

# Nicotine Use in Diabetes: Understanding the Connection and Pathways to Cessation

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## Indian Health Service

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# The Nicotine Landscape



- In the 21<sup>st</sup> century, the tobacco marketplace saw growth in a variety of new **nicotine** products
- In some products, nicotine is the primary ingredient
- Nicotine products are not without Risk
- Emerging evidence has found that periods of dual use of cigarettes and e-cigarettes can result in harms to health like, or in addition to, the harms from exclusive use of cigarettes



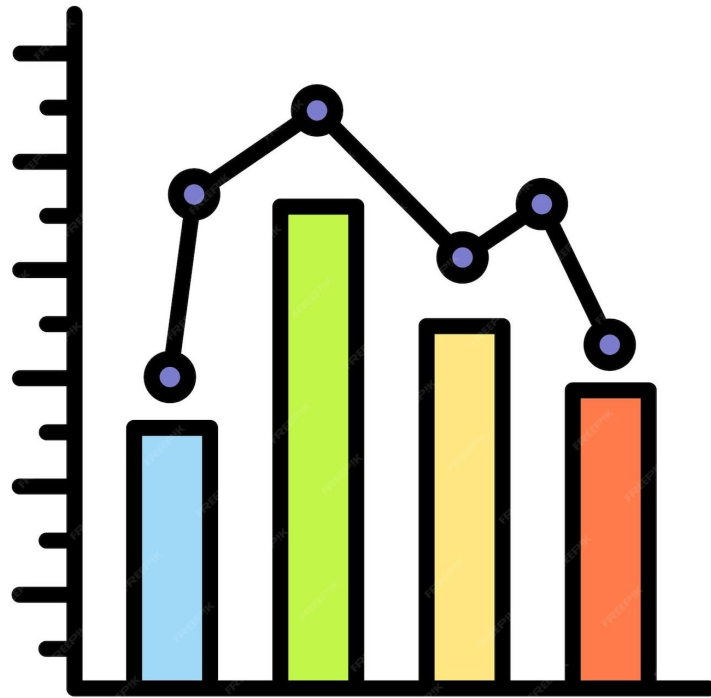
[A Common Language](#)

Source:

Global Tobacco Control <https://www.youtube.com/watch?v=afd-ciayb5U>

<https://www.fda.gov/tobacco-products/health-effects-tobacco-use/nicotine-why-tobacco-products-are-addictive>

# Current Nicotine Product Use in the US



- Prevalence of cigarette use from 2023 to 2024. No apparent changes were observed for cigars or e-cigarettes. Prevalence of smokeless tobacco use could not be compared because of definitional changes.
- In 2024, 12.6% of adults reporting using cigarettes or cigars
- In 2024, 18.8% of adults use at least one tobacco product
- Certain groups reported higher e-cigarette use than cigarettes, including those 18–24 years of age (14.8% vs. 3.4%), single/never married individuals (10.9% vs. 8.6%), and lesbian/gay individuals (19.3% vs. 10.6%)
- For adults that reported use, 80.0% used a single product, 17.4% used two products, 2.3% used three products, and 0.3% used all four products assessed.

Source: <https://evidence.nejm.org/doi/full/10.1056/EVIDpha2500339>

# What is Nicotine?

- Nicotine is a highly addictive chemical compound present in the tobacco plant
- Nicotine is what keeps people using tobacco products
- Products that contain nicotine are regulated as tobacco products by the Food and Drug Administration (FDA)
- Exposure to the thousands of chemicals contained in tobacco products and tobacco smoke make tobacco use harmful.
- Nicotine can affect multiple areas of the body including the brain, heart, lungs, bones, muscles, skin, and gastrointestinal tract

