

# Tobacco Use & Dependence

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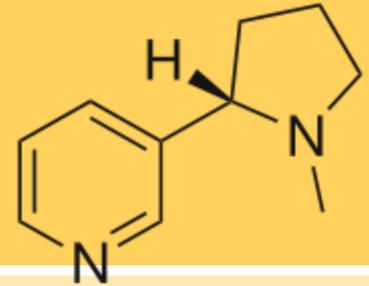
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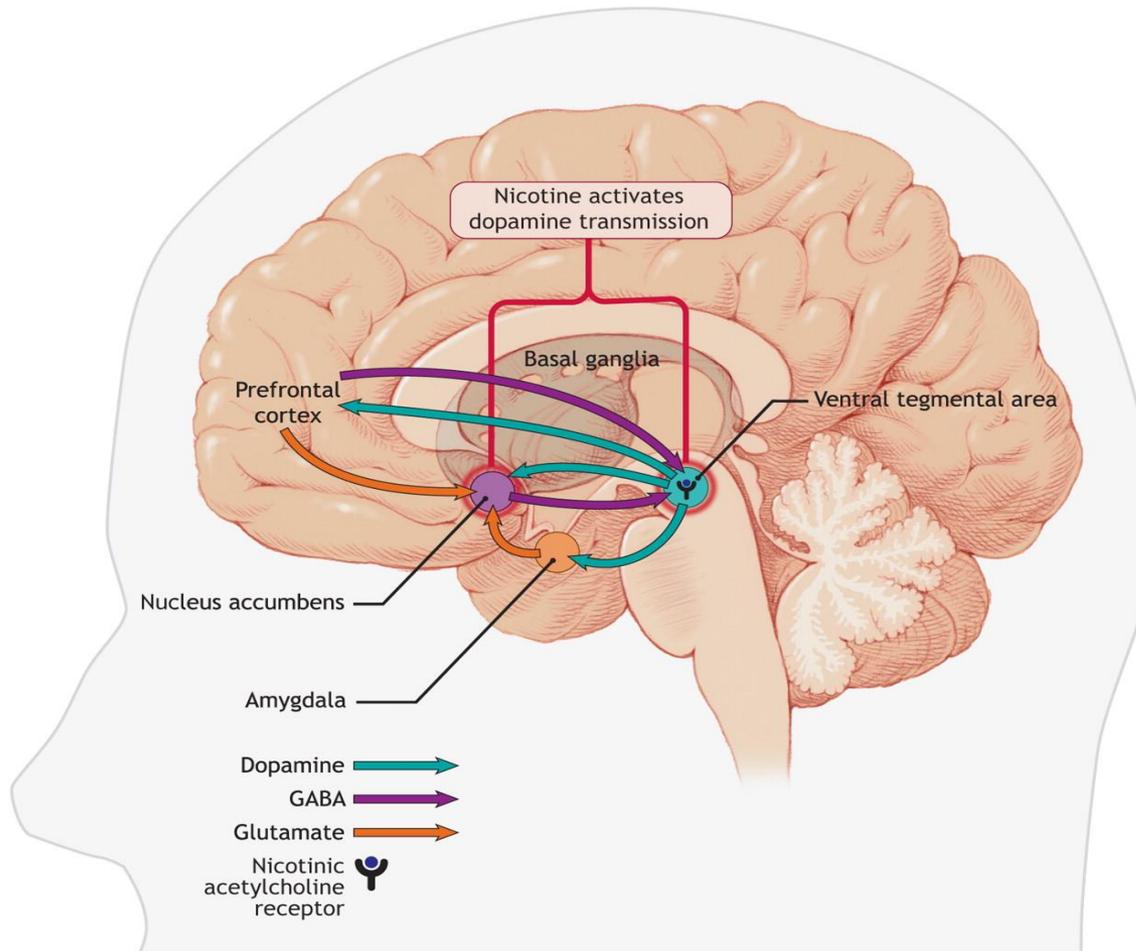
# Introduction

