PHARMACOTHERAPY | CONTINUING PHARMACY EDUCATION

Tobacco Use & Dependence

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February 2023

Electronic Tobacco Products

E-Cigarettes, Vaping Devices

Heated Tobacco Products

Combustible Tobacco Products

Cigarettes

Cigars/Cigarillos

Hookah

Pipe

Bidis

Roll-Your-Own

Non-Combustible Tobacco Products

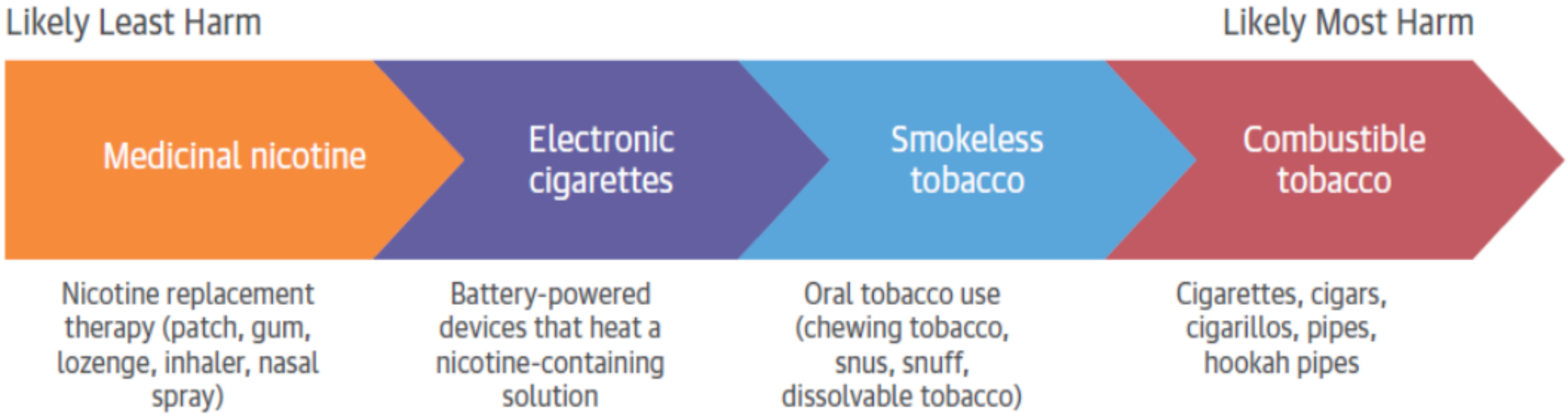
Dissolvable Tobacco

Nicotine Pouch

Smokeless Tobacco

Snus

Risk Continuum of Nicotine-Containing Products



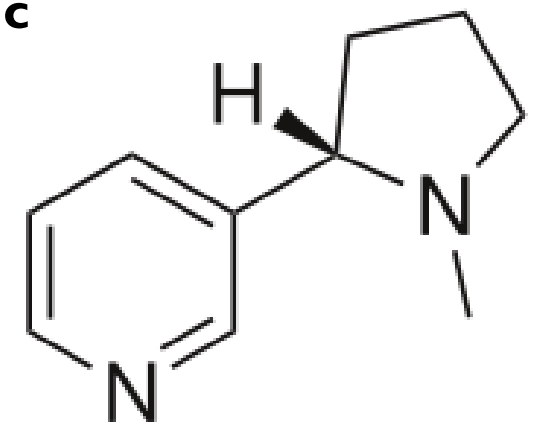
Nicotine comes in many forms, with varying degrees of potential harm to users. Medicinal nicotine, such as that contained in nicotine replacement therapy, is least likely to cause harm, whereas combustible tobacco, such as cigarettes, is most likely to cause harm. It is not known where heat-not-burn tobacco (also known as heated tobacco) products fall on this spectrum given the limited evidence on their health effects.

Chemicals in a cigarette

Nicotine

- Meets the criteria for an **addictive substance**:
  - It induces **psychoactive effects**
  - It is used in a **highly controlled or compulsive manner**
  - **Behavioral patterns** of tobacco use are **reinforced by the pharmacologic effects of nicotine**.

- **The addictive properties of nicotine are well documented**.
- **Nicotine addiction is** a form of **chronic brain disease** resulting from **alterations in brain chemistry**.



Factors Contributing to Tobacco Use

- Tobacco dependence is a result of the interplay of complex processes, including:
  - The desire for the direct pharmacologic actions of nicotine
  - The relief of withdrawal
  - Learned associations
  - Environmental cues (e.g., Advertising, the smell of a cigarette, or observing others who are smoking)

- Physiological factors, such as **pre-existing medical conditions** (e.g., psychiatric comorbidities) & one's **genetic profile**, also can predispose individuals to tobacco use.
  - It has been estimated in twin studies that **40-60% of smoking is heritable**.

Nicotine Pharmacology

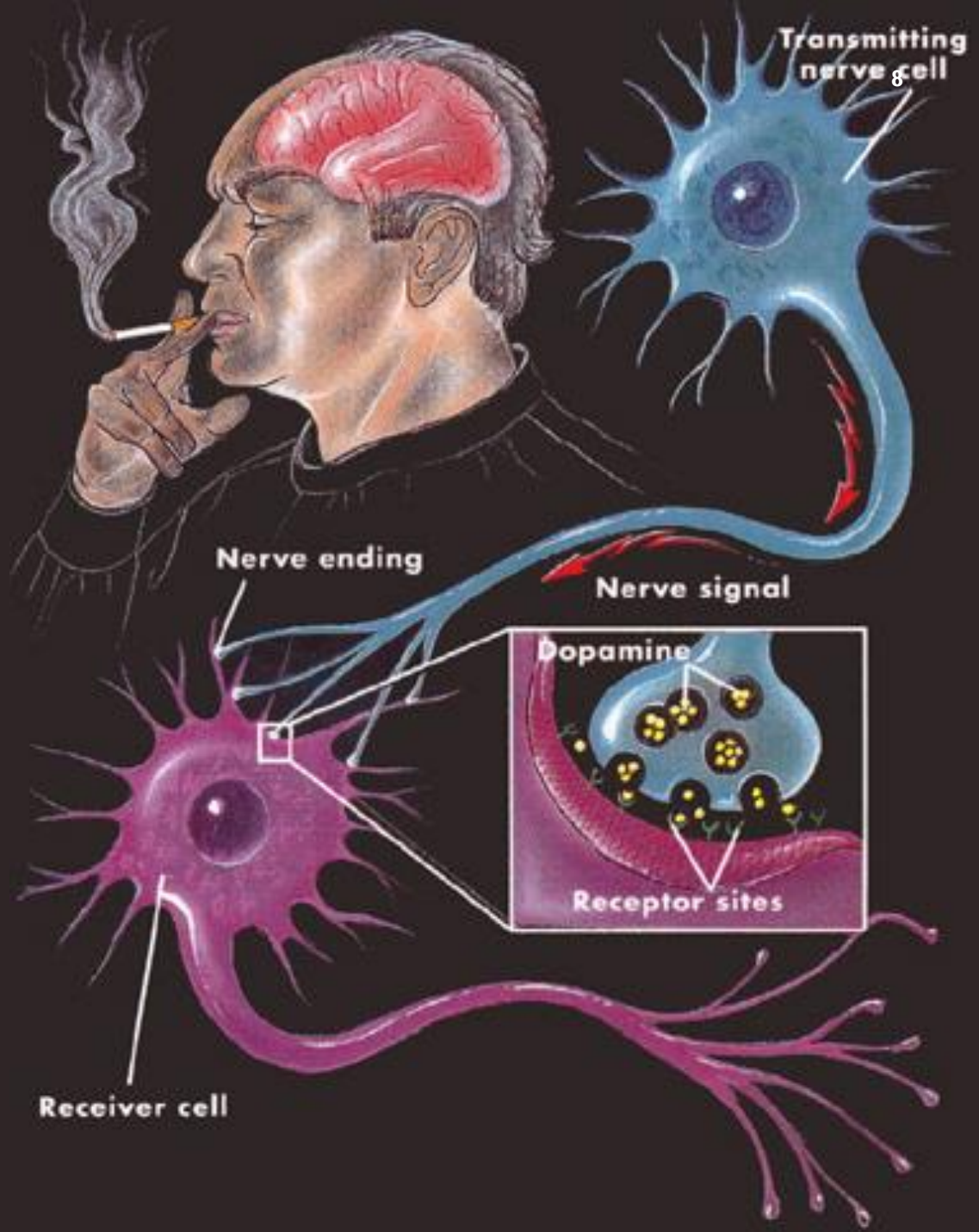
- Nicotine is one of the few **natural alkaloids** that exist in the **liquid state**. Nicotine is a clear, **weak base** that **turns brown & acquires the characteristic odor of tobacco after exposure to air.**

- The rapidity with which nicotine is absorbed & passes through the BBB contributes to its addictive nature. After inhalation, nicotine reaches the brain within seconds. As such, smokers experience nearly immediate onset of positive effects of nicotine. These effects, mediated by **alterations in neurotransmitter levels**, reinforce continued use of nicotine-containing products.

(*Nicotiana tabacum*)

Nicotine stimulates the release of several neurotransmitters:

