"I don't dig your cig": Strategies for tobacco cessation

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Disclosure statement

- Dr. Nigro has no financial relationships with ineligible companies

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Self-assessment question 1

Which patient characteristic supports initiation of combination therapy for smoking cessation?

A. Age < 65 years
B. Presence of 3+ chronic conditions
C. Heavy smoker with high dependence
D. Patient who failed NRT patch therapy previously

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Self-assessment question 2

When should a patient begin varenicline relative to their quit date if they are following an approach with a traditional fixed quit date?

A. 1 week prior
B. 3 days prior
C. 8-35 after starting therapy
D. The same day

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Self-assessment question 3

Which of the following combinations is the most effective for smoking cessation?

A. Combination NRT
B. NRT patch + varenicline
C. Bupropion SR + patch
D. Varenicline + e-cigarettes

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Learning Objectives

1. Recall the medicinal uses of tobacco
2. Describe the cycle of tobacco addiction
3. Identify strategies for counseling patients on the behavioral and cognitive techniques recommended for tobacco cessation
4. Compare the safety and efficacy of FDA approved pharmacotherapies for tobacco cessation
5. Discuss recommendations from national practice guidelines for tobacco cessation and apply them to a patient case

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A (brief) history of tobacco

- *Nicotiana tabacum, Nicotina rustica*
- Medicinal uses
  - Whitening toothpaste
  - Insecticides
  - Poultice
  - Laxative
  - Analgesia
  - Allergen relief
- Ceremonial uses

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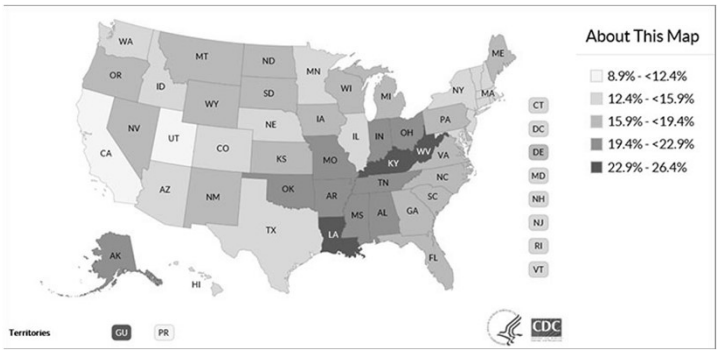
Prevalence of Current Smokers



- 2020 – **12.5%** of adults smoked in the US
- Decline since 2005 when 20.9% of adults smoked

https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

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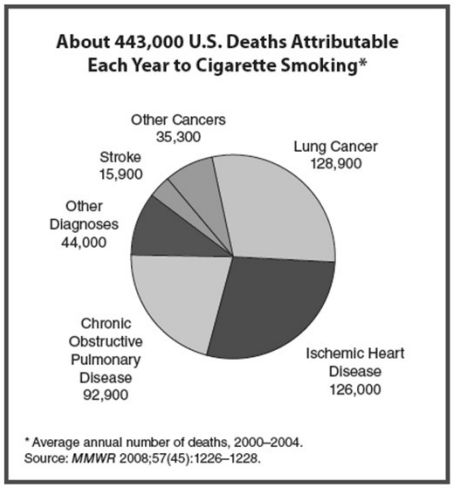
Consequences of Tobacco Smoking

- Remains the leading cause of **preventable** deaths
- Accounts for 1 out of every 5 deaths in the US
- More than 16 million Americans live with a smoking-related disease