- ❖ As a major risk factor for a wide range of diseases, including cardiovascular conditions, cancers, & pulmonary disorders, tobacco is **the primary known preventable cause of premature death** in our society.
- ❖ During the 20th century, 100 million deaths were caused by tobacco, & currently, an estimated 5.4 million deaths occur annually.
- ❖ **Unless** tobacco control efforts are able to reverse this trend, the number of annual deaths is likely to exceed **8 million by the year 2030**.
- ❖ In addition to the harm imposed on users of tobacco, **exposure to secondhand smoke** results in an estimated 50,000 deaths each year.

# Nicotine



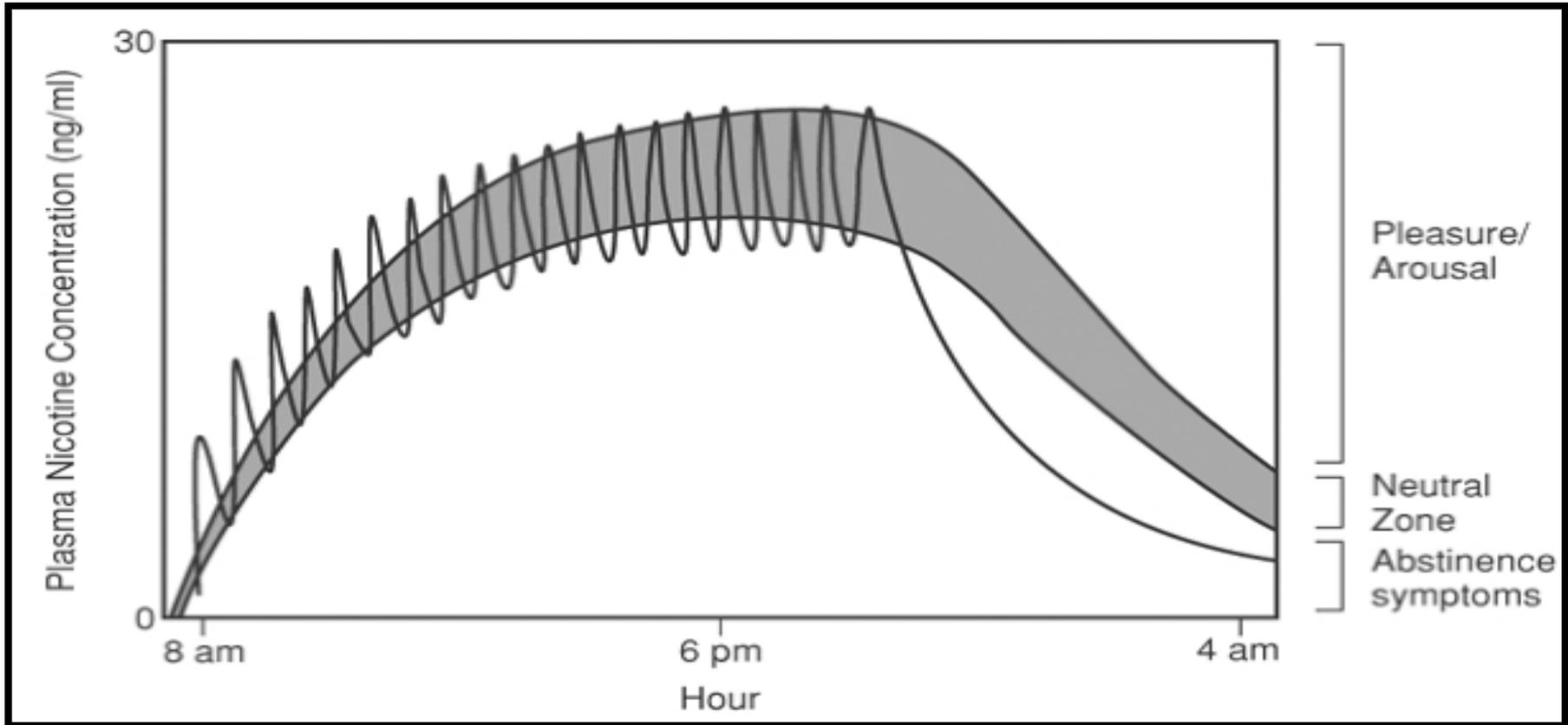
- ⊙ **Meets the criteria for an addictive substance:**
  - ❖ It induces **psychoactive effects**
  - ❖ It is used in a **highly controlled or compulsive manner**
  - ❖ **Behavioral patterns** of tobacco use are **reinforced by the pharmacologic effects of nicotine.**
  
