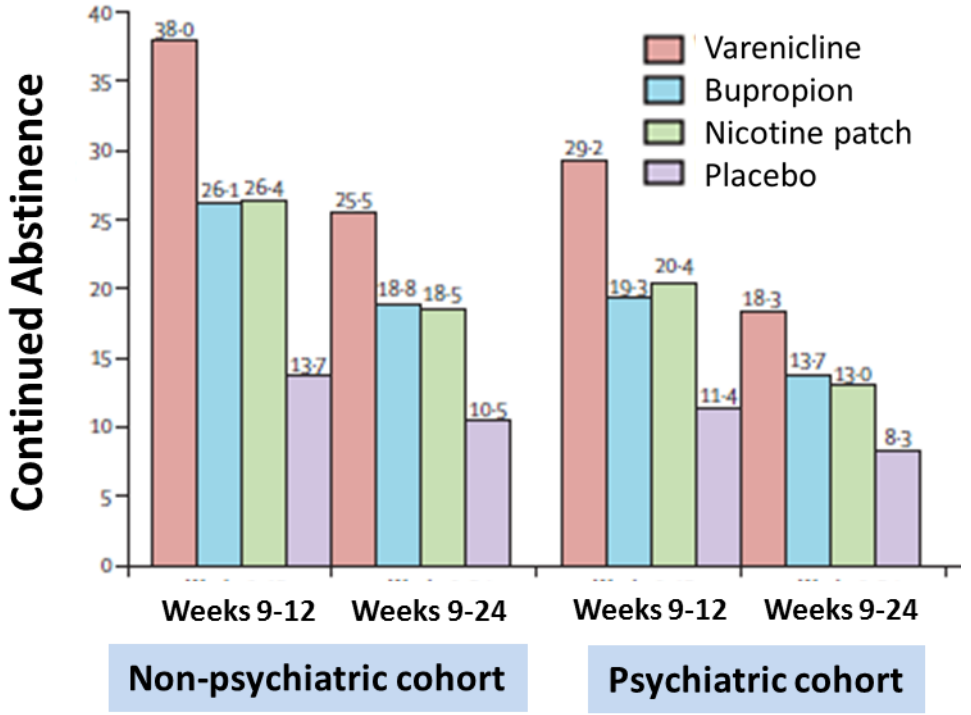
Leone FT et al. Initiating Pharmacologic Treatment of Tobacco Dependence in Adults: An Official ATS Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 2020;202(2):e5-e31
Baker TB et al. Effects of Combined Varenicline With Nicotine Patch and of Extended Treatment Duration on Smoking Cessation: A Randomized Clinical Trial. JAMA. 2021;326(15):1485–1493.

Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial

Neuropsychiatric safety and efficacy of Varenicline, Bupropion, and nicotine patch in individuals with and without psychiatric disorders

Double-blind, randomized, placebo-controlled clinical trial (8000 patients, 16 countries)

- Study included smokers with stable and treated psychiatric disorders.
- Excluded patients with substance use disorder in past 12 months



Conclusions: Patients with and without a psychiatric disorder

- No significant increase in neuropsychiatric AEs in varenicline or bupropion relative to patch or placebo.
- Varenicline was more effective than placebo, nicotine patch, and bupropion in smoking abstinence

Anthenelli, R.M., et al., Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet, 2016. **387**(10037): p. 2507-20.

Initiation and Duration of varenicline

4 RCT that addressed the efficacy of initiation of tobacco-dependence treatment in individuals unready to abstain

- Varenicline increased abstinence compared to waiting for affirmation of readiness
- (RR 2.00, 95% CI 1.70– 2.35; ARR 173 more per 1,000, 95% CI 121 to 234 more)

2 RCT comparing varenicline with a nicotine patch in patients with mental illness

- Varenicline increased abstinence assessed at 6-month follow-up in smokers with MI
- (RR, 1.31; 95% CI, 1.12 to 1.53; ARR 36 more per 1,000; 95% CI 14 to 62 more)

8 RCT that addressed the efficacy of extended duration therapy

- Extended duration therapy probably increased abstinence at one-year follow-up
- (RR 1.22, 95% CI 1.07–1.39; ARR 53 more per 1,000, 95% CI 17 to 94 more)

Leone FT et al. Initiating Pharmacologic Treatment of Tobacco Dependence in Adults: An Official ATS Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 2020;202(2):e5-e31

Cytisinicline (Cytisine)

Partial agonist at the alpha-4 beta-2 nicotinic acetylcholine receptor (similar to varenicline)

Low-cost pharmacologic alternative to varenicline (available in Central and Eastern Europe)