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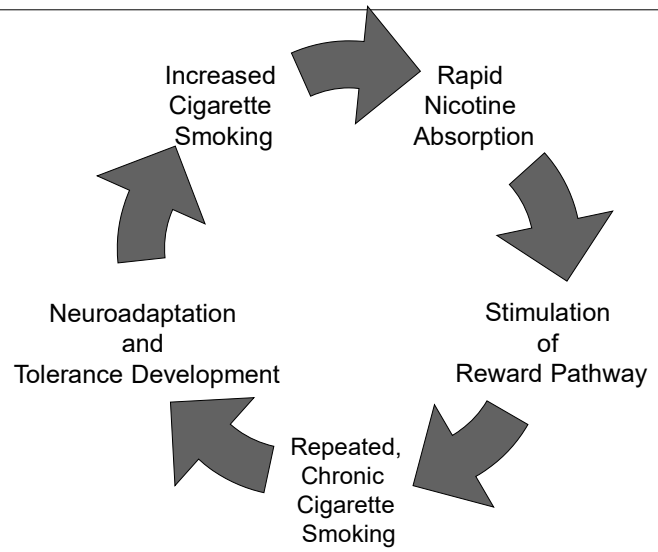
The Cycle of Tobacco Addiction



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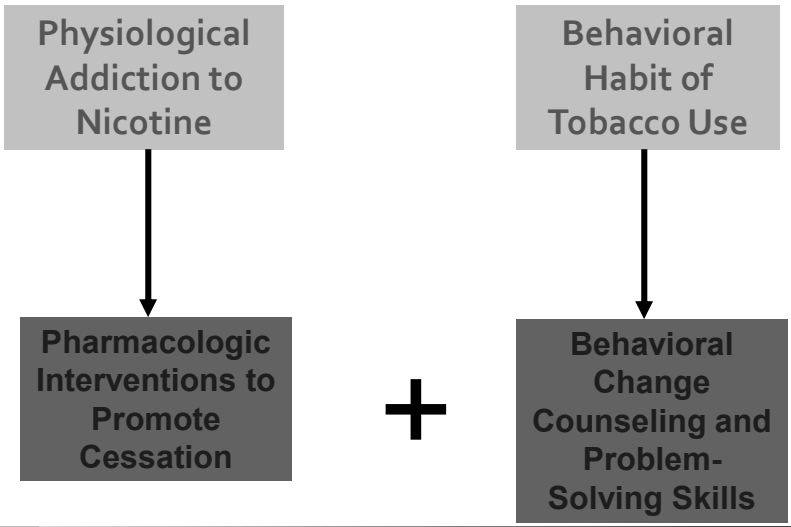
Tobacco Dependence is Multifactorial



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Foundations of Tobacco Dependence Treatment

- **Screen all patients** for tobacco use and assess for potential diagnosis of tobacco dependence
- Diagnosis of tobacco dependence should be on the patient's problem list
- Encouraging a patient to stop smoking is insufficient. All patients should be provided with evidence-based treatment to help them stop
- Tobacco dependence interventions require longitudinal follow-up, akin to management of other chronic illnesses

Leone FT et al. Initiating pharmacologic treatment in tobacco-dependent adults. Am J Resp Crit Care Med 2020;202:e5-e31.

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BEHAVIORAL INTERVENTIONS

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The 5 A's: A framework to engage patients

1. ASK about tobacco use
2. ADVISE to quit
3. ASSESS willingness to make a quit attempt
4. ASSIST in quit attempt
5. ARRANGE follow-up

Model assumes the patient is ready to quit prior to initiating pharmacotherapy

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Preparing to Quit

- Phone-a-friend
- Pros and cons list
- Motivating factors
- Reflections on prior quit attempts
- Initiation of certain pharmacotherapies
- Address concerns of the patient
- Positive self-talks
- Removing reminder of smoking
- Tobacco use log and coping mechanisms

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Tobacco Use Log (pack wrap)

Date / Time	Situation / Emotions	Score
8/14 2am	Woken up by crying infant, irritable	3
8/14 6am	Woke up tired, didn't sleep well, groggy	2
8/14 8:30a	On my way to work, noticed that I lit up at the stop light, relaxed	1