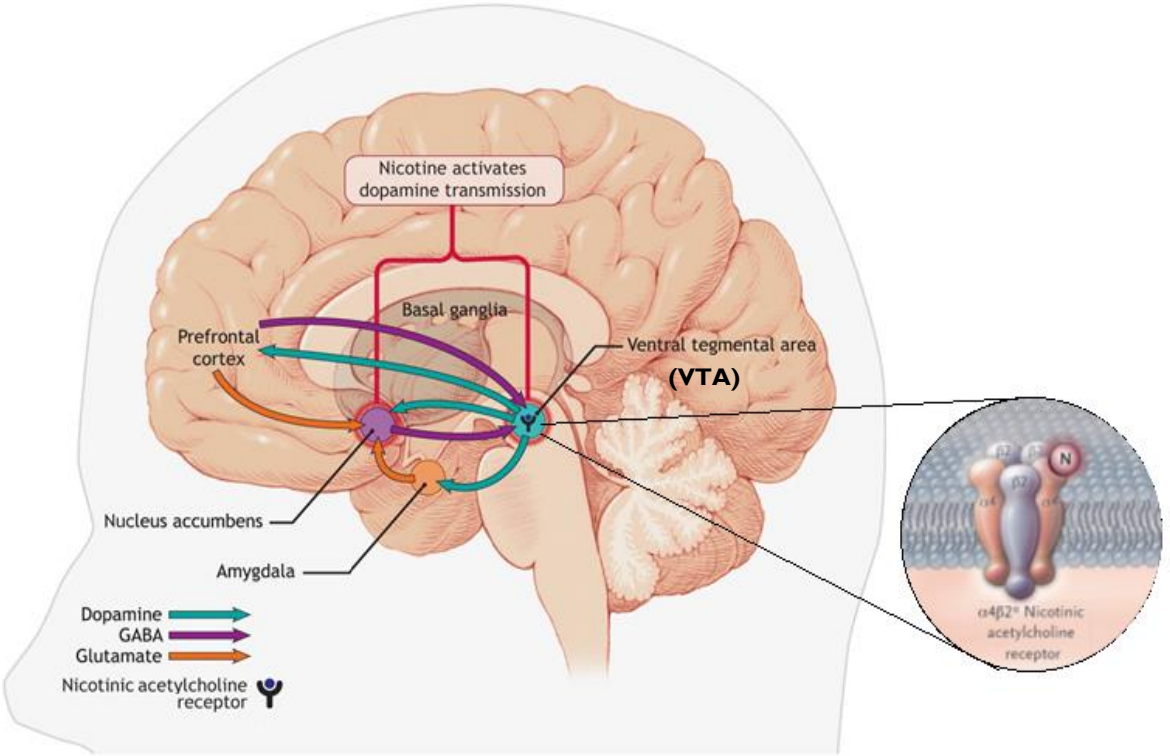
- **Pleasure** (Dopamine)
- **Arousal** (Ach, NEP)
- **Cognitive enhancement** (Ach)
- **Appetite suppression** (Dopamine, NEP, 5-HT)
- **Learning** (Glutamate)
- **Memory enhancement** (Glutamate)
- **Mood modulation** (5-HT)
- **Reduction of anxiety & tension** (β-endorphin & GABA)



Dopamine reward pathway

- Nicotine releases dopamine in the mesolimbic area, the corpus striatum, & Prefrontal cortex.
  - Neurons of the VTA contain **dopamine**, which is released in the nucleus accumbens & in the prefrontal cortex.

- Nicotine also augments both **glutamate release (**facilitates release of dopamine) & **GABA release (**inhibits dopamine release).
  - With long-term exposure to nicotine, some nicotinic cholinergic receptors become desensitized but some do not. As a result, **GABA-mediated inhibitory tone diminishes while glutamate-mediated excitation persists**, thereby increasing excitation of dopaminergic neurons & enhancing responsiveness to nicotine.



- It also increases activity in the prefrontal cortex, thalamus, & visual system, reflecting activation of corticobasal ganglia–thalamic brain circuits (part of the reward network), & releases dopamine in the striatum.

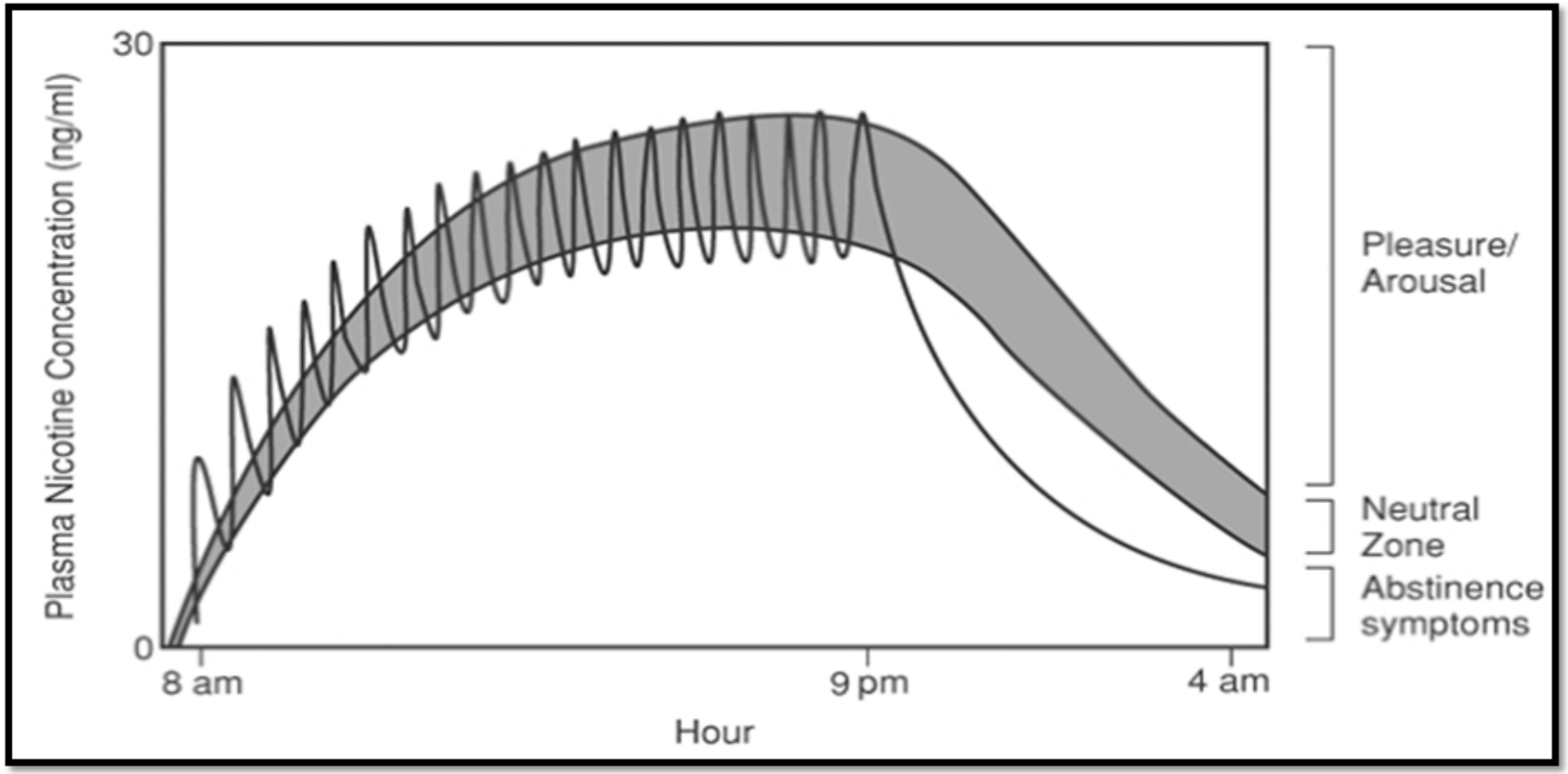
Monamine Oxidase

- MAOs, enzymes located in catecholaminergic & other neurons, catalyze the metabolism of dopamine, norepinephrine, & serotonin. **Condensation products of acetaldehyde in cigarette smoke with biogenic amines inhibit the activity of MAOA & MAOB,** & there is evidence that inhibition of MAO contributes to the addictiveness of smoking by reducing the metabolism of dopamine.

Neuroadaptation

- With repeated exposure to nicotine, neuroadaptation (tolerance) to some of the effects of nicotine develops. As neuroadaptation develops, **the number of binding sites on the nicotinic cholinergic receptors in the brain increases**, probably in response to nicotine-mediated desensitization of receptors. Desensitization is believed to play a role in tolerance & dependence: the symptoms of craving & withdrawal begin in smokers when desensitized $\alpha 4\ \beta 2^*$ nicotinic cholinergic receptors become responsive during periods of abstinence, such as nighttime sleep. Nicotine binding of these receptors during smoking alleviates craving & withdrawal.

Tobacco Addiction Cycle



Cigarette is smoked every 40 minutes

- Smoking behavior in women is more strongly influenced by **conditioned cues & negative affect;** men are more likely to smoke in response to **pharmacologic cues**, regulating their intake of nicotine more precisely than women.

- On average, **women metabolize nicotine more quickly than men**, which may contribute to their increased susceptibility to nicotine addiction & may help to explain **why, among smokers, it is more difficult for women to quit.**

Psychoactive Effects of Nicotine

- Nicotine induces **pleasure & reduces stress & anxiety**.
- Smokers use it to modulate **levels of arousal & to control mood**.
- Smoking **improves concentration, reaction time, & performance of certain tasks**.
  - Relief from withdrawal symptoms is probably the primary reason for this enhanced performance & heightened mood.

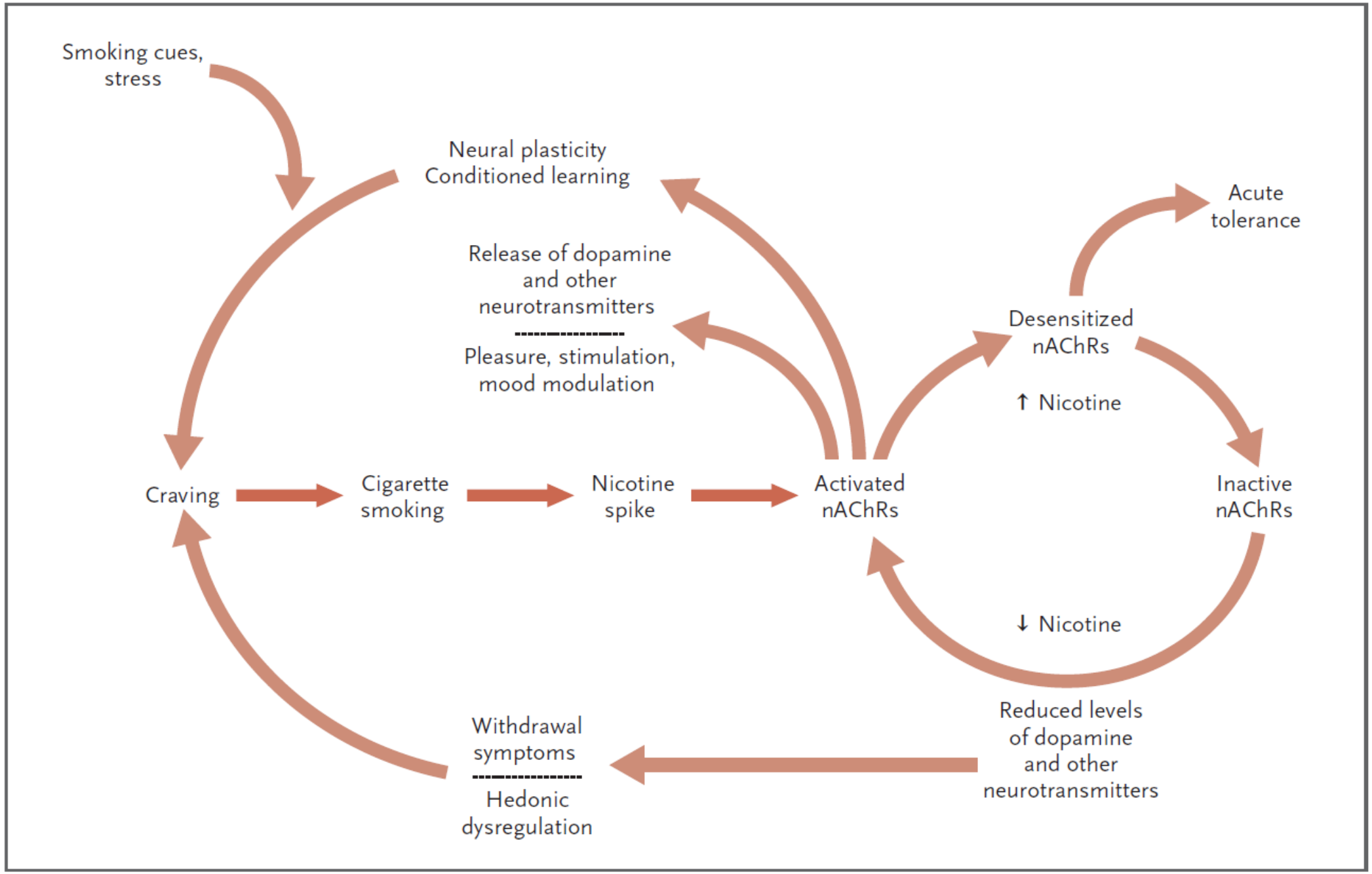
- Cessation of smoking causes the emergence of withdrawal symptoms: irritability, depressed mood, restlessness, & anxiety.
- Anhedonia (feeling that there is little pleasure in life) can also occur with withdrawal from nicotine.