Not yet available in the United States

Meta-analysis found that cytisine was

- More effective than placebo (RR 1.30; 95% CI 1.15-1.47)
- More effective than single-product NRT (RR 1.43; 95% CI 1.134-1.80).
- May be inferior to varenicline (RR .83; 95% CI .66-1.05) but results imprecise

Orca -2 trial

- Novel cytisinicline dosing regimen (3 mg three times per day) given for 6 and 12 weeks
- Both regimens had significantly higher continuous smoking abstinence rates than placebo
  - 6-week regimen: 8.9% vs 2.6% during weeks 3 to 24 (OR, 3.7 [95% CI, 1.5-10.2]; P = .002).
  - 12-week regimen: 21.1% vs 4.8% during weeks 9 to 24 (OR, 5.3 [95% CI, 2.8-11.1]; P < .001).

Rigotti NA, Benowitz NL, Prochaska J, Leischow S, Nides M, Blumenstein B, Clarke A, Cain D, Jacobs C. Cytisinicline for Smoking Cessation: A Randomized Clinical Trial. JAMA. 2023 Jul 11;330(2):152-160. PMID: 37432430;

Treatment for E-cigarette cessation

Varenicline and counseling for vaping cessation

- Randomized to 12 weeks of varenicline + counseling vs. placebo + counseling (N=140)
- Higher continuous abstinence with varenicline vs placebo at weeks 4–24

  [34.3% vs 17.2%; OR = 2.52, 95% CI = [1.14–5.58], P = 0.0224]

Nicotine replacement therapy and counseling for vaping cessation

- Randomized to 28-days of combination NRT + supportive booklet or Quitline referral (N=30)
- Exploratory aim evaluated abstinence (7-day point-prevalence) at end of treatment
- 50 % (n = 15) dual users; 50 % (n = 15) were mono-vapers of whom 8 previously smoked
- 6/18 (33.3 %) in intervention group reported abstinence vs. 0 in control group (Fisher = 5.00, p =.057).

This is Quitting (Truth Initiative)

- Text “DITCHVAPE” to 88709
- This is Quitting is tailored based on age (within 13 to 24 years old) and product usage to give teens and young adults appropriate recommendations about quitting

Caponnetto P, Campagna D, Ahluwalia JS, Russell C, Maglia M, Riela PM, Longo CF, Busa B, Polosa R. Varenicline and counseling for vaping cessation: a double-blind, randomized, parallel-group, placebo-controlled trial. BMC Med. 2023 Jul 5;21(1):220. doi: 10.1186/s12916-023-02919-2. PMID: 37403047; PMCID: PMC10321010.
Palmer AM, Carpenter MJ, Rojewski AM, Haire K, et al. Nicotine replacement therapy for vaping cessation among mono and dual users: A mixed methods preliminary study. Addict Behav. 2023 Apr; PMID: 36549102

Effectiveness of e-cigarettes (not FDA-approved) on smoking cessation

Clinical trial (England): E-cigarettes were more effective than NRT at 12-month abstinence.

- 1-year abstinence: 18.0% with e-cigarette; 9.9% with NRT (RR, 1.83; 1.30 to 2.58; P<0.001)
- Among participants with 1-year abstinence, 80% were still using e-cigarettes at 52 weeks

Cochrane review (2024)

- People are more likely to stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy (7 studies, 2544 people), or e-cigarettes without nicotine (6 studies, 1613 people)
- May help more people to stop smoking than no support or behavioral support only (9 studies, 5024 people)

American Thoracic Society CPG (2020) For tobacco-dependent adults, ATS CPG suggest varenicline over electronic cigarettes (conditional recommendation, very low certainty in the estimated effects)

Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2016;(9):CD010216.
Wang RJ, Bhadriraju S, Glantz SA. E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis. Am J Public Health. 2021.
Hajek P, Waller AP, Przulj D, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629–637.
Lindson N, Butler AR, McRobbie H, Bullen C, Hajek P, et al. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2024, Issue 1
Frank T. Leone et al; *Am J Respir Crit Care Med* 2020 e5-e31.

Summary of pharmacotherapy

When initiating pharmacotherapy to treat tobacco dependence strongly consider:

Initiating treatment with varenicline

- The tobacco cessation clinical pathway (American College of Cardiology): consider adding nicotine to varenicline for individuals not successful with NRT or varenicline alone

Extending treatment beyond 3 months after quit date

***This includes patients with substance use disorder and psychiatric disorders*

***This includes initiating treatment with individuals not ready to set a quit date*

Leone FT et al. Initiating Pharmacologic Treatment of Tobacco Dependence in Adults: An Official ATS Clinical Practice Guideline. Am J Respir Crit Care Med 2020; 2020;202(2):e5-e31

Anthenelli, R.M., et al., *Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial.* Lancet, 2016. **387**(10037): p. 2507-20.