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Coping Strategies

Trigger	Coping Mechanism
Coffee	Different flavor or brand, switch to tea, change morning pattern, use a flavored creamer
Alcohol	Avoid, limit quantity, change drink
Stress	Deep breathing, imagery, phone-a-friend
Oral gratification	Cigarette substitutes: straw, pretzel rods, carrot sticks
After meals	Get up from table, ban smoking in house, have a mint, brush teeth
Other smokers	Set rules, notify others of quit attempt, ask others to refrain from smoking around you

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Action Phase

- Quit date through 6 months
- Implementation of cognitive and behavioral strategies discussed during planning
- Continued identification of triggers and coping strategies
- Social support
- Initiation of pharmacologic treatments
- Slips vs. relapse

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Alternative Approach to “Ready to Quit”

- 5 A’s framework established need for patient to be “ready to quit” on a set quit date prior to initiating pharmacotherapy
- Mounting evidence suggested starting pharmacotherapy **prior to** “readiness to quit” is effective and is now acceptable clinical practice
  - Patient may not be ready to quit but willing to try pharmacotherapy
  - Shift goals of care away from the outcome of quitting smoking and towards mediating compulsion to smoke
  - Patient goal shifts from complete abstinence to willingness to consider abstinence attempt
  - Pharmacotherapy becomes an intervention to increase readiness to quit
  - Increases the number of patients that will go on to stop smoking
  - Variability in how long “pretreatment” is needed, pushing to set a quit date too soon may be counterproductive
  - Studies support varenicline and NRT in this strategy

Leone FT et al. Initiating pharmacologic treatment in tobacco-dependent adults. Am J Resp Crit Care Med 2020;202:e5-e31.

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FIRST-LINE PHARMACOTHERAPIES- NICOTINE REPLACEMENT THERAPY

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FDA Approved Therapies for Tobacco Cessation

- Nicotine replacement therapy (NRT)
  - Patch (Nicoderm and various generics)
  - Gum (Nicorette and various generics)
  - Lozenge (Nicorette and various generics)
  - Nasal spray (Nicotrol NS)
  - Oral inhaler (Nicotrol)
- Varenicline (Chantix)
- Bupropion SR (Zyban)

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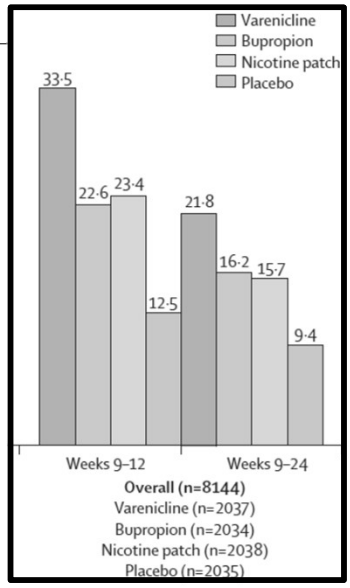
Efficacy of First-line Monotherapy



Comparison	24-week abstinence (OR, 95% CI)
Varenicline vs. placebo	**2.74 (2.28 to 3.30)**
Bupropion vs. placebo	**1.89 (1.56 to 2.29)**
Nicotine patch vs. placebo	**1.81 (1.49 to 2.19)**
Varenicline vs. nicotine patch	**1.52 (1.29 to 1.78)**
Bupropion vs. nicotine patch	1.04 (0.88 to 1.24)
Varenicline vs. bupropion	**1.45 (1.24 to 1.70)**

Anthenelli et al. 2016

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Efficacy of Combination Therapies

Comparison	52-week abstinence (OR, 95% CrI)
Varenicline vs. combination NRT	1.06 (0.75 to 1.48)
Combination NRT vs. single NRT- patch	**1.43 (1.08 to 1.91)**
Combination NRT vs. single NRT- gum	**1.63 (1.21 to 2.20)**
Combination NRT vs. single NRT- 'other'	**1.34 (2.40 to 3.47)**
NRT patch + bupropion SR vs. NRT patch	1.30 (1.00 to 1.80)
Varenicline + NRT patch vs. varenicline	**1.98 (1.25 to 3.14)**