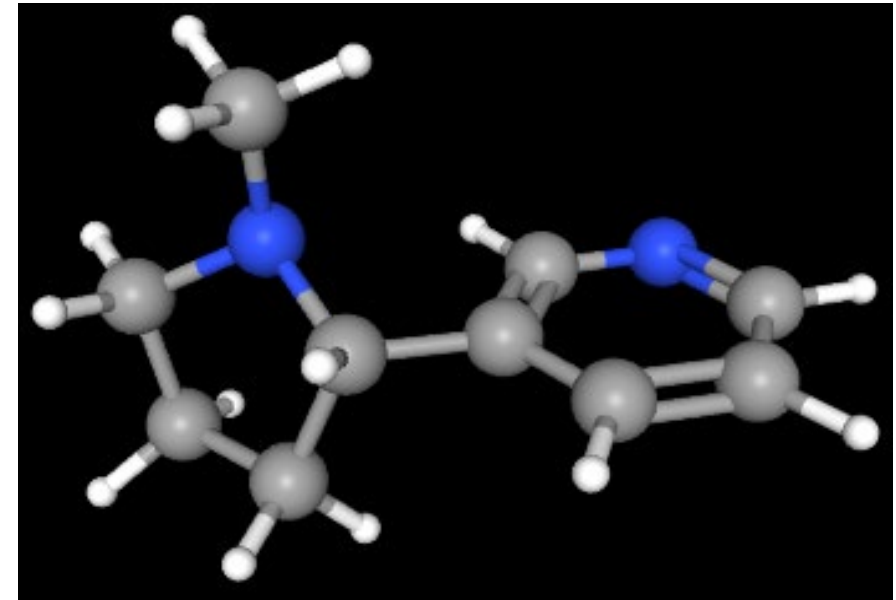


Image: <https://pubchem.ncbi.nlm.nih.gov/compound/Nicotine#section=3D-Conformer>

Source: <https://www.fda.gov/tobacco-products/health-effects-tobacco-use/nicotine-why-tobacco-products-are-addictive>