Rohsenow, D. J., Tidey, J. W., Martin, R. A., Colby, S. M., Swift, R. M., Leggio, L., Monti, P. M. *Varenicline versus nicotine patch with brief advice for smokers with substance use disorders with or without depression: effects on smoking, substance use and depressive symptoms.* Addiction; Oct2017

Ebbert JO, et al. Effect of Varenicline on Smoking Cessation Through Smoking Reduction – A Randomized Clinical Trial. JAMA 2015;313(7):687-694.

Barua RS, et al. *2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents*. J Am Coll Cardiol. 2018 Dec 17;72(25):3332–65.

Maryland Tobacco Quitline Services

Tobacco Users

5 interactions via outbound phone, inbound chat, text or group video scheduling (3 1:1, 2 group)

Unlimited inbound support via phone, text & chat

Expert led online courses, articles and trackers centralized in a digital dashboard experience

- *Medicaid – 4 weeks combo therapy*
- *Non-Medicaid – 12 weeks combo therapy*

Pregnant Tobacco Users

7 interactions pregnancy
Online/chat

Tobacco Users with Behavioral Health Conditions

7 Calls or as many calls necessary

12 weeks of combination NRT (patches, gum and lozenges)

Youth

4 Calls or as many calls necessary

No NRT

Currently developing a youth vaping curriculum

Stand Alone Web

12 weeks of combination NRT (patches, gum and lozenges)

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TOBACCO

Easy steps to help patients break free

DOCUMENT

- ☐ Ask your patient: *Have you ever used any tobacco products? Vapes, e-cigarettes?*
- ☐ In Epic: **Vitals → Edit Tobacco Use**. Don't forget to document vaping!

EDUCATE

- ☐ Ask your patient: *Can I refer you to the UMMC Tobacco Health Practice?*
  - ☐ No quit dates
  - ☐ Judgment-free zone
  - ☐ Affordable medicines
  - ☐ Whole lung health exam

REFER

- ☐ In a visit or encounter, type "**smoking**" into order box (lower left-hand corner)
- ☐ Double-click on the 1st option **(REF139)** and then select **MTC Pulmonary**
- ☐ Staff: **Pend** referral to attending provider
- ☐ Providers: choose a **tobacco** diagnosis code (F17.200s)

Other options: call 410-328-8141, email Sherri Webster (SWebster@som.umaryland.edu), or refer to the Maryland Quitline (REF100)

Thank you for your referrals! Questions?

Contact Julia Melamed: 443-827-3933, Julia.Melamed@umm.edu, or TigerConnect

Flip for more info →

Frequently Asked Questions

Why is this important?
Tobacco use is a chronic disease and a leading cause of death and disability in the United States. We do not ask patients with diabetes or COPD to get better on their own. Patients with tobacco use disorder need the same level of care.

Who is eligible for treatment?
Anyone 16+ who uses tobacco or nicotine. You do not have to feel "ready" to stop.

Why is it hard to stop using tobacco?
Tobacco contains nicotine, which is even more addictive than opioids. Nicotine manipulates the brain's "survival center" and tells users that as long as the brain sees nicotine, it will feel safe. Stopping tobacco can feel like going against a basic instinct.

What if my patient says "I'm not ready" or "I want to do this on my own"?
Most people who use tobacco would like to stop but struggle to fight the instinct without expert help. Stopping "cold turkey" is uncomfortable and usually unsuccessful long-term. Patients may be more open to treatment if they know that the clinic can help them breathe better and will not force them to stop using tobacco.

What if my patient is elderly or has cancer?
It is never too late to stop using tobacco. Patients with cancer who stop using tobacco after diagnosis are much more likely to have good outcomes.

Is vaping a safe alternative to smoking?
No! Vapes/e-cigarettes contain very high nicotine levels, heavy metals, and toxic flavorings. They can cause lung injury (EVALI). Marijuana vapes are also dangerous.

Is treatment expensive?
The clinic accepts most insurance plans and can provide some free medications.

What happens during an appointment?
It is a private visit between the patient, the provider, and a tobacco coach. We talk about breathing, the tobacco journey, and how nicotine affects the brain. If patients are eligible, we offer **lung cancer screening**. We create a medication plan and call the patient after the appointment to offer ongoing support.

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We've moved!

UMMC Tobacco Health Practice
Pulmonary Clinic
800 Linden Ave, 9th Floor
Baltimore, MD 21201

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Maryland Tobacco Control Resource Center

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Thank you! Questions?

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UMMidtown.org/TobaccoHealth

MARYLAND TCRC Tobacco Control Resource Center