Cahill K et al. 2013
Koegelenberg 2014

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  - Gum (Nicorette and various generics)
  - Lozenge (Nicorette and various generics)
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  - Oral inhaler (Nicotrol)
- Varenicline (Chantix)
- Bupropion SR (Zyban)

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Nicotine Replacement Therapy (NRT)

- RX: Nasal spray, oral inhaler
- OTC: patch, gum, lozenge, (≥ 18y)
- Begin therapy on quit date or “preload” prior to quit date
- Initial therapy for 8-12 weeks but some will require indefinite use of NRT, this is safer than smoking

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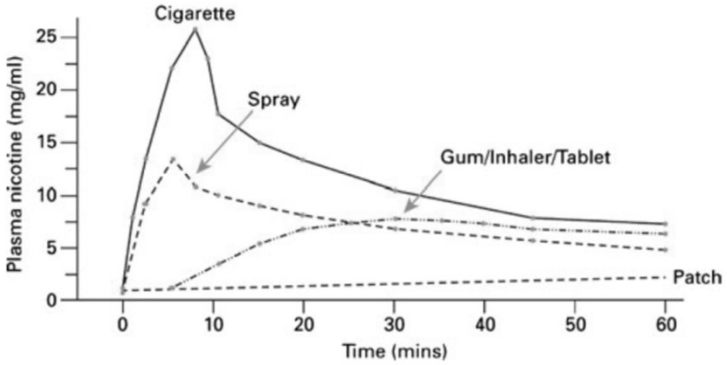
Absorption of Nicotine, Long vs. Short-acting Formulations



Long-acting	Short-acting
Patch	Gum
	Lozenge
	Nasal spray
	Oral spray

Combination NRT =
patch daily
+
1 short-acting NRT PRN

McNeill JJ et al. Cardiovasc Drug Ther.2010. A head of print. DOI: 10.1007/s10557-010-6246-80.

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NRT Dosing Guide

Drug	Dosing
Patch	≤10 cig/d: 14mg/d x 6w, 7mg/d x 2w >10 cig/d: 21mg/d x 6w, 14mg/d x 2w, 7mg/d x 2w
Lozenge	1st cigarette <30 min: 4mg 1st cigarette >30 min: 2mg 1 q1-2h X 6 w, 1 q2-4h X 3 w, 1 q4-8h X 3w (max 5 per 6h, 20 per day)
Gum	1st cigarette <30 min: 4mg 1st cigarette >30 min: 2mg 1 q1-2h X 6 w, 1 q2-4h X 3 w, 1 q4-8h X 3 w (max 24 pieces/d)
Nasal spray	1 -2 doses per hour (each dose = 2 sprays, 1 in each nostril), increasing as needed for symptom relief (min 8 sprays/day, max 40 sprays/d or 5 sprays/hr) 6-8 w of therapy followed by gradual taper
Oral inhaler	6-16 cartridges/d, 1 every 1-2h, gradual taper over last 6-12w

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NRT- Notable Adverse Effects, Warnings and Precautions

Drug	Adverse Effects / Safety
Patch	Common AE: Local skin reactions, headache, vivid dreams, insomnia **Caution** in patients with skin diseases such as psoriasis or eczema, or in those with allergy to adhesives. May contain aluminum – remove prior to MRI.
Lozenge	Common AE: Nausea, hiccups, heartburn, headache, coughing, flatulence **Caution** in those on a sodium-restricted diet
Gum	Common AE: Mouth soreness, hiccups, dyspepsia, jaw aches **Caution** in patients with extensive dental work, jaw disorders or those on a sodium-restricted diet
Nasal spray	Common AE: Headache (18-26%), nasal discomfort (94%), nasal congestion, transient changes in smell and taste. **Avoid** in those with chronic nasal disorders (allergy, rhinitis, polyps, sinusitis) or with severe reactive airway disease. Reduced absorption in patients with common cold and rhinitis. Exacerbations in asthmatics has been reported.
Oral inhaler	Common AE: Mouth and throat irritation (up to 66%), coughing (32%), rhinitis (23%), dyspepsia (18%) **Caution** in patients with asthma or COPD, other NRTs preferred.