- The basis of nicotine addiction is a combination of positive reinforcements, including **enhancement of mood & avoidance of withdrawal symptoms**.
- In addition, **conditioning** has an important role in the development of tobacco addiction.

Conditioned Behavior

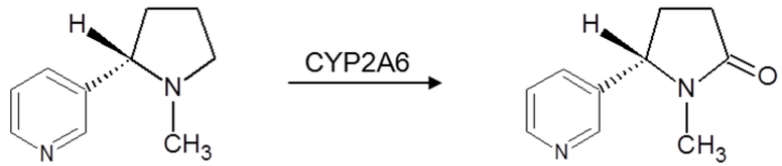
- When a person who is addicted to nicotine stops smoking, **the urge to resume is recurrent & persists long after withdrawal symptoms dissipate**. With regular smoking, the smoker comes to associate specific moods, situations, or environmental factors (**smoking-related cues)** with the rewarding effects of nicotine.
- The association between such cues & the anticipated effects of nicotine, & the resulting urge to use nicotine, constitute a form of **conditioning.**
- Nicotine exposure causes changes in the protein expression of brain cells & in their synaptic connections (neural plasticity) which underlie conditioning.

- The desire to smoke is maintained, in part, by such conditioning. Smokers usually **take a cigarette after a meal, with a cup of coffee or an alcoholic drink, or with friends who smoke.** When repeated many times, such situations become a powerful cue for the urge to smoke.
- Aspects of smoking itself (manipulation of smoking materials, or the taste, smell, or feel of smoke in throat) also become associated with the pleasurable effects of smoking.
- Even unpleasant moods can become conditioned cues for smoking: a smoker may learn that not having a cigarette provokes irritability & that smoking one provides relief. After repeated experiences like this, a smoker can sense irritability from any source as a cue for smoking.


Smoking cues, stress
Neural plasticity
Conditioned learning
Release of dopamine and other neurotransmitters
Pleasure, stimulation, mood modulation
Acute tolerance
Desensitized nAChRs
↑ Nicotine
Craving
Cigarette smoking
Nicotine spike
Activated nAChRs
Inactive nAChRs
↓ Nicotine
Reduced levels of dopamine and other neurotransmitters
Withdrawal symptoms
Hedonic dysregulation

Nicotine Metabolism

- Nicotine is **extensively** metabolized in the **liver** &, to a lesser extent, in the **kidney** & **lung**.
- 70-80% of nicotine is metabolized to **cotinine**, an inactive metabolite.
  - The rapid metabolism of **nicotine ($t_{1/2}$ = 2 h)** to **inactive compounds** underlies tobacco users' needs for frequent, repeated administration.
  - The half-life of **cotinine** is **18–20 h** & for this reason, cotinine is commonly used as **marker** of tobacco use as well as **a marker for exposure to secondhand smoke**.
  - Cotinine cannot, however, differentiate between nicotine from tobacco & nicotine from NRT products.
- Nicotine & other metabolites are excreted in the **urine**.
- **Nicotine crosses the placenta & accumulates in breast milk.**



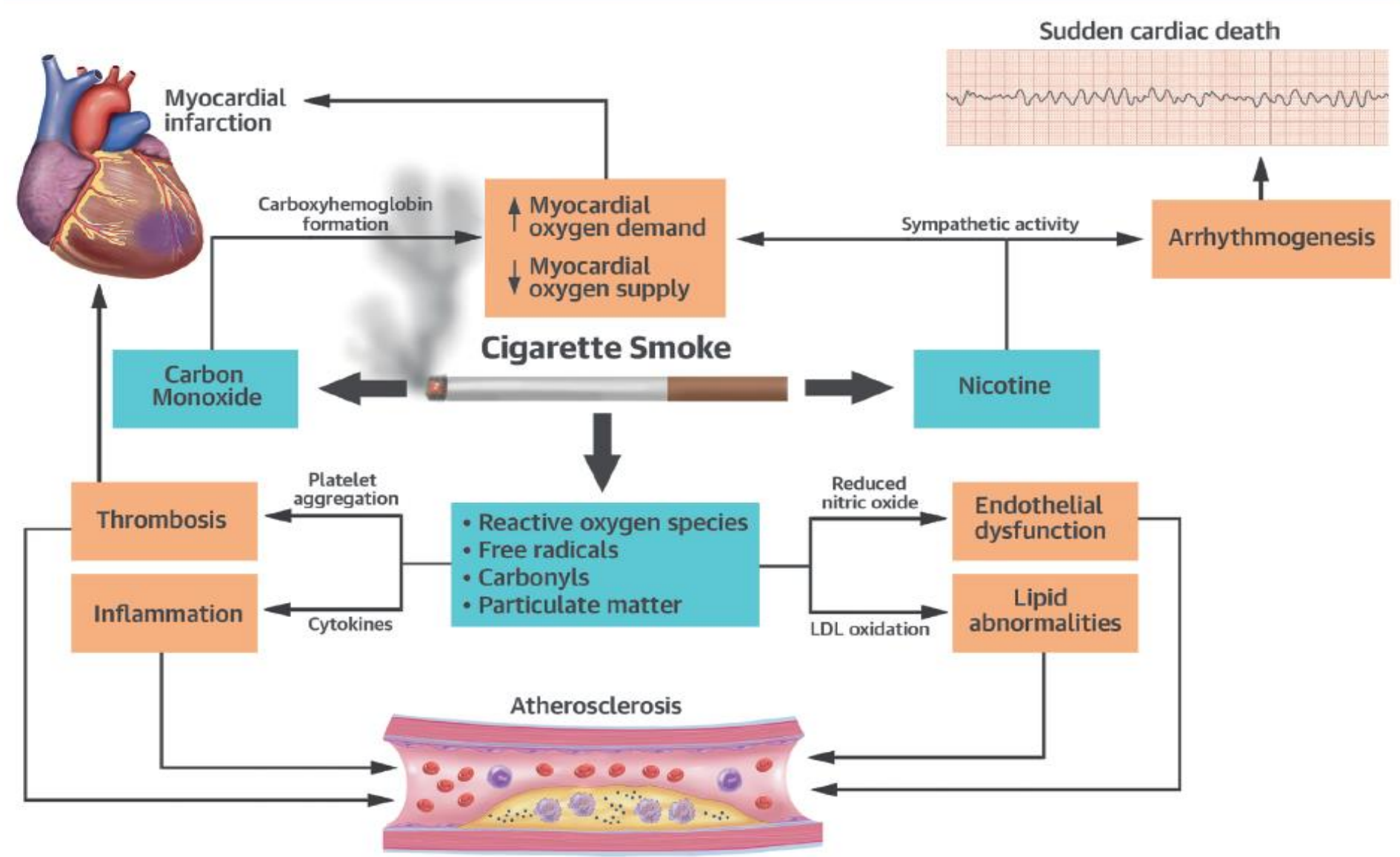
Nicotine Cotinine

Health Consequences of Tobacco Use

All forms of tobacco are harmful, & there is no safe level of exposure to tobacco products.

Cancer	•Acute myeloid leukemia• Bladder• Cervical• Esophageal• Gastric• Kidney• Laryngeal• Lung• Oral cavity & pharyngeal• Pancreatic
Cardiovascular disease	•Abdominal aortic aneurysm• Coronary heart disease (angina pectoris, IHD, MI) • Cerebrovascular disease (TIAs, stroke) • Peripheral arterial disease
Pulmonary disease	•Acute respiratory illnesses• Upper respiratory tract (rhinitis, sinusitis, laryngitis, pharyngitis) • Lower respiratory tract (bronchitis, pneumonia) • Chronic respiratory illnesses• **COPD**• Respiratory symptoms• Poor asthma control• Reduced lung function
Reproductive effects	•↓ **fertility in women**• Pregnancy & pregnancy outcomes• Preterm, premature rupture of membranes• Placenta previa• Placental abruption• Preterm delivery • Low infant birth weight• Infant mortality• Sudden infant death syndrome
Other effects	•Cataract• **Osteoporosis (↓ BMD in postmenopausal women, ↑ risk of hip fracture)** • Periodontitis• PUD (in patients who are infected with H. pylori) • Surgical outcomes • Poor wound healing • Respiratory complications

Smoking & Cardiovascular Disease



Secondhand Smoke Exposure

- **Causes disease & premature death in children & adults who do not smoke.**
- **Children** exposed to secondhand smoke are at a **↑ risk for sudden infant death syndrome, acute respiratory infections, ear problems, & more severe asthma.**
- **Smoking by parents causes respiratory symptoms & slows lung growth in their children.**

- **Exposure of adults** to secondhand smoke has immediate adverse events on the **cardiovascular system** & causes **coronary heart disease & lung cancer.**

- **Eliminating** smoking in indoor spaces **fully protects** nonsmokers from exposure to secondhand smoke.
- **Separating** smokers from nonsmokers, **cleaning the air**, & **ventilating buildings cannot eliminate** exposures of nonsmokers to secondhand smoke.

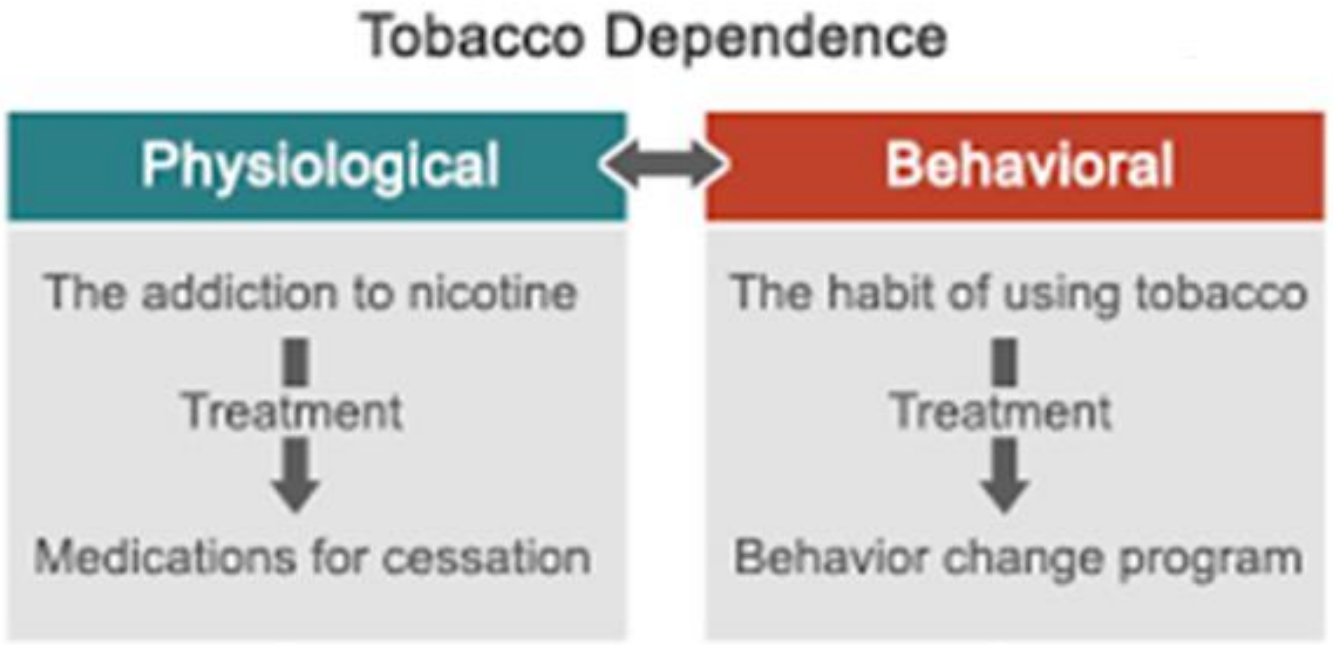
Benefits of Quitting

- Benefits incurred **soon after quitting** (e.g., **within 2 weeks to 3 months**).
  - **Within 1-9 months**, the **ciliary function** of the lung epithelial cells is **restored**; initially, this might result in ↑ coughing as the lungs clear excess mucus & tobacco smoke particulates.
  - **1 year after cessation**, the **excess** risk of **CHD** is ↓ **to half** that of continuing smokers.
  - **After 5-15 years**, the risk of **stroke** is ↓ to a rate **similar** to that of people who are lifetime nonsmokers.
  - **10 years after quitting**, the **chance of dying of lung cancer** is **half** that of continuing smokers.
  - **15 years after quitting**, the risk of **CHD** is ↓ to a rate that is **similar** to that of people who have never smoked.

- Quitting at ages 30, 40, 50, 60 years is associated with 10, 9, 6, 3 years of life gained, respectively.
- On average, cigarette smokers die 10 years younger than do nonsmokers. Persons who quit before age 35 add 10 years of life & have a life expectancy similar to those who have never smoked.

- ↓ in smoking **does not equate** to ↓ in harm; **even low levels of smoking (e.g., 1–4 cigarettes per day) have documented risks** & therefore, a ↓ in the number of cigarettes smoked per day should be viewed as **a positive step toward quitting**, but should **not** be recommended as a **targeted end point**.

Treatment



Although both pharmacotherapy & behavioral counseling are **effective independently**, patients' odds of quitting are substantially ↑ when the two approaches are used simultaneously.

Evaluation of Nicotine Dependence

The Heaviness of Smoking Index

How many cigarettes do you smoke a day?

	Score
10 or fewer	0
11–20	1
21–30	2
31 or more	3

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

	Score
60 minutes	0
31–60 minutes	1
6–30 minutes	2
Within 5 minutes	3

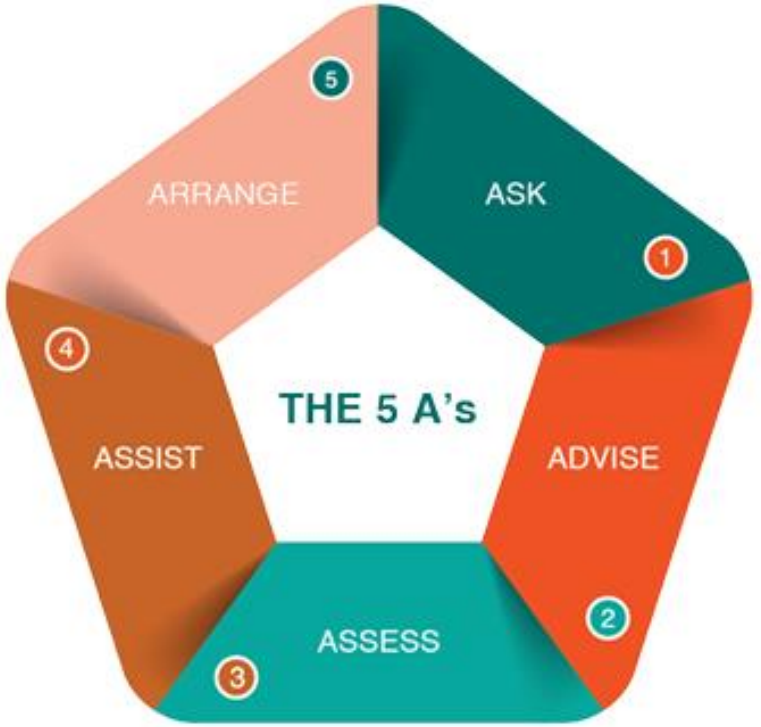
Level of nicotine dependence by total score:

0–2 = low
3–4 = moderate
5–6 = high

Behavioral Counseling

"5 A's" model for treating tobacco use & dependence

Ask about tobacco use.	Identify & document tobacco use status for every patient at every visit.
Advise to quit.	In a clear, strong, & personalized manner, urge every tobacco user to quit.
Assess willingness to make a quit attempt.	Is the tobacco user willing to make a quit attempt at this time?
Assist in quit attempt.	❖For the patient willing to make a quit attempt, offer medication & provide or refer for counseling or additional treatment to help the patient quit. ❖For patients unwilling to quit at the time, provide interventions designed to ↑ future quit attempts.
Arrange follow up.	❖For the patient willing to make a quit attempt, arrange for follow up contacts, beginning within the **first week** after the quit date. ❖For patients unwilling to make a quit attempt at the time, address tobacco dependence & willingness to quit at next clinic visit.



Enhancing Motivation to Quit Tobacco: "5 R's"

- **Patients should be advised to select a quit date that is > 3 days but <2 weeks away**.
  - This time frame **provides patients** with sufficient time to **prepare for the quit attempt**, including **mental preparation**, as well as **preparation of the environment**, such as by removing all tobacco products & ashtrays from the home, car, & workspace & informing their family, friends, & coworkers about their upcoming quit attempt & requesting their support.

Postcessation Withdrawal Symptoms

Symptoms	Duration
Chest tightness	A few days
Constipation, stomach pain, gas	1–2 weeks
Cough, dry throat, nasal drip	A few days
Craving for a cigarette	Frequent for 2–3 days; can persist for months or years
Difficulty concentrating	2–4 weeks
Dizziness	1–2 days
Fatigue	2–4 weeks
Hunger	Up to several weeks
Insomnia	1 week
Irritability	2–4 weeks

Pharmacotherapy

- **First-line Agents (FDA approval for smoking cessation):**
  - Five NRT dosage forms (Gum, Inhaler, Lozenge, Patch, Nasal Spray)
  - Sustained-release Bupropion
  - Varenicline

- **Second-Line Agents (Not FDA approval for smoking cessation):**
  - Clonidine
  - Nortriptyline

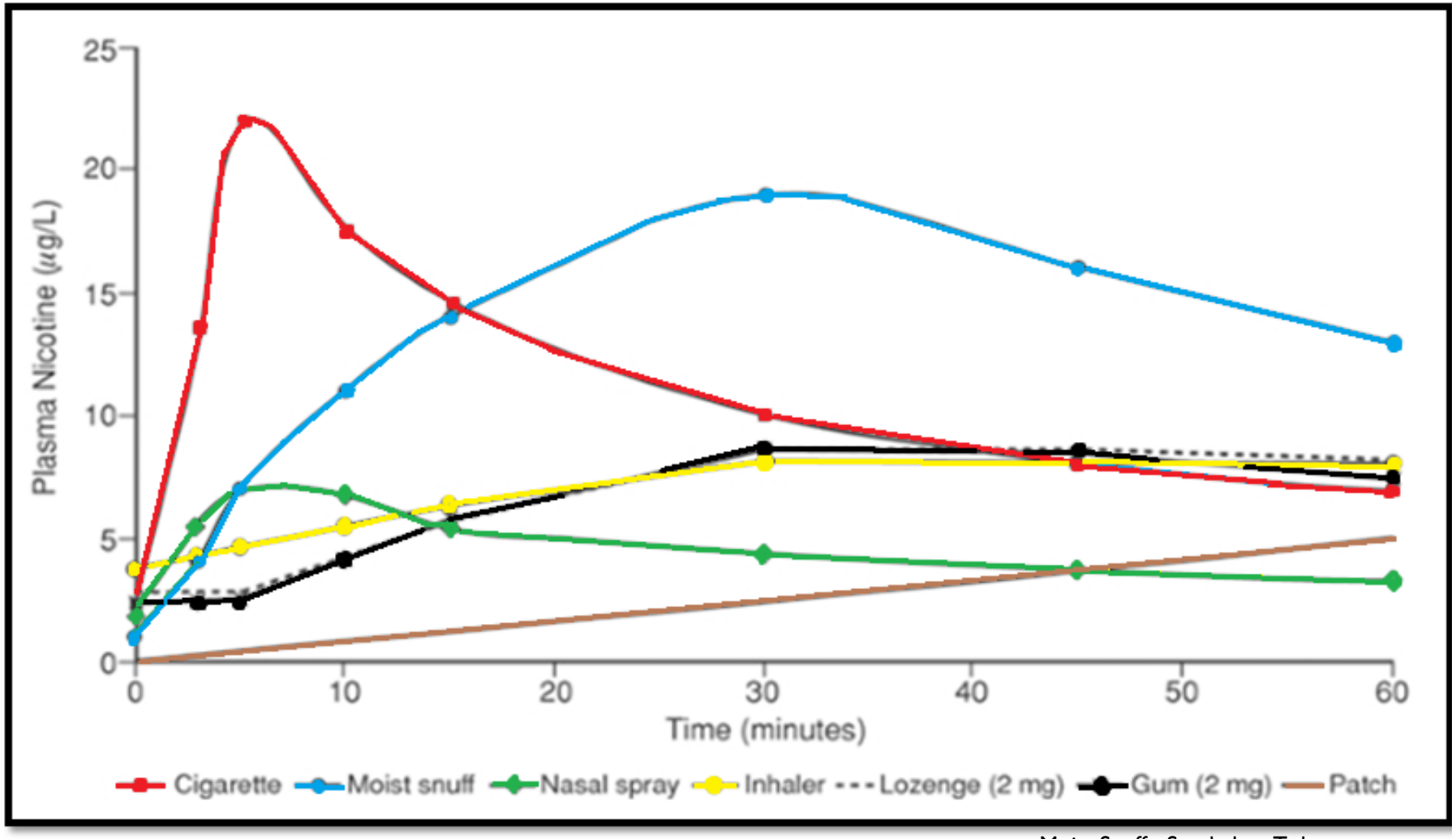
History of Approved Medications

- **Nicotine gum** in **1984**.(The first medication)
- **Nicotine transdermal patch** (Rx in **1991** & OTC in **1996**)
- **Bupropion SR & Nicotine nasal spray** in **1996**
- **Nicotine oral inhaler** in **1997**
- **Nicotine lozenge** in **2002**
- **Varenicline** in **2006**

Nicotine Replacement Therapy (NRT)

- **Increase success for quitting by**
  - **Reduce the physical withdrawal symptoms** associated with tobacco cessation **while the patient focuses on modifying his or her behavior** & coping with the psychological aspects of quitting.
  - Because **the onset of action for NRT is not as rapid as that of nicotine obtained through smoking**, patients become less accustomed to the nearly immediate, reinforcing effects of inhaled tobacco.
- Each product has about same efficacy, **increasing quit rates by 50-70% compared with placebo**. However, NRT is most effective when the nicotine patch is used in conjunction with a more rapidly absorbed form of NRT (e.g., gum).
- In general, NRT is recommended for **2 to 3 months after smoking cessation.** However, it may be used through the period when patients are at high risk for relapse.

Plasma nicotine concentrations for various nicotine-containing products



Moist Snuff= Smokeless Tobacco

- The **nicotine nasal spray** reaches its C_{max} **most rapidly**.
- The nicotine gum, lozenge, & oral inhaler have similar concentration curves
- The **patch** has the **slowest onset**, but offers **more consistent blood levels** of nicotine over a sustained period of time.

Transdermal Nicotine Patch

7 mg, 14 mg, 21 mg (24-h release)

- Deliver nicotine **more slowly** than **the gum, lozenge, nasal spray, & inhaler.**
- **Plasma nicotine** levels obtained via transdermal delivery are **50% lower than those achieved with cigarette smoking but still alleviate the symptoms of withdrawal**.
- **Dosing**
- **>10 cigarettes/day:**
  a) **21 mg/day × 6 weeks**
  b) **14 mg/day × 2 weeks**
  c) **7 mg/day × 2 weeks**
- **≤10 cigarettes/day:**
  a) **14 mg/day × 6 weeks**
  b) **7 mg/day × 2 weeks**

Duration: 8–10 weeks

Precautions/Warnings & Contraindications

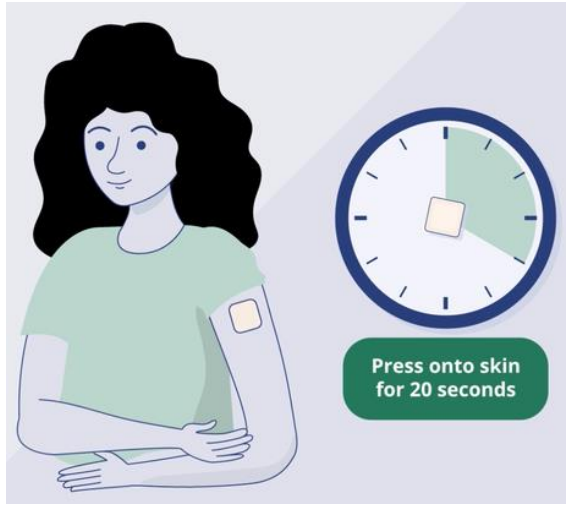
- **Recent (≤2 weeks) MI**
- Serious underlying arrhythmias
- Serious or worsening angina pectoris

Adverse Effects

- Local skin reactions (erythema, pruritus, burning)
- **Headache**
- **Sleep disturbances** (**insomnia, abnormal/vivid dreams**); associated with nocturnal nicotine absorption
  - May wear patch for 16 h if patient experiences sleep disturbances (remove at bedtime)

Patient Education

- Apply the patch to a **clean, dry, hairless area of skin** on the **upper body** or the upper outer part of her arm at **the same time each day**.
- To minimize the potential for local skin reactions, the patch **application site should be rotated daily**, & **the same area should not be used again for at least 1 week.**
- Smoking cessation rates are similar whether the patch is left on for 24 h or taken off at night. Patients who remove the patch at night & experience morning cravings for nicotine can use a rapid-acting form of NRT (eg, gum, lozenge) while waiting for the nicotine patch to take effect.
- **Water will not ↓ the effectiveness of the nicotine patch if it is applied correctly**, & user may bathe, swim, or exercise while wearing the patch.



Nicotine Gum

OTC 2 mg, 4 mg

- **Nicotine polacrilex gum** is **a resin complex** of nicotine & polacrilin in a chewing gum base that allows for **slow release** & absorption of nicotine across the oral mucosa.
- The gum contains **buffering agents** (**sodium carbonate & sodium bicarbonate**) to **↑ the salivary pH**, which **enhances the buccal** absorption of nicotine.
- The amount of nicotine absorbed **from each piece is variable**, but **1.1 & 2.9 mg** of nicotine are extracted from the **2- & 4-mg** gum formulations, respectively.
- **C_{max} of nicotine** are achieved **30 min** after chewing a single piece of gum & then slowly ↓ thereafter.

Dosing

- ≥25 cigarettes/day: **4 mg**
- <25 cigarettes/day: **2 mg**

  - **Weeks 1–6:** 1 piece **Q 1–2 h** while awake
  - **Weeks 7–9:** 1 piece **Q 2–4 h** while awake
  - **Weeks 10–12:** 1 piece **Q 4–8 h** while awake

Maximum: 24 pieces/day

Duration: up to 12 weeks

- It is preferable to use the gum **on a fixed schedule of administration**, **tapering over 1- 3 months rather than using it "as needed" to control cravings.**

❖ Precautions/Warnings & Contraindications

- ❖ **Recent (≤2 weeks) MI**
- ❖ Serious underlying arrhythmias
- ❖ Serious or worsening angina pectoris
- ❖ **Temporomandibular joint disease**

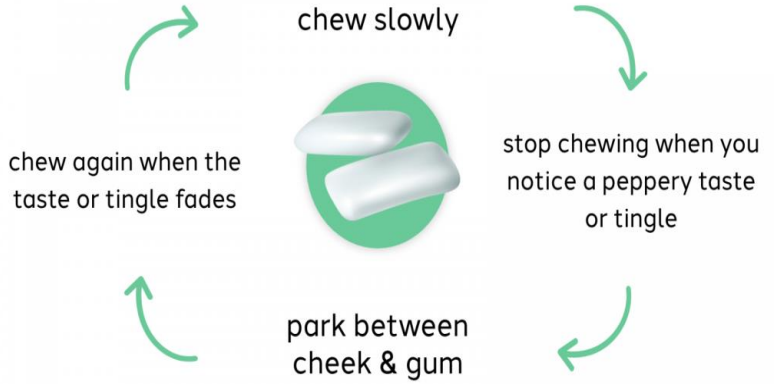
■ Adverse Effects

- ❖ Mouth/jaw soreness
- ❖ **Hiccups**
- ❖ Dyspepsia
- ❖ **Hypersalivation**
- ❖ **Effects associated with incorrect chewing technique:**
  - ○ Lightheadedness
  - ○ Nausea/vomiting
  - ○ Throat & mouth irritation

Patient Education

- Chew each piece slowly
- Park between cheek & gum when peppery or tingling sensation appears
- Resume chewing when taste or tingle fades (generally after 1–2 min)
- Repeat chew/park steps until most of nicotine is gone (generally 30 min)
- Park in different areas of mouth (helps ↓ the incidence of oral irritation)

- **No food or acidic beverages (e.g., coffee, juices, wine, soft drinks) 15 min before or during use** (↓ absorption by transiently ↓ salivary PH)



Nicotine Lozenge

OTC 2 mg, 4 mg

- Is a resin complex of nicotine & polacrilin in a sugar-free lozenge.
- Because the nicotine lozenge **dissolves completely**, it delivers **25% more nicotine than does an equivalent dose of nicotine gum**.
- **C_{max} of nicotine** with the lozenge are achieved after **30-60 min** of use & then slowly ↓ thereafter.

- Unlike other NRT formulations, which use the number of cigarettes smoked per day as the basis for dosing, the recommended dosage of the **nicotine lozenge is based on the time to first cigarette (TTFC).**

- **Some experts believe that the best indicator of nicotine dependence is the need to smoke soon after waking.**
  - People who smoke their **first cigarette of the day within 30 min of waking** are considered **more highly dependent on nicotine** than those who smoke their first cigarette more than 30 min after waking.

Dosing

- First cigarette ≤30 min after waking: 4 mg
- First cigarette >30 min after waking: 2 mg
  - Weeks 1–6: 1 lozenge Q 1–2 h
  - Weeks 7–9: 1 lozenge Q 2–4 h
  - Weeks 10–12: 1 lozenge Q 4–8 h

Maximum: 20 lozenges/day

Duration: up to 12 weeks

- Patients are more likely to succeed if they use the lozenge on a fixed schedule rather than as needed.

Precautions/Warnings & Contraindications

- Recent (≤2 weeks) MI
- Serious underlying arrhythmias
- Serious or worsening angina pectoris

Adverse Reactions

- Nausea
- **Hiccups**
- Cough
- Heartburn
- Headache
- Insomnia

Patient Education

- Allow to dissolve slowly (20–30 min)
- Nicotine release may cause a warm, tingling sensation
- Do not chew or swallow (↑ the incidence of GI-related side effects)
- Occasionally rotate to different areas of the mouth(↓ mucosal irritation)

- **No food or acidic beverages (e.g., coffee, juices, wine, soft drinks) 15 min before or during use** (↓ absorption by transiently ↓ the salivary PH)

Nicotine Nasal Spray
Rx

- Is an **aqueous solution** of nicotine available in a **metered-spray pump** for administration to the nasal mucosa.
  - Each actuation delivers a metered 50-µL spray containing 0.5 mg of nicotine.
- Nicotine in the nasal spray is **more rapidly absorbed than other NRT formulations**, with **C_{max} achieved within 11-18 min** after administration.
- Although the nasal spray more closely mimics changes seen with smoking, **it does not deliver nicotine nearly as fast as smoking a cigarette.**

Dosing

- **One dose** of **nicotine (1 mg)** is administered **as 2 sprays, one (0.5-mg spray) in *each* nostril.**
- The recommended **initial regimen is 1-2 doses Q1h while awake for 6-8 weeks.**

- This may be ↑, as needed, to a **maximum** recommended dosage of **5 doses per hour or 40 mg/day**.
- For best results, patients should be encouraged to use **at least 8 doses per day during the initial 6-8 weeks of therapy** because less frequent administration may be less effective.

- **After 6-8 weeks**, the dose should be gradually ↓ **over an additional 4-6 weeks**.
- **Duration: 3–6 months**

Precautions/Warnings & Contraindications

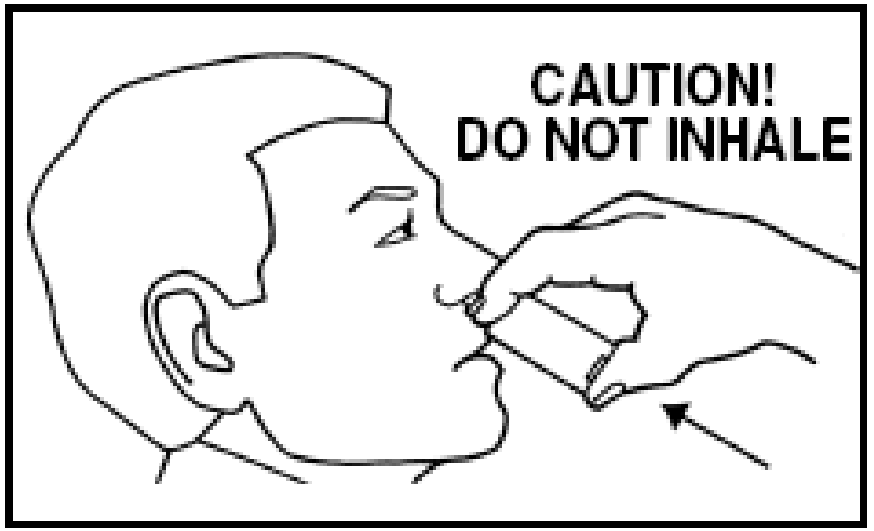
- Recent (≤2 weeks) MI
- Serious underlying arrhythmias
- Serious or worsening angina pectoris
- Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis)
- Severe reactive airway disease

Adverse Reactions

- Nasal &/or throat irritation (hot, peppery, or burning sensation)
- Rhinitis
- Tearing
- Sneezing
- Cough
- Headache

Patient Education

- When administering a dose, the patient should tilt the head back slightly & insert the tip of the bottle into the nostril as far as is comfortable.
- After actuation of the pump, the patient should not sniff, swallow, or inhale through the nose because this ↑ the irritant effects of the spray.
- **Patients should wait 5 min before driving or operating heavy machinery (because of the ↑ likelihood of tearing, coughing, & sneezing).**



Nicotine Inhaler

Rx 10 mg cartridge Delivers 4 mg inhaled nicotine vapor

- Each foil-sealed cartridge contains a porous plug with **10 mg of nicotine & 1 mg of menthol.**
- **Menthol is added to ↓ the irritant effect of nicotine**.

- Given that the usual **pack-a-day** smoker repeats the **hand-to-mouth motion** **up to 200 times per day** or **73,000 times each year**, it is not surprising that many smokers **find they miss the physical manipulation of the cigarette & associated behaviors** that accompany smoking.

- The nicotine inhaler was designed to provide nicotine replacement **in a manner similar to smoking** while **addressing the sensory & ritualistic factors** that are important to many patients who smoke.

- As a patient puffs on the inhaler, the **nicotine vapor is delivered to the mouth & throat**, where it is absorbed through the **mucosa**.
- Only a small amount **(<5% of a dose)** of nicotine **reaches the lower respiratory tract**.

- With an intensive inhalation regimen (80 puffs over 20 min), **about 4 mg of nicotine is delivered, & of that, 2 mg is absorbed.**
- **C_{max} of Nicotine** with the inhaler are achieved after **30 min** of use & then slowly ↓ thereafter.

Dosing

- During the initial 3 to 6 weeks of treatment, the patient should use 1 cartridge every 1 to 2 h while awake. This should be ↑, as needed, **to a maximum of 16 cartridges per day.**

- The manufacturer recommends that each cartridge be depleted of nicotine by frequent continuous puffing over 20 min.

- **The recommended duration of treatment is 3 months**, after which patients may be weaned from the inhaler by gradual ↓ of the daily dose over the following 6 to 12 weeks.
- **Duration: up to 6 months**

Precautions/Warnings & Contraindications

- Recent (≤2 weeks) MI
- Serious underlying arrhythmias
- Serious or worsening angina pectoris
- **Bronchospastic disease**

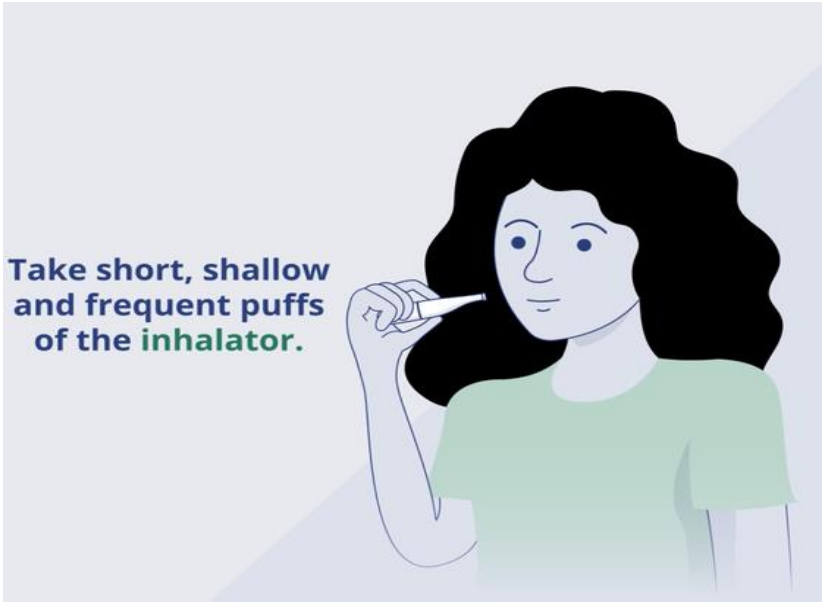
Adverse Reactions

- Mouth &/or throat irritation (40%)
- Cough(32%)
- Unpleasant taste
- Rhinitis
- Dyspepsia
- Hiccups
- Headache

Patient Education

- Inhale shallowly to minimize the likelihood of throat irritation.
- **The release of delivery of nicotine from the inhaler is temperature dependent & significantly ↓ at temperatures below 40°F.**
- In cold conditions, patients should store the inhaler & cartridges in a warm place (e.g., inside pocket).
- Conversely, under warmer conditions, more nicotine is released per puff. However, nicotine plasma concentrations achieved using the inhaler in hot climates at maximal doses will not exceed levels normally achieved with smoking.

- **No food or acidic beverages (e.g., coffee, juices, wine, soft drinks) 15 min before or during use (↓ absorption by transiently ↓ the salivary PH)**



Safety of NRT in Patients With CV Disease

- **Smokers often worry that they will remain dependent on nicotine** if they use these products when stopping smoking. **This may occur, although it is rare**. The dose of nicotine delivered with NRT is smaller & the delivery of nicotine is slower than inhaled tobacco smoke, **which prevent nicotine dependence**.

- **Nicotine replacement is safe to use in patients with known cardiovascular disease (CVD).**
- Concerns about excess cardiac toxicity associated with NRT in patients with acute coronary syndromes (ACS) also appear to be unfounded, as patients with ACS receiving NRT are not at increased risk for cardiovascular events.

- **It is likely that the benefits of nicotine replacement through smoking cessation outweigh any potential risks in most smokers with CVD.**

Bupropion SR

- Hypothesized to promote smoking cessation **by blocking the reuptake of dopamine & NEP** in the CNS & **possibly by acting as a nicotine receptor antagonist**.
- These neurochemical effects are believed to **modulate the dopamine reward pathway** & **↓ cravings for nicotine & symptoms of withdrawal**.

- Absolute bioavailability: 5-20%
- Undergoes extensive hepatic metabolism to 3 active metabolites; one of the metabolites, hydroxybupropion, is formed by the CYP2B6.
- Bupropion & its metabolites are eliminated in urine (87%) & feces (10%), with < 1% being excreted unchanged in the urine.
- The half-life for bupropion is 21 h, & its metabolites have a half-life range of 20-27 h; C_{ss} are reached within 5 & 8 days, respectively.

Dosing

- **150 mg PO Q am × 3 days, then 150 mg PO BID**
- Allow at least 8 h between doses
- Treatment should be initiated while patient is still smoking; **Set quit date 1–2 weeks after initiation of therapy**
- Avoid bedtime dosing to minimize insomnia
- **Dose tapering is not necessary**
- **Can be used safely with NRT**
- **Duration: 7–12 weeks, with maintenance up to 6 months in selected patients**
- **Bupropion is safe for use among smokers with stable CVD & COPD.**
- **It is effective comparable to the nicotine patch in efficacy. However, the combination of bupropion with NRT is more effective than bupropion or NRT alone.**

- **Contraindications:**
  - Seizure disorder
  - Concomitant bupropion (e.g., Wellbutrin) therapy
  - Current or prior diagnosis of bulimia or anorexia nervosa
  - Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)
  - MAOI therapy in previous 14 days
  - Severe hepatic cirrhosis

Patient Education

- Advise patients experiencing **insomnia** to **avoid taking the second dose close to bedtime.**
- Inform patients that bupropion might cause **dizziness, drowsiness, or ↓ alertness**, & caution should be exercised when **driving or operating machinery**.
- **Because alcohol use might ↑ the likelihood of seizures**, patients should **avoid or drink alcohol only in moderation** while taking bupropion.
- Patients should also be advised **not to take Zyban & Wellbutrin or generic bupropion formulations concomitantly** to avoid dose-related adverse effects, including seizures

Varenicline

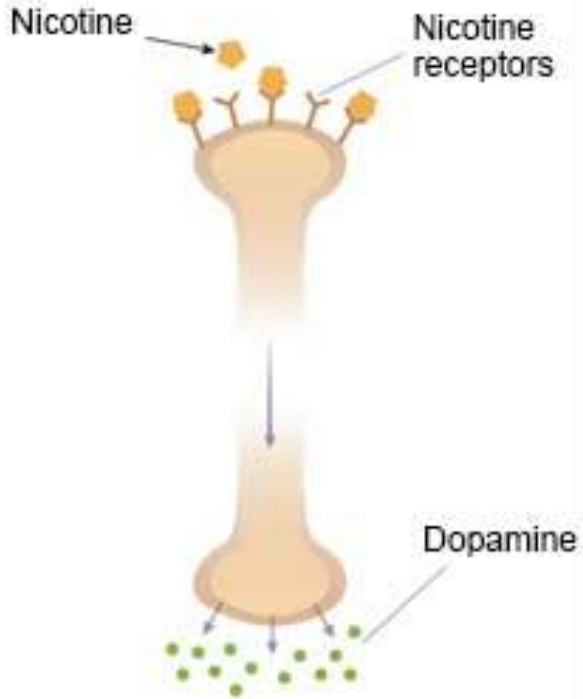
- **Partial agonist**, highly selective for the **α4β2 nicotinic acetylcholine receptor.**
  - The partial agonist activity induces **modest receptor stimulation** leading to ↑ **dopamine levels that attenuate the symptoms of nicotine withdrawal.**
  - By **competitively blocking** the binding of nicotine to nicotinic acetylcholine receptors in CNS, **varenicline inhibits the surges of dopamine release that occur immediately following inhalation of tobacco smoke;** may be effective in **preventing relapse by ↓ the pleasure** associated with smoking.

- **It is superior to placebo, bupropion, & NRT.**
- **It may be used in combination with NRT to achieve higher rates of abstinence.**

How Varenicline Can Help You Quit Smoking

When you smoke, nicotine activates cells in the reward center of the brain.

Brain cell when smoking



Nicotine attaches to brain cell receptors.

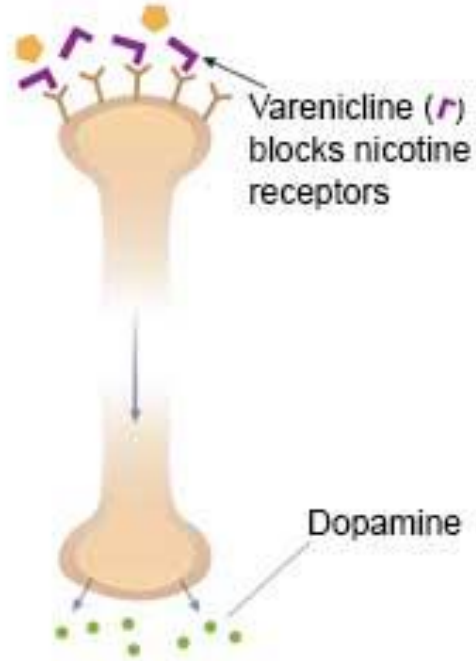
This causes dopamine to release, making you feel good.

Brain cell when not smoking

When you quit smoking, there is no nicotine attaching to the receptors.

Less dopamine is released, which can cause withdrawal symptoms and cravings.

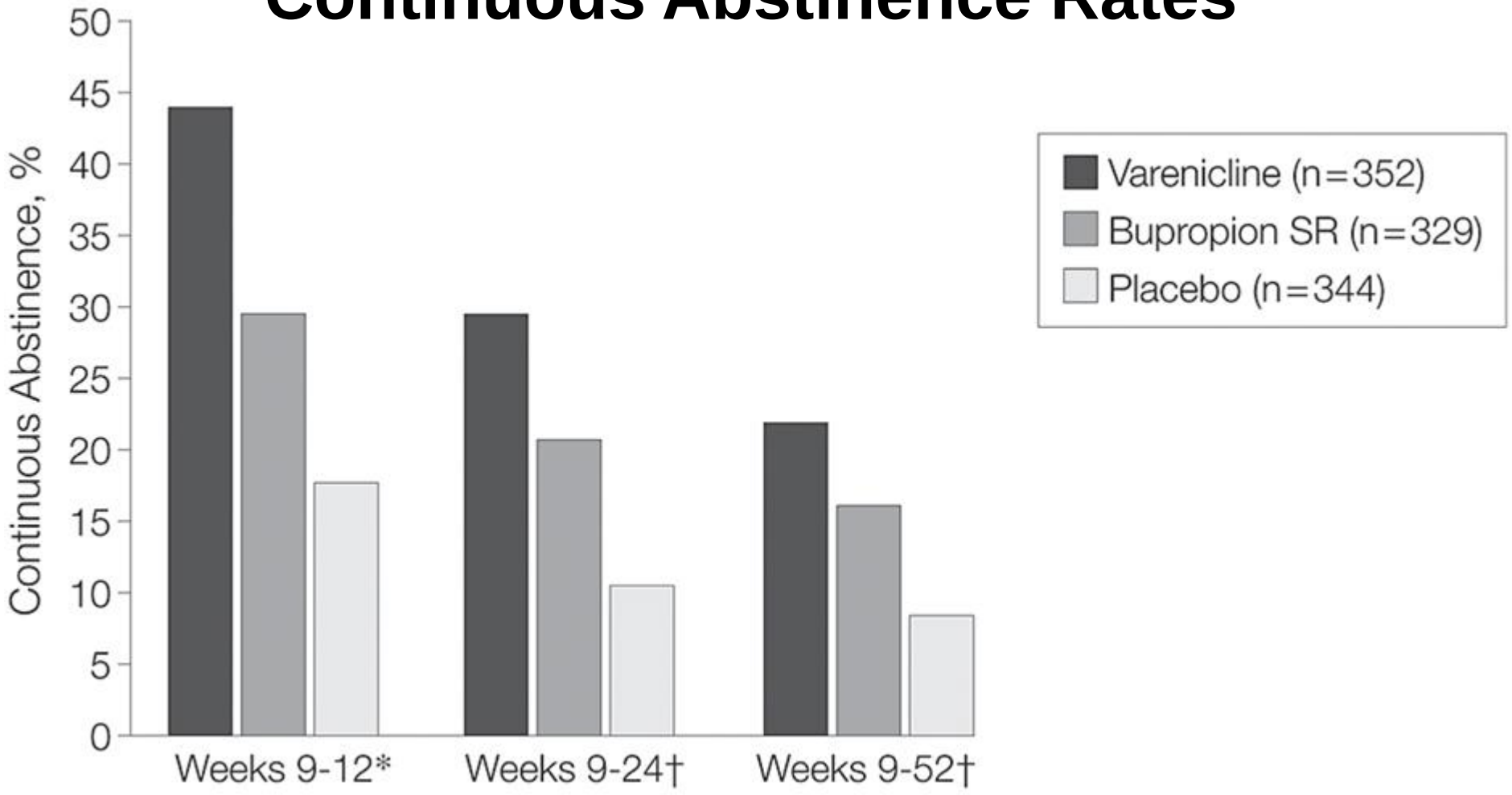
Brain cell with varenicline



If you use varenicline to quit smoking, it blocks the nicotine receptors.

But varenicline still triggers some dopamine release, so you don't feel as bad.

Continuous Abstinence Rates



Three randomized trials found varenicline to be superior to bupropion.

Gonzales, D. et al. JAMA 2006;296:47-55.

Pharmacokinetics

- Varenicline absorption is **virtually complete** after oral administration, & **oral bioavailability is unaffected by food or time-of-day dosing.**
- Undergoes **minimal metabolism**, with **92% excreted unchanged in urine**.
- **The half-life is 24 h,** & following administration of multiple oral doses, **C_{ss} are reached within 4 days**.

Dosing

- Treatment should be initiated **1 week before the patient stops smoking.**
  - **Days 1–3: 0.5 mg PO Qam**
  - **Days 4–7: 0.5 mg PO BID**
  - **Weeks 2–12: 1 mg PO BID**

- **Duration: 12 weeks; an additional 12-week course may be used in selected patients**

Precautions/Warnings & Contraindications

- **Severe renal impairment** (dosage adjustment is necessary)
- **Neuropsychiatric symptoms** (behavior changes, agitation, depressed mood, suicidal ideation or behavior). Safety & efficacy have not been established in patients with serious psychiatric illness.

Adverse Reactions

- **Nausea (dose dependent)**
- **Sleep disturbances (insomnia, abnormal/vivid dreams)**
- Constipation
- Flatulence
- Vomiting
- **Neuropsychiatric symptoms (rare)**

Patient Education

- The tablets are to be taken orally, **after eating, with a full glass of water**.
- **Nausea & insomnia are side effects that are usually temporary.**
- However, if these symptoms **persist**, patients should notify their provider so **dosage reduction** can be considered.
- **Dose tapering is not necessary**
- **Varenicline is safe for use among smokers with COPD.**

Clonidine

- **Is now generally regarded as having limited efficacy for smoking cessation**.
  - Although a meta-analysis suggested that clonidine was superior to placebo in facilitating smoking cessation, the majority of individual studies evaluating the drug have not demonstrated statistically significant efficacy.

- The recommended starting dose is **0.1 mg BID** or 0.1 mg/day transdermally, **↑ by 0.1 mg/day/week as tolerated for up to 10 weeks.**

- **The high incidence of side effects**, including **dry mouth, sedation, dizziness, & constipation**, relegate clonidine as a second-line agent reserved for individuals who have failed or are intolerant of first-line agents.

Nortriptyline

- Has demonstrated efficacy for smoking cessation, **approximately doubling long-term (6-month) abstinence rates compared with placebo.**
- The regimen used for treating tobacco dependence is **25 mg/day**, **↑ gradually to a target dosage of 75 to 100 mg/day, for ~ 12 weeks.**
- Because the half-life of nortriptyline is prolonged (**up to 56 h**), **therapy should be initiated at least 10 days before the quit date to allow it to C_{ss} at the target dose.**
- **The side effects**: sedation, dry mouth, blurred vision, urinary retention, lightheadedness, & tremor.

Combination Therapy

Combination of NRT

- Combination NRT involves the use of a **long-acting formulation (patch)** in combination with a **short-acting formulation (gum, lozenge, inhaler, or nasal spray).**
- The **long-acting** formulation is used **to prevent the onset of severe withdrawal symptoms**, whereas the **short-acting** formulation is used **as needed to control withdrawal symptoms that may occur during potential relapse situations (e.g., after meals, when stressed, or around other smokers).**

Nicotine Patch & Bupropion SR in Combination

- Patients receiving combination therapy with **bupropion SR** & the **nicotine patch** in standard dosages were significantly **more likely to quit** than were patients randomized to the **nicotine patch alone**. The odds of long-term (>6 months) abstinence were 1.3, with the combination compared to nicotine patch monotherapy (95% CI, 1.0–1.8).

Varenicline & NRT in Combination

High-Dose NRT

- Plasma levels of nicotine achieved with NRT are generally **much lower than** those **observed during regular smoking**.
- Given this incomplete level of nicotine replacement, standard doses of NRT **may be insufficient** for some individuals, & in particular, **for moderate-to-heavy smokers**.

- Studies using **transdermal nicotine** in doses up to **44 to 63 mg/day** **suggest that high-dose NRT is safe**. However, **trials** evaluating higher doses of NRT have yielded **conflicting results.**

- This approach should be **reserved for patients not able to quit using conventional doses of transdermal NRT.**

Extended Use of Medications

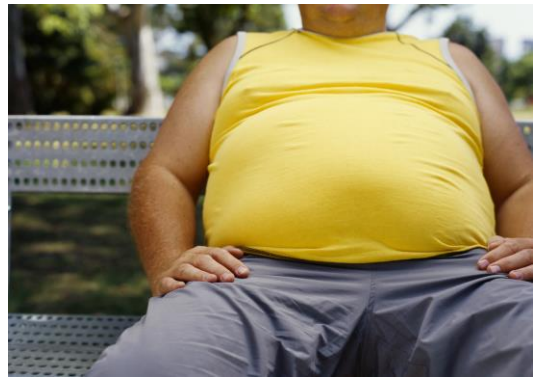
- 2008 Clinical Practice Guideline states that extended use of medications might be beneficial in individuals
  - Who report persistent withdrawal symptoms during treatment
  - Who have relapsed shortly after medication discontinuation
  - Who are interested in long-term therapy

- Clinicians should be aware that many of the medications (bupropion SR, varenicline, nicotine nasal spray & inhaler) are FDA approved for **long-term (6-month) use**.
- Although the goal should be complete abstinence from all nicotine-containing products, **continued use of medicinal nicotine is substantially safer than any level of smoking.**

Postcessation Weight Gain

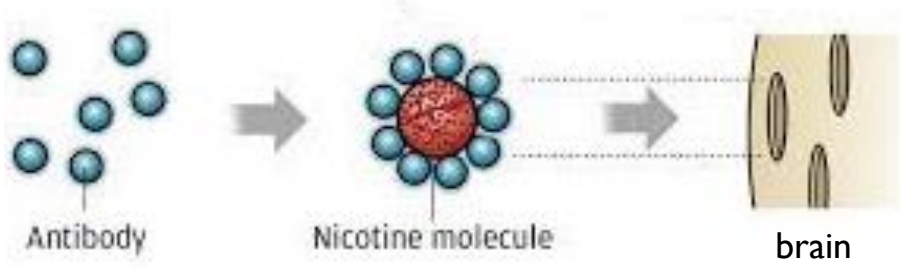
- Most tobacco users **gain weight after quitting.**
- Studies suggest that **most quitters gain < 4.5 Kg**, but there is a broad range of weight gain reported, **with up to 10% of quitters gaining as much as 13.5 Kg.**
- **In general, women tend to gain more weight than men.**

- **The weight-suppressing effects of tobacco are well known.** However, **the mechanisms** to explain why most successful quitters gain weight are **not completely understood**.
  - **Smokers** have been found to have **10% higher metabolic rate compared with nonsmokers**. In some studies, **higher caloric intakes** were documented after cessation.
  - The ↑ caloric intake may result from an ↑ **in appetite, improved sense of taste**, or a **change in the hand-to-mouth ritual through the substitution of tobacco with food.**



Nicotine Vaccine

- Work continues on the development of vaccines to be used in treating nicotine addiction.
- **NicVAX (an experimental nicotine conjugate vaccine)** is designed to cause the immune system to produce **antibodies that bind to nicotine & prevent it from entering the brain**. As a result, the positive stimulus in the brain that is normally caused by nicotine is no longer present, **thereby taking away the physical motivation for smoking, consequently helping people to quit.**
- Results from the phase II clinical studies on 301 patients who were smoking an average of 24 cigarettes a day showed the vaccine "induced the production of a long lasting antibody which helped in the prevention of a smoking relapse **for up to 2 months in ~25% of the study participants**."



Noncigarette Forms of Tobacco

Hookah or Water Pipes

- **Maassel: a mixture of tobacco, dried fruit pulp, honey, & molasses in a variety of flavors.**

  - Although many water pipe users **assume** that the **water will filter out toxins & believe this form of smoking is less harmful than cigarette smoking**, **data are lacking** to substantiate this belief.

  - Indeed, studies have found that water pipe smokers who inhale **are exposed to nicotine & other toxins in levels that are comparable to or exceed** those found in cigarette smoke, suggesting **that water pipe smoking is not "safe."**

  - Water pipe smokers are **at risk for developing dependence** & other adverse health-related conditions associated with smoking.

Smokeless Tobacco

- Forms of tobacco that are **not burned** & **inhaled** but rather **held in the mouth** to allow absorption of nicotine across the **oral (buccal) mucosa**.

- Users of smokeless tobacco are often **under the mistaken impression that these formulations are a "safe" alternative to smoking cigarettes** because it is not inhaled.
  - Although smokeless tobacco products do not yield many of the risks associated with the inhalation of combusted tobacco (e.g., pulmonary disease, lung cancer), these products impose harm & should not be recommended as aids for smoking cessation.

Moist snuff

Dry snuff

Snus

Cigars

- Cigars are conventionally defined as **"any roll of tobacco wrapped in leaf tobacco or in any substance containing tobacco."**
- Cigar tobacco is generally **air cured** & **produces smoke with a more alkaline pH**, which allows **for buccal absorption of nicotine**.
- The adverse health effects of cigar smoking have been well described & include an **↑ risk of cancer of the lung, oral cavity, larynx, esophagus, & pancreas.**
- In addition, cigar smokers **who inhale deeply** are at ↑ risk for developing **cardiovascular disease & COPD**.
- Cigarette smokers who switch to smoking only cigars **reduce their risk of developing lung cancer**, but their risk is markedly higher than if they were to quit smoking altogether.

Electronic Cigarettes

- E-cigarettes have been proposed as a method to reduce the harms of tobacco use & as a nicotine replacement product. However, e-cigarettes can also cause **nicotine dependence**.

- One randomized trial compared nicotine containing e-cigarettes with NRT.
  - The e-cigarette group abstinence rate was **18%** at 12 months, though **80% continued use** of e-cigarettes, compared with a **9%** abstinence rate in the NRT group & a **9% rate of continued** use of NRT.
  - Although e-cigarettes were beneficial in achieving abstinence, the concern is that individuals continued to use them.

- While nicotine inhalation with e-cigarettes is thought to release fewer toxic by-products than combustible cigarettes, there are concerns regarding their safety. Carcinogens & toxins have been found in the liquid used for vaporization & in the aerosols emitted, & e-cigarettes have been associated with an outbreak of cases of **acute lung injury** that caused hospitalizations & even deaths.

Generation	Description and characteristics	
First-generation, AKA ‘cigalike’	• Disposable • Appearance mimics traditional cigarettes • Closed systems	
Second-generation, AKA ‘pens’	• Rechargeable • Similar in appearance to a fountain pen • Larger than first-generation devices • Refillable cartridges	
Third-generation, AKA ‘mods’	• Larger • Longer charge time • Refillable separate cartridges • Increased ability for modification	

First-line pharmacologic options for tobacco cessation

Drug	Dosing	Administration	Comments
Nicotine patch (7 mg, 14 mg, 21 mg)	≤ 10 cigarettes/day: start with nicotine patch 14 mg/day > 10 cigarettes/day: start with nicotine patch 21 mg/day	Apply one patch each morning to any non-hairy, clean, dry skin on upper body or outer outer arm. Rotate the site daily to avoid skin irritation. After 6 weeks, taper to lower doses for 2–4 weeks.	Consider removing patch at bedtime in case of insomnia and vivid dreams.
Nicotine gum (2 mg, 4 mg)	Smokers wait > 30 min after waking to smoke: use 2 mg Smokers smoke within 30 min of waking: use 4 mg	"Chew and park" is recommended: chew until tingling sensations occurs, then "park" until tingling disappears. Then chew again to repeat. Chew one piece of gum every 1–2 hours or whenever there is an urge to smoke. Use up to 24 pieces of gum/day per day for 6 weeks. Gradually reduce use over a second 6 weeks, for a total duration of 3 months.	Avoid acidic beverages (eg, coffee, carbonated drinks) 15 minutes before and during gum use, as they reduce nicotine absorption.
Nicotine lozenge (2 mg, 4 mg)	Smokers wait > 30 min after waking to smoke: use 2 mg Smokers smoke within 30 min of waking: use 4 mg	Place lozenge in the mouth and allow it to dissolve for 30 minutes. Use 1 lozenge every 1–2 hours for 6 weeks. Maximum five lozenges every six hours or 20 lozenges per day. Gradually reduce number of lozenges used per day over a second 6 weeks.	Do not chew lozenge. Avoid acidic beverages (eg, coffee, carbonated drinks) 15 minutes before and during gum use, as they reduce nicotine absorption.
Nicotine inhaler (10 mg/cartridge)	Puff into mouth as needed; use 6–16 cartridges per day (at least 6 cartridges per day for the first 3–6 weeks) for up to 12 weeks	Inhale deeply into back of throat or puff in short breaths. Maximum 16 cartridges per day. Gradually reduce dose over 6–12 weeks	Required frequent use. Each cartridge lasts about 20 minutes if continuously puffing. Inhaled nicotine may cause bronchospasm.
Nicotine nasal spray (10 mg/mL)	Use 1 spray in each nostril 1–2 times per hour	Maximum of 10 sprays per hour or 80 spray per day. Adjust dose as needed based in response. Gradually reduce dose after 12 weeks.	Provides a more rapid rise in plasma nicotine concentration than that produced by agents absorbed via the oral mucosa.
Bupropion SR (sustained release) (150 mg)	150 mg once daily for 3 days, then increase to 150 mg twice daily	Begin at least 1–2 weeks before target quit date. May use longer than 12 weeks if needed for maintenance. Consider combination therapy, discontinuation, or alternative agent if no progress is made by seventh week.	Consider lowering dose to 150 mg daily if full dose not tolerated. Decreases seizure threshold.
Varenicline (0.5 mg, 1 mg)	Days 1–3: 0.5mg once daily Days 4–7: 0.5 mg twice daily Day 8 and later: 1 mg twice daily	Treatment should be continued for 12 weeks but can be extended. Consider dose reduction if usual dose is not tolerated.	Varenicline does not increase the risk of depression, suicidal ideation, or cardiovascular disease.

Thanks

Dr_Taraz_Drugstore