# Nicotine and the Brain

## Nicotine effects

- Judgement
- Attention
- Memory
- Reward System

## Withdrawal symptoms

- Irritability
- Depression
- Anxiety
- Sleep disturbances
- Increased appetite

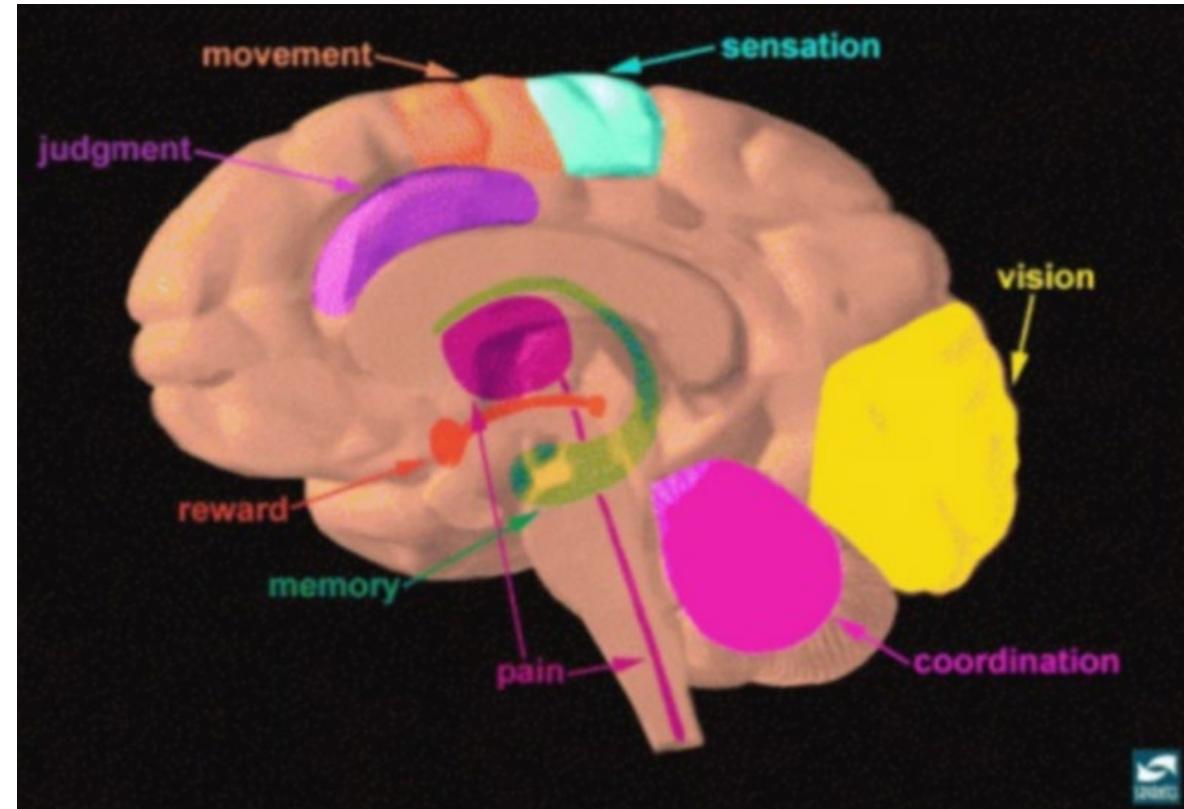


Image: <https://nida.nih.gov/sites/default/files/1922-the-neurobiology-of-drug-addiction.pdf>

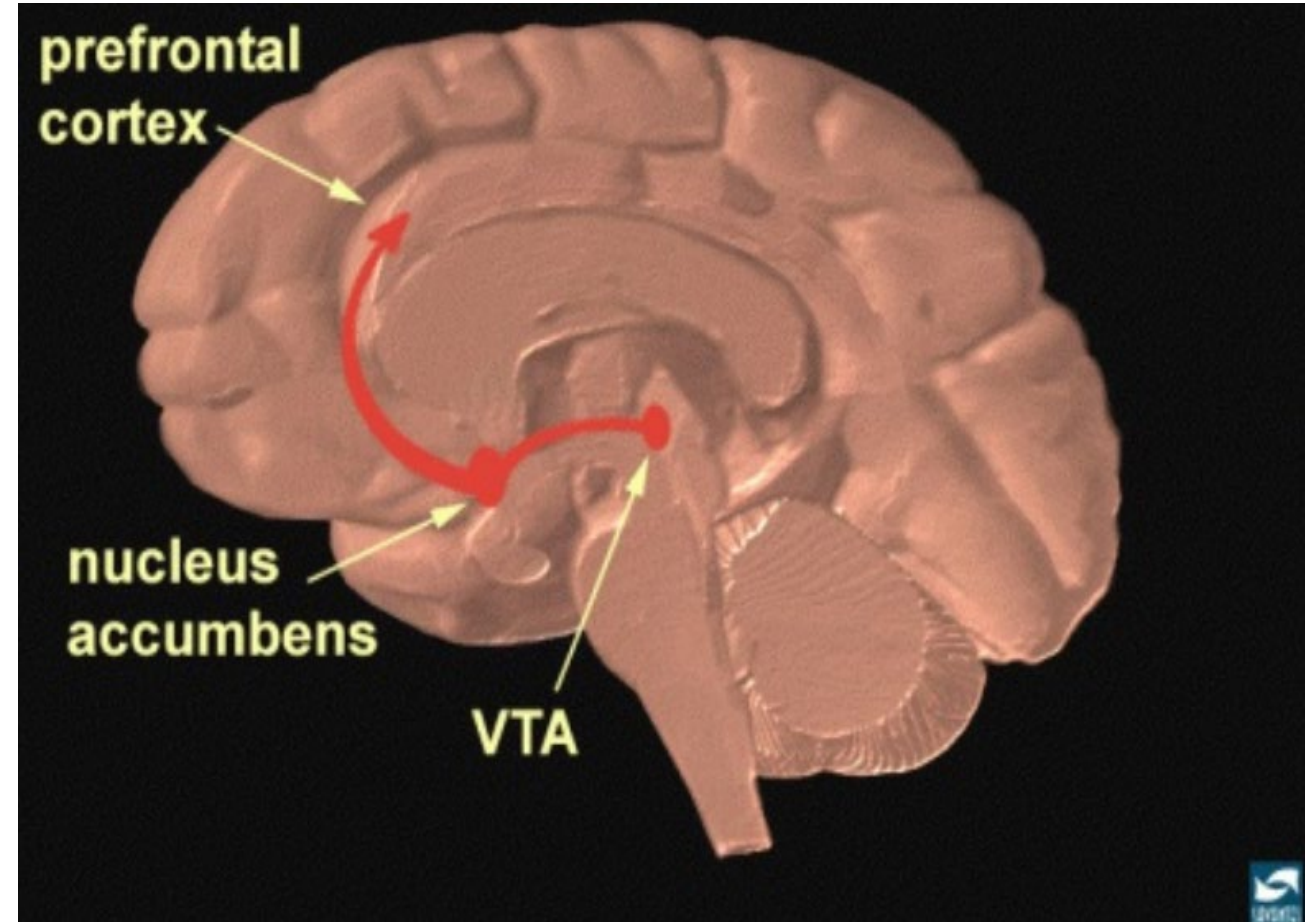
Source:

<https://nida.nih.gov/research-topics/drugs-a-to-z#N>

<https://pubmed.ncbi.nlm.nih.gov/37841907/>

# The Reward Pathway

- The ventral tegmental area (VTA) is connected to both the nucleus accumbens and the prefrontal cortex via this pathway, and it sends information to these structures via its neurons. The neurons of the VTA contain the neurotransmitter dopamine, which is released in the nucleus accumbens and in the prefrontal cortex.
- This pathway is activated by a rewarding stimulus, such as nicotine
- Increased dopamine
  - Pleasure / + Reinforcement



# Addiction



- Addiction is characterized by compulsive drug-seeking and use, even in the face of negative health consequences.
- Nicotine exposure leads to the upregulation of nicotinic acetylcholine receptors (nAChRs) in the brain
- Brain receptors can be conditioned to expect nicotine in certain situations
  - Trigger “situations” in which your body expects nicotine can include alcohol, stress, after meals
- The half life of nicotine is 120 minutes
- Without nicotine, the pleasure response is cut off
- In addition, withdrawal symptoms can occur when nicotine leaves the body leaving the receptors craving for nicotine
- The number of receptors and the and the speed of receptor upregulation can vary from person to person

Source:

<https://nida.nih.gov/publications/research-reports/tobacco-nicotine-e-cigarettes/nicotine-addictive>

<https://newsnetwork.mayoclinic.org/discussion/smokers-brains-change-in-response-to-high-levels-of-nicotine/>

# Nicotine and Neurotransmitter Release



## Short Term Benefits (Perceived)

- Dopamine-Pleasure
- Norepinephrine-Arousal, Appetite Suppression
- Acetylcholine-Arousal, Cognitive Enhancement
- Glutamate-Learning, Memory Enhancement
- Serotonin-Mood Modulation, Appetite Suppression
- Beta-endorphin-Reduced anxiety and tension
- GABA-Reduced anxiety and tension

## Long-Term Harms

- Addiction
- Anxiety
- Depression
- Insomnia
- Cognitive Deficits
- Attention Deficits



# Nicotine and the Gastrointestinal System

- **Nicotine can promote damage to epithelial cells of the oral mucosa**
- In the intestine, increased eosinophils accompany these changes.
  - Dry Mouth
  - Nausea
  - Heartburn
  - Dyspepsia
  - Diarrhea
  - Peptic Ulcers

The Digestive System

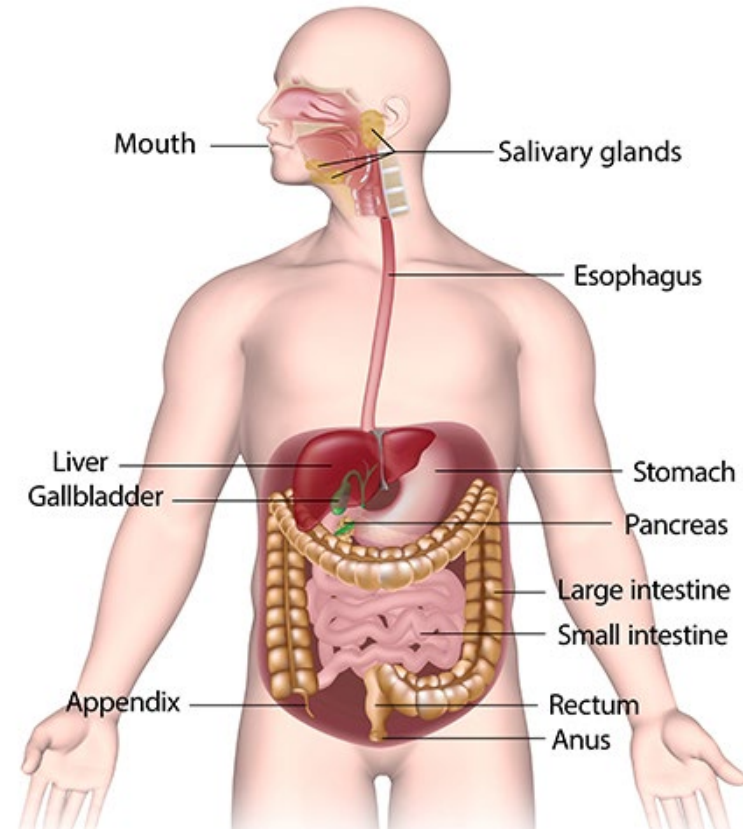


Image: <https://www.niddk.nih.gov/health-information/digestive-diseases/digestive-system-how-it-works>

Source: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3509054/>

# Nicotine and the Respiratory System

## **Nicotine can promote damage to epithelial cells in the lungs**

- Nicotine stimulates increased eosinophil number in the lamina propria (the thin connective tissue layer supporting mucous membranes) leading to edema and damage to basal cells in the trachea
- Nicotine directly affected the ionic homeostasis of lung cells and provokes an inflammatory reaction that contributes to cellular damage
- Lung damage may lead to Chronic Obstructive Pulmonary Disease (COPD)
- Respiratory side effects of nicotine may manifest as bronchospasm and shortness of breath

Source: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3509054/>

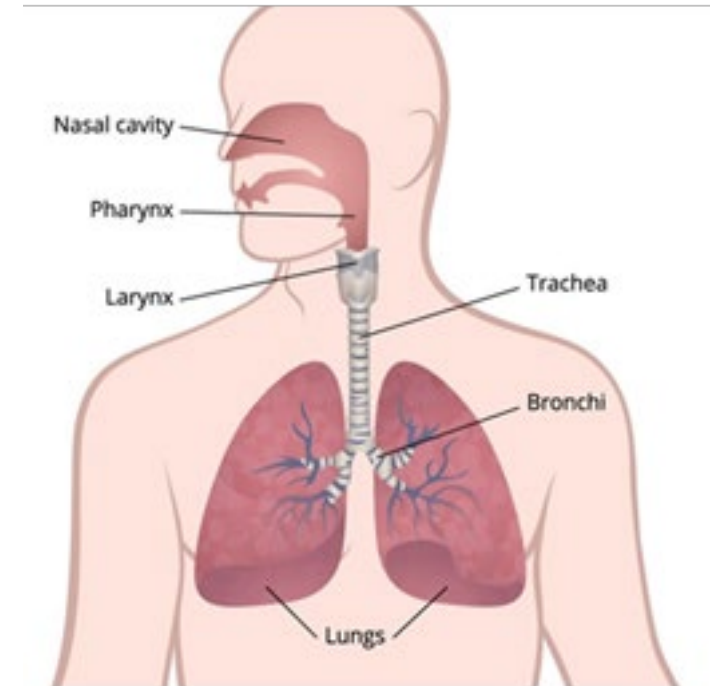


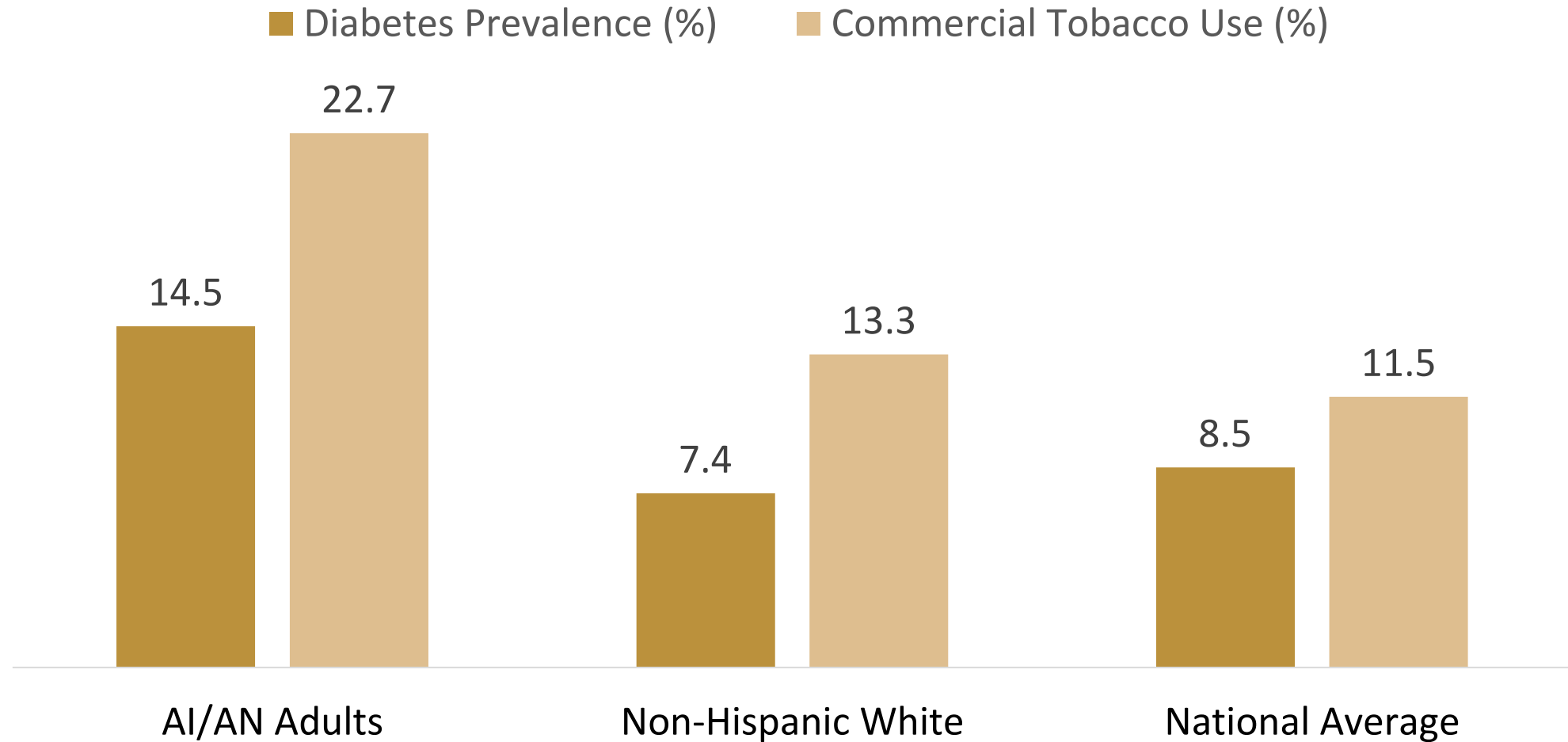
Image: <https://www.cdc.gov/lung-cancer/about/index.html>

# Nicotine and Other Organ Systems



- ❖ Nicotine alone was sufficient to stimulate increased expression of markers of oxidative stress and augment fibrotic and inflammatory pathways
  - Nicotine can damage kidney cells (podocytes) that play an important role in kidney filtration
- ❖ Musculoskeletal
  - Nicotine may shift bone metabolism in favor of catabolism (vs anabolism)
  - Nicotine exposure may increase risk for lower bone mineral density
  - Nicotine can increase cortisol level which can lead to muscle breakdown
- ❖ Immune – Nicotine can act as an immunosuppressant and weaken the body's immune response
- ❖ Reproductive
  - Nicotine may damage testicular cells leading to lower testosterone levels
  - Nicotine can lower fertility in men and women
- ❖ Additional mechanisms by which nicotine impacts disease progression are not well known but are the subject of current research.
  - Answer to the question: what promotes disease progression? cigarette vs nicotine vs a combination

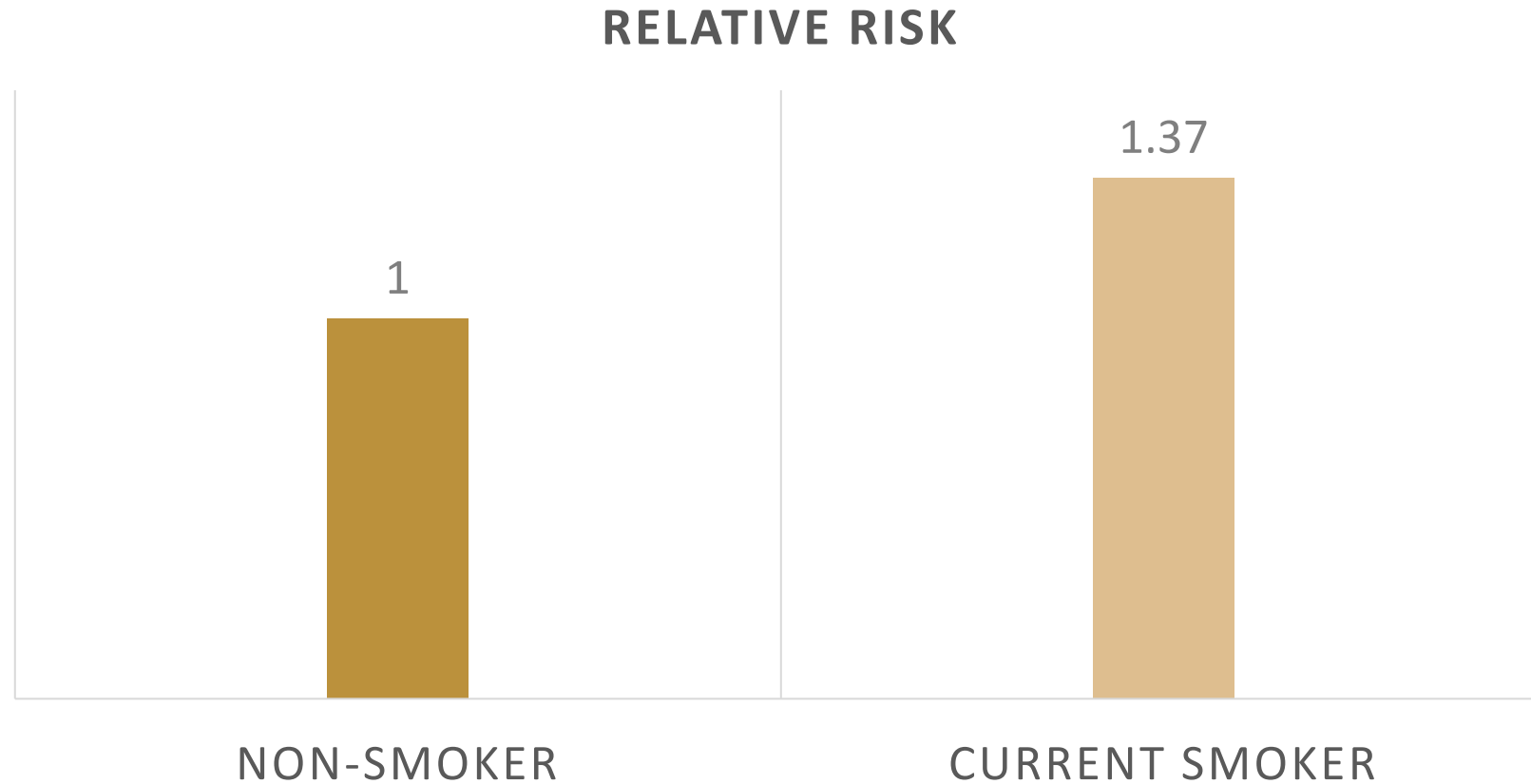
# The Dual Burden in AI/AN Populations



CDC National Diabetes Statistics Report, 2023.

CDC Office on Smoking and Health – Tobacco Use by Race/Ethnicity. *The National Health Interview Survey*

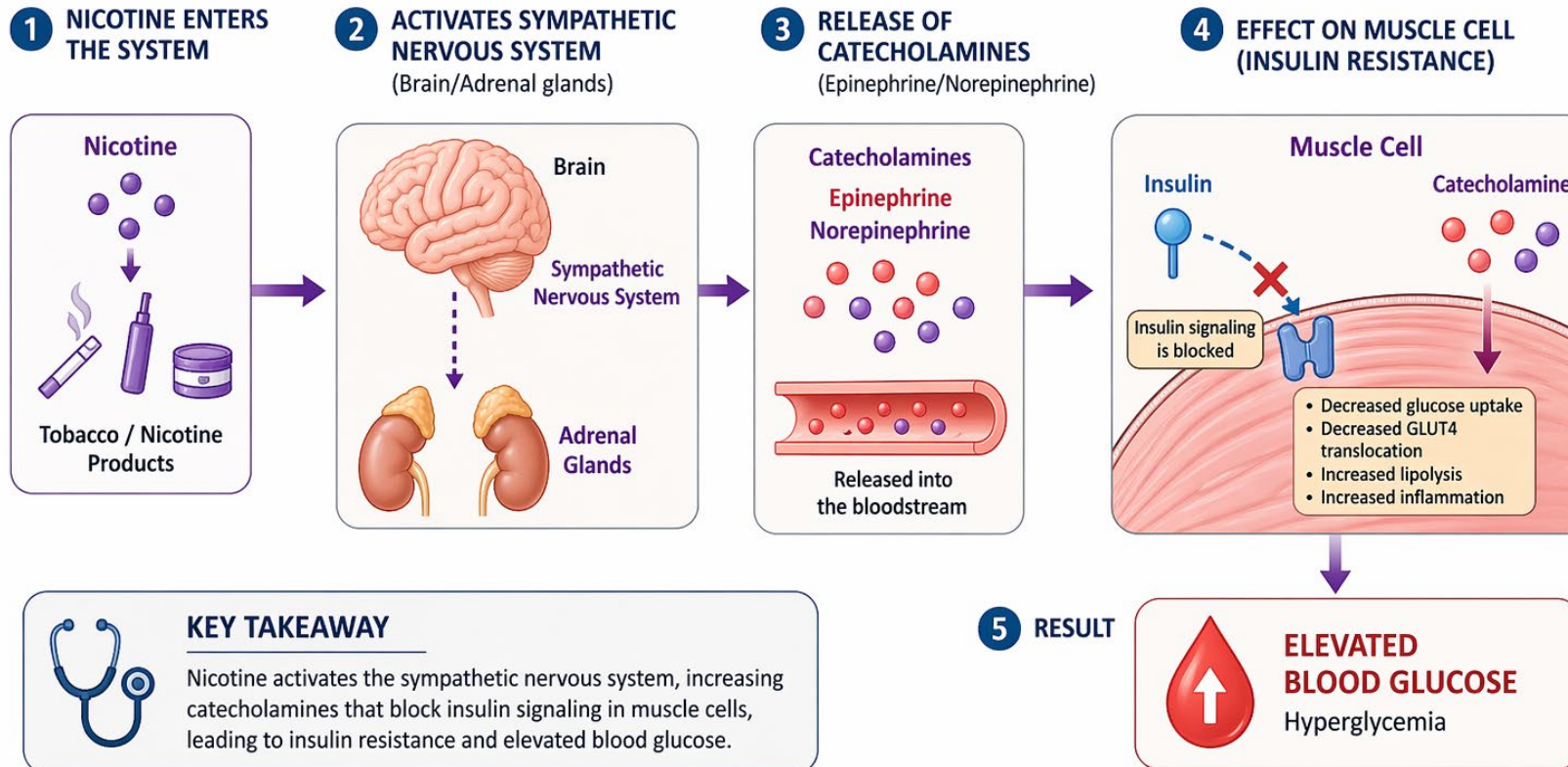
# Smoking and Risk of Type 2 Diabetes



*Pan A et al. Diabetes Care. 2015;38(4):574-586.*

# PATHOPHYSIOLOGY OF INSULIN RESISTANCE

## How Nicotine Leads to Elevated Blood Glucose



### KEY TAKEAWAY

Nicotine activates the sympathetic nervous system, increasing catecholamines that block insulin signaling in muscle cells, leading to insulin resistance and elevated blood glucose.