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NRT and Cardiovascular Disease

- Nicotine leads to sympathomimetic stimulation
  - Transient changes in HR (10-15 bpm) and BP (5-10 mmHg) increase myocardial work
- Cigarette smoking causes hypercoagulability, exposure to oxidizing chemical and free radicals – LDL oxidation, inflammation, endothelial dysfunction
- NRT delivers less nicotine and at a more controlled rate than smoking
- Historically trials excluded patients with recent MI (2 weeks), unstable angina or serious arrhythmias
- Reasonable to be cautious in these patients but ACC 2018 Guidelines do not comment otherwise
- Risks of NRT appears low and **MUCH LESS** than continued smoking

Benowitz et al. JACC.1997;29:1422-31.
Barua RS. JACC 2018; DOI: 10.1016/j.jacc.2018.10.027

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Counseling Highlights- Nicotine Gum and Lozenge

- Technique essential for success
  - Gum: chew-park-chew ~30 min
  - Lozenge: Park and dissolve ~ 20-30 min
- Refrain from food and beverages 15 min prior and during use due to pH alterations
- Chewing rapidly/swallowing can cause excessive side effects
- Advantage in patients with oral cravings

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Counseling Highlights- Nicotine Nasal Spray

- Requires priming with first use and if not used within 24h
- Insert tip into nostril, exhale through mouth and spray but do not inhale through nostril while spraying. Wait several minutes before blowing nose
- NRT with highest dependency risk

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Counseling Highlights – Nicotine Oral Inhaler

- Inhale gently to back of throat not into lungs
- Depleted after ~ 20 minutes of active puffing
- Open cartridge retains potency for 24h
- May deliver less nicotine when <59° F
- Refrain from food and beverages 15 min prior and during use due to pH alterations
- Benefit for hand-to-mouth habit

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VARENICLINE AND BUPROPION

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FDA Approved Therapies for Tobacco Cessation

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  - Gum (Nicorette and various generics)
  - Lozenge (Nicorette and various generics)
  - Nasal spray (Nicotrol NS)
  - Oral inhaler (Nicotrol)
- Varenicline (Chantix)
- Bupropion SR

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Varenicline - Dosing

- MOA: Partial, competitive nicotinic receptor agonist at α-4 β-2 receptor leading to moderate and consistent dopamine levels
- Dosing: 0.5mg daily x3d then BID x 3d then 1mg BID thereafter x 12w initially, after a meal and with water
- Renal dose adjustments: 0.5mg BID for CrCl<30; 0.5mg daily in hemodialysis
- Nausea intolerance: 0.5mg BID
- Initiation
  - Traditional fixed quit date: Start 1 week prior to quit date
  - Alternative flexible quit date: Set quit date between days 8-35 after starting therapy
  - Alternative gradual quit date: Goal to reduce smoking by 50% by week 4, additional 50% by week 8, and continued reduction with goal abstinence by week 12

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Varenicline – ADRs, Warnings, Precautions

- Common (>10%) ADRs
  - Nausea (16-40%), vomiting (5-11%), headache (12-19%), insomnia (9-19%), abnormal dreams (8-13%), irritability (11%), depression (4-11%)
- Contraindicated if prior skin reaction to varenicline
- CNS depression, sleep walking
  - Post marketing traffic accidents, accidental injuries, sleep walking
- Cardiovascular risks
  - Notify HCP if worsening cardiac symptoms
  - EVITA trial in ACS patients, ACC/AHA endorses use regardless of CVD history
- Increased effects of alcohol consumption - reduce intake until it is known how this impacts the individual
- Seizures - caution in those with seizure history or reduced threshold

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Varenicline- Neuropsychiatric Effects Precaution