- ❖ **The addictive properties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



- ❖ The **dopamine reward pathway**, a network of nervous tissue that elicits **feelings of pleasure** in response to certain stimuli, is central to drug-induced reward.
- ❖ Key structures of the reward pathway include the **ventral tegmental area**, **nucleus accumbens**, & **prefrontal cortex**. The neurons of the ventral tegmental area contain the neurotransmitter **dopamine**, which is released in the nucleus accumbens & in the prefrontal cortex.

- ⊙ **Chronic administration also leads to tolerance to the behavioral & cardiovascular effects of nicotine over the course of the day; however, tobacco users regain sensitivity to the effects of nicotine after overnight abstinence from nicotine.**
- ⊙ **Notably, after smoking the first cigarette of the day, the smoker experiences marked pharmacologic effects, particularly arousal.**
- ⊙ **No other cigarette throughout the day produces the same degree of pleasure/arousal. For this reason, many smokers describe the first cigarette as the most important one of the day.**

# Nicotine addiction cycle throughout the day



Cigarette is smoked every 40 minutes

# Smoking & Cardiovascular Disease

- ⊙ Oxidant gases & other compounds in tobacco smoke are believed to **induce a hypercoagulable state** characterized by ↑ platelet aggregation & thrombosis, which greatly ↑ the risk of MI & sudden death.
- ⊙ The CO in smoke ↓ **the amount of oxygen available to tissues & organs**, including myocardial tissue, & may ↓ the ventricular fibrillation threshold.
- ⊙ **Accelerate atherosclerosis** through effects on serum lipids; smokers tend to have higher levels of total cholesterol, LDL, & TG & lower HDL than nonsmokers.
- ⊙ **↑ the levels of inflammatory mediators** (CRP, leukocytes, & fibrinogen), which may contribute to the development & progression of atherosclerosis.
- ⊙ **Stimulates the release of neurotransmitters** (e.g., EP, NEP) that ↑ myocardial workload & induce coronary vasoconstriction leading to ischemia, arrhythmias, & sudden death.
- ⊙ **Fortunately, the effects of smoking on lipids, coagulation, myocardial workload, & coronary blood flow appear to be reversible.**

# Treatment

- ❖ Behavioral Counseling Strategies
- ❖ Pharmacotherapy Interventions
- ❖ Although both pharmacotherapy & behavioral counseling are **effective independently**, patients' odds of quitting are substantially ↑ when the 2 approaches are used simultaneously.

# Treating Tobacco Use And Dependence

CLINICAL PRACTICE GUIDELINE  
2001 UPDATE

U.S. Department of  
Health and Human Services  
Public Health Service

# Postcessation Withdrawal Symptoms

<b>Symptoms</b>	<b>Duration</b>
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

# Pharmacotherapy

- ❖ **First-line Agents ( FDA approval for smoking cessation ):**
  - ❖ Five NRT dosage forms (Gum, Inhaler, Lozenge, Patch, Nasal Spray)
  - ❖ Sustained-release Bupropion
  - ❖ Varenicline (var e NI kleen)
- ❖ **Second-Line Agents (Not FDA approval for smoking cessation):**
  - ❖ Clonidine
  - ❖ Nortriptyline



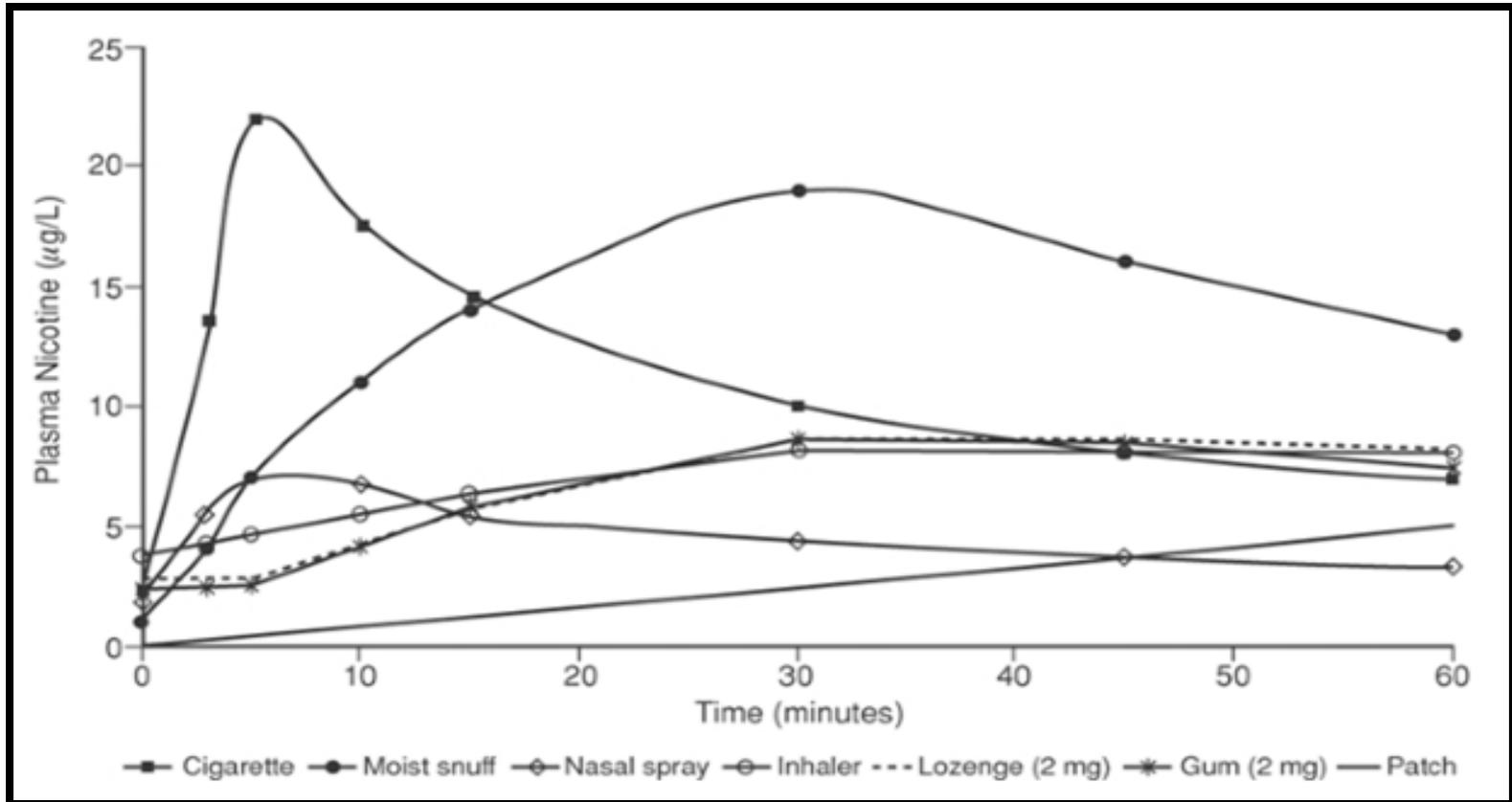
# History of Approved Medications

- ❖ 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 ↑ success for quitting **by ↓ 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.
- ❖ A meta-analysis of 111 controlled trials, enrolling > 43,000 participants, found that all NRT formulations result in statistically significant improvements in abstinence rates when compared with placebo.
- ❖ Patients using NRT are **1.6 times as likely to quit** smoking than are those receiving placebo.

## Plasma nicotine concentrations for various nicotine-containing products



- 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)

- ⊙ NicoDerm CQ uses a rate-controlling membrane.
- ⊙ The generic patches use drug-dispersion-type systems whereby release of nicotine is controlled by diffusion of the drug across an adhesive layer.
- ⊙ The currently marketed formulations (which continuously release nicotine over 24 h) deliver nicotine **more slowly** than the gum, lozenge, nasal spray, & inhaler.
- ⊙ Plasma nicotine levels obtained via transdermal delivery are approximately **50% lower than those achieved with cigarette smoking** but still alleviate the symptoms of withdrawal.

# Dosing

## ❖ >10 cigarettes/day:

- a) **21 mg/day × 4 weeks** (generic)
- b) 21 mg/day × 6 weeks (Nicoderm CQ)
- c) **Then 14 mg/day × 2 weeks**
- d) **Then 7 mg/day × 2 weeks**

## ❖ ≤10 cigarettes/day:

- ❖ **14 mg/day × 6 weeks**
- ❖ **Then 7 mg/day × 2 weeks**

❖ May wear patch **for 16 h** if patient experiences sleep disturbances (remove at bedtime)

❖ **Duration: 8–10 weeks**

# Nicotine Gum (Nicorette)<sup>®</sup>

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 approximately **1.1 & 2.9 mg** of nicotine are extracted from the 2- & 4-mg gum formulations, respectively.
- ❖ **C<sub>max</sub> of nicotine** are achieved approximately **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 to 3 months rather than using it “as needed” to control cravings.**

# Nicotine Lozenge (Commit)<sup>®</sup>

OTC 2 mg, 4 mg

- ❖ The nicotine polacrilex lozenge is a resin complex of nicotine & polacrilin in a sugarfree lozenge.
- ❖ Because the nicotine lozenge **dissolves completely**, it delivers approximately 25% more nicotine than does an equivalent dose of **nicotine gum**.
- ❖ Like the nicotine gum, the lozenge also contains **buffering agents** (sodium carbonate & potassium bicarbonate) to ↑ salivary pH, thereby enhancing buccal absorption of the nicotine.
- ❖ **C<sub>max</sub> of nicotine** with the lozenge are achieved after 30 to 60 min of use & then slowly ↓ thereafter.

# Dosing

- ⊙ 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.
- ❖ 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.

# Nicotine Nasal Spray

Rx

- ⊙ The nicotine nasal spray is an aqueous solution of nicotine available in a metered-spray pump for administration to the nasal mucosa.
- ⊙ Each actuation delivers a metered **50- $\mu$ L 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 to 18 min** after administration.

# Dosing

- ❖ A dose of nicotine (1 mg) is administered as 2 sprays, one (0.5-mg spray) in *each* nostril. The recommended **initial regimen is 1 to 2 doses every hour while awake for 6 to 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 to 8 weeks of therapy** because less frequent administration may be less effective.
- ❖ After 6 to 8 weeks, the dose should be gradually ↓ over an additional 4 to 6 weeks.
- ❖ **Duration: 3–6 months**

# Nicotine Inhaler

Rx

10 mg cartridge Delivers 4 mg inhaled nicotine vapor

- ❖ The nicotine inhaler consists of a two-piece plastic device designed to deliver nicotine contained in individual cartridges. 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.** Plastic spikes located on the interior of both mouthpiece components pierce the protective foil covering on the cartridge, allowing the **release of 4 mg of nicotine vapor following inhalation.**
- ❖ 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<sub>max</sub> of Nicotine** with the inhaler are achieved after approximal **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**.
- ❖ In clinical trials, most successful quitters used an average of 6 to 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**

# ***Bupropion SR***



# ***Bupropion SR***

- ❖ **Atypical antidepressant medication 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.**

# Pharmacokinetics of Bupropion

- ❖ Absolute bioavailability: 5% to 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 to 27 h;  **$C_{ss}$  are reached within 5 & 8 days**, respectively.

# Dosing

- ❖ 150 mg PO Q am × 3 days, then ↑ to 150 mg PO BID
- ❖ Do not exceed 300 mg/day
- ❖ Treatment should be initiated while patient is still smoking
- ❖ Set quit date 1–2 weeks after initiation of therapy
- ❖ Allow at least 8 h between doses
- ❖ 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

# Adverse Reactions

- ❖ **Insomnia (35%–40%) & dry mouth (10%);** these usually lessen with continued use.
- ⦿ **Less common side effects:** headache, nausea, tremors, rash, Constipation , Dry mouth, Nervousness/difficulty concentrating
- ❖ **Seizures are a dose-related toxicity** associated with bupropion therapy (risk is 1/1,000 [0.1%]) . For this reason, bupropion is **contraindicated in patients with underlying seizure disorders** & those receiving concurrent therapy with other forms of bupropion.
- ❖ Bupropion also is contraindicated in patients with **anorexia or bulimia nervosa**, **patients undergoing abrupt discontinuation of alcohol or sedatives (including BZDs)**, & **patients currently taking MAOIs** due to the ↑ potential for seizures in these populations.

# Varenicline

# Varenicline

- ⊙ **Partial agonist**, highly selective for the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor.
- ⊙ The partial agonist activity induces modest receptor stimulation leading to **↑ dopamine levels** that attenuate the symptoms of nicotine withdrawal.
- ⊙ In addition, by competitively blocking the binding of nicotine to nicotinic acetylcholine receptors in the CNS, **varenicline inhibits the surges of dopamine release that occur immediately following inhalation of tobacco smoke.**
- ⊙ The latter mechanism may be effective in preventing relapse **by ↓ the pleasure** associated with smoking.

# Pharmacokinetics

- ⊙ Varenicline absorption is **virtually complete** after oral administration, & **oral bioavailability is unaffected by food or time-of-day dosing**.
- ⊙ Once absorbed, varenicline undergoes minimal metabolism, with **92% excreted unchanged in the urine**.
- ⊙ Renal elimination is primarily through glomerular filtration, along with active tubular secretion, possibly via the organic cation transporter, OCT2.
- ⊙ **The half-life is approximately 24 h**, & following administration of multiple oral doses,  **$C_{ss}$  are reached within 4 days**.

# Dosing of Varenicline

- ⊙ Treatment should be initiated **1 week before the patient stops smoking.**
  - Days 1–3: 0.5 mg PO Q am
  - 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**
- ❖ **Pregnancy category: C**

## ❖ **Adverse Reactions** (Varenicline is generally well tolerated.)

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

# Second-Line Agents

# Clonidine

- ❖ Clonidine is approved for use **as an antihypertensive agent**, but it is also effective in **↓ the autonomic symptoms** of both opioid & alcohol withdrawal.
- ❖ Dosages for tobacco cessation have ranged from **0.15 to 0.75 mg/day PO & 0.1 to 0.3 mg/day transdermally**.
- ❖ 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 approximately 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 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, which delivers relatively constant levels of drug, is used **to prevent the onset of severe withdrawal symptoms**, whereas the short-acting formulation, which delivers nicotine at a faster rate, 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).

- ⊙ Although many herbal & homeopathic products are available to help people quit smoking, **data that support their safety & effectiveness are lacking.**
- ⊙ Most herbal preparations for smoking cessation contain **lobeline**, an herbal alkaloid with partial nicotine agonist activity.
- ⊙ Although direct-to-consumer advertisements suggest that lobeline-containing preparations are safe & effective, **a meta-analysis found no evidence to support the role of lobeline as an effective aid for smoking cessation.**

# Postcessation Weight Gain

- ❖ Most tobacco users gain weight after quitting, & clinicians should neither deny the likelihood of weight gain nor minimize its significance.
- ❖ For nearly all patients, the health risks associated with postcessation weight gain are **negligible compared to the risks of continued smoking.**
- ❖ Studies suggest that most quitters gain < 4.53 Kg, but there is a broad range of weight gain reported, **with up to 10% of quitters gaining as much as 13.6 Kg.**
- ❖ In general, women tend to gain more weight than men.

- ⊙ For men & women, subgroups that are **more likely** to gain weight after quitting are African Americans, younger tobacco users (**younger than 55 years**), & heavier tobacco users (**those smoking >25 cigarettes per day**).
- ⊙ 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 an approximately **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**.

- ⊙ In general, a patient is less likely to be successful **if he or she attempts to change multiple behaviors at once**. For this reason, **strict dieting** to prevent weight gain, especially during the early stages of quitting, is generally not recommended.
- ⊙ Even modest physical activity (**e.g., walking 30 min daily**) has been found to attenuate the weight gain associated with smoking cessation.
- ⊙ Patient may consider pharmacotherapy options that have been shown to **delay weight gain** —this would include the **4-mg nicotine gum or lozenge or bupropion SR**.
- ⊙ It is important to note, however, that once the medication is terminated, the quitter gains, on average, an amount of weight that is comparable to that which would have been gained in the absence of medication.

# Drug Interactions With Smoking

# Smoking & Combined Hormonal Contraceptives

- ❖ **Estrogens** are known to **promote coagulation** by altering clotting factor levels & ↑ platelet aggregation.
- ❖ Substances present in tobacco smoke, including oxidant gases & other products of combustion, **induce a hypercoagulable state** ↑ the risk of acute CV events.
- ❖ **Exposure to both factors (smoking & high levels of estrogen)** greatly ↑ the risk of **thromboembolic** & thrombotic disorders.

- ⊙ Because of the ↑ risk of adverse CV events, current guidelines from the American College of Obstetricians & Gynecologists (ACOG) & the WHO state that combination estrogen-progestin contraceptives **should not** be used in women who are **older than 35 years of age & smoke**.
- ⊙ These organizations **recommend the use of progestin-only contraceptives** (oral & injectable formulations) & intrauterine devices in this population.

# Other Drug Interactions With Smoking

- ⊙ It is widely recognized that **polycyclic aromatic hydrocarbons (PAHs)**, present in appreciably large quantities in tobacco smoke, are responsible for most drug interactions with smoking.
- ⊙ PAHs, which are the products of incomplete combustion of tobacco, are **potent inducers of several hepatic CYP450 enzymes (CYP1A1, CYP1A2, & possibly CYP2E1)**.
- ⊙ Although other substances in tobacco smoke, including acetone, pyridines, benzene, nicotine, carbon monoxide, & heavy metals (e.g., cadmium), might also interact with hepatic enzymes, their effects appear to be less significant.
- ⊙ **Patients who begin smoking, or quit smoking, might require dosage adjustments for some medications.**

# Water Pipes

- ⦿ Hookah or water pipe smoking is an ancient method of tobacco use whereby users inhale smoke that is passed through water.
- ⦿ **Maassel:** a mixture of **tobacco, dried fruit pulp, honey, & molasses** in a variety of flavors.
- ⦿ Data suggest this form of tobacco use is becoming increasingly popular among **young adults.**
- ⦿ Recent surveys estimate a 13% to 20% prevalence of current water pipe smoking (use within the previous 30 days) among U.S. **college students.**

# Is this form of tobacco “safe”?

- ⊙ 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.”**
- ⊙ Furthermore, preliminary data suggest that water pipe smokers are **at risk for developing dependence** & other adverse health-related conditions associated with smoking.

# Thank you