- Case reports and post-marketing surveillance of neuropsychiatric events prompted FDA review
- Possibly association between suicidal events and bupropion or varenicline, regardless of psychiatric history or medication use, but complicated by nicotine withdrawal
- Subsequent trials (EAGLES) found no increase in risk
- **FDA concluded risk is lower than anticipated and BBW was removed in December 2016**
- Warning remains
  - Monitor for changes in behavior, agitation, depressed mood, suicidal ideation and behavior
  - Stop drug and contact healthcare provider immediately

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EAGLES Trial

- Largest RCT in smoking cessation to date – requested by the FDA
- 8144 smokers regardless of psychiatric history
- NRT vs. varenicline vs. bupropion SR x 12 weeks
- Outcome: moderate to severe neuropsychiatric events

	Non-psychiatric	Risk difference vs. placebo	Psychiatric	Risk difference vs. placebo
Varenicline	1.3%	-1.28 (-2.40 to -0.15)	6.5%	1.59 (-0.42 to 3.59)
Bupropion SR	2.2%	-0.08 (-1.37 to 1.21)	6.7%	1.78 (-0.24 to 3.81)
Nicotine patch	2.5%	--	5.2%	--

- Varenicline was superior in abstinence vs. other arms
  - OR 3.61 vs. placebo; OR 1.75 vs. bupropion; OR 1.68 vs. nicotine patch
- Bupropion & nicotine patch superior in abstinence vs. placebo by OR 2.07 and OR 2.15, respectively

Anthenelli RM et al. Lancet 2016;387:2507-20.

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  - Oral inhaler (Nicotrol)
- Varenicline (Chantix)
- Bupropion SR

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Bupropion SR - Dosing

- Unclear mechanism; inhibits dopamine and NE re-uptake and weak antagonist at nicotine receptors
- 150mg daily X 3d then BID thereafter x12w
  - Start 1 week prior to quit
  - If unsuccessful by week 7 may change plan or d/c
  - May reduce to 150mg daily if intolerable side effects
  - Reduce dose to 150mg every other day in severe cirrhosis
- Caution with renal impairment (GFR<90mL/min)- no specific adjustments provided
- Do not crush, swallow whole

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Bupropion SR – Safety

- Common (<10%) ADRs
  - Tremor (up to 21%), dry mouth (10-28%), headache (25-34%), agitation (up to 32%), dizziness (6-22%), sweating (5-22%), constipation (up to 26%), N/V (23%), runny nose, rhinitis (13%)
  - May try reduced dose if side effects occur (150mg daily)
- Contraindications:
  - Seizure disorder, current or prior anorexia or bulimia, use within 14d of MAOi, abrupt discontinuation of benzodiazepines, barbiturates, antiepileptics or alcohol
- Seizure risk is dose related, gradual dose increases, do not exceed max 300mg/d
- Neuropsychiatric warning like varenicline
- May lead to elevations in blood pressure (2.5%), less common to require d/c

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Pharmacokinetic Interactions

- Polycyclic aromatic hydrocarbons in tobacco smoke induce CYP1A2
  - Increase in CYP1A2 substrates upon cessation
  - Ex. clopidogrel, clozapine, caffeine, theophylline, olanzapine, fluvoxamine
- Bupropion is metabolized by CYP2B6
  - Inducers: ritonavir, lopinavir, efavirenz
  - Inhibitors: ticagrelor, clopidogrel
- Bupropion and metabolites inhibit CYP2D6
  - Increase CYP2D6 substrates upon initiation
  - Ex. Nortriptyline, paroxetine, haloperidol, propafenone, metoprolol

Fiore et al. (2008). *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: USDHHS, PHS.
Zyban [Package insert].Research triangle Park, NC.GSK. 07/2019.

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Pharmacodynamic Interactions

- Concurrent smoking and use of combination hormonal contraceptives (pill, patch, ring) increases risk of thromboembolism, stroke and myocardial infarction
  - **Do not use (unacceptable health risks)** combination hormonal contraception in patients ≥35y of age and smoke ≥15 cigarettes per day
  - **Not recommended (theoretical or proven risks usually outweigh advantages)** in patients ≥35y of age and smoke <15 cigarettes per day
- NRT can cause tachycardia which may attenuate antihypertensive drugs' effects

Fiore et al. (2008). *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: USDHHS, PHS
https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf.

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CLINICAL PRACTICE GUIDELINES AND SUMMARY

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Who Should Receive Pharmacotherapy

All patients* willing to quit or willing to try pharmacotherapy should be offered pharmacotherapy

**consider contraindications and patient characteristics to tailor selection*
** consider special populations- pregnancy, adolescents, light smokers*

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What Pharmacotherapies?

- Consider relative efficacy and safety of first-line drugs
  - What is the most effective therapies? Which are second?
  - Can you list the contraindications and main safety parameters for each first-line drug?
  - ATS Guidelines: Varenicline is strongly recommended over NRT or bupropion SR
- Consider combination therapy
  - Which combinations?
  - ATS Guidelines: varenicline + nicotine patch conditionally recommended over varenicline alone
    - Failed monotherapy, heavy smokers or high nicotine dependence, patient preference, difficulty with adherence to 2 products, different direction
- E-cigarettes are not currently recommended as an intervention to quit smoking
  - ATS Guidelines: Varenicline conditionally recommended over e-cigarettes

Leone FT et al. Initiating pharmacologic treatment in tobacco-dependent adults. Am J Resp Crit Care Med 2020;202:e5-e31.c

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When should the pharmacotherapy be started? For **How Long**?

- Traditional dosing relative to quit date
  - Which drugs?
- Alternative dosing in patients not ready to quit but willing to try medication and reduce
  - Which drugs?
  - ATS Guidelines: Strong recommendation to start even if the patient isn't ready to quit yet
- Duration is success dependent, but evidence supports longer duration vs. shorter/initial course
  - ATS Guidelines: strong recommendation for treatment of 12 weeks or more versus shorter treatment

Leone FT et al. Initiating pharmacologic treatment in tobacco-dependent adults. Am J Resp Crit Care Med 2020;202:e5-e31.c

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American College of Cardiology Expert Consensus Decision Pathway for Tobacco Cessation 2018

- Applicable to adults who smokes combustible cigarettes, **with emphasis on people with CVD**
- Pharmacotherapy should be offered to every patient willing to accept it (with rare exception) including those not ready to quit because it could help motivate them to reducing their smoking and eventually quit.

TABLE 4 Recommended Pharmacotherapy for Smoking Cessation in Patients with CVD

	Outpatient With Stable CVD	Inpatient With ACS
1st line	Varenicline OR combination NRT*	*In-hospital to relieve nicotine withdrawal:* Nicotine patch OR combination NRT* *At discharge:* Combination NRT or varenicline†
2nd line	Bupropion OR single NRT product	*At discharge:* Single NRT product
3rd line	Nortriptyline‡	Bupropion§
If single agent is insufficient to achieve abstinence	Combine categories of FDA-approved drugs: Varenicline + NRT (single agent) Varenicline + bupropion Bupropion + NRT (single agent)	n/a

Barua RS. JACC 2018; DOI: 10.1016/j.jacc.2018.10.027

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Patient case

Melissa is a 34-year-old female that smokes 2 packs per day since she was 19 years old. She walks into the pharmacy and asks you, the pharmacist, if there is a medication that can help her feel more ready to quit. She does not feel ready to set a quite date but wants to try and work towards this goal. What can you discuss with her?

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Patient case

Chad is a 55-year-old male patient with a past medical history including diabetes mellitus type 2, hyperlipidemia, hypertension, and chronic obstructive pulmonary disease. He is currently hospitalized due to a myocardial infarction but has been stabilized. Chad recognizes that quitting smoking is critical to his cardiovascular health and wants to try to quit. According to the American College of Cardiology what smoking cessation strategies can be trialed for Chad?

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Questions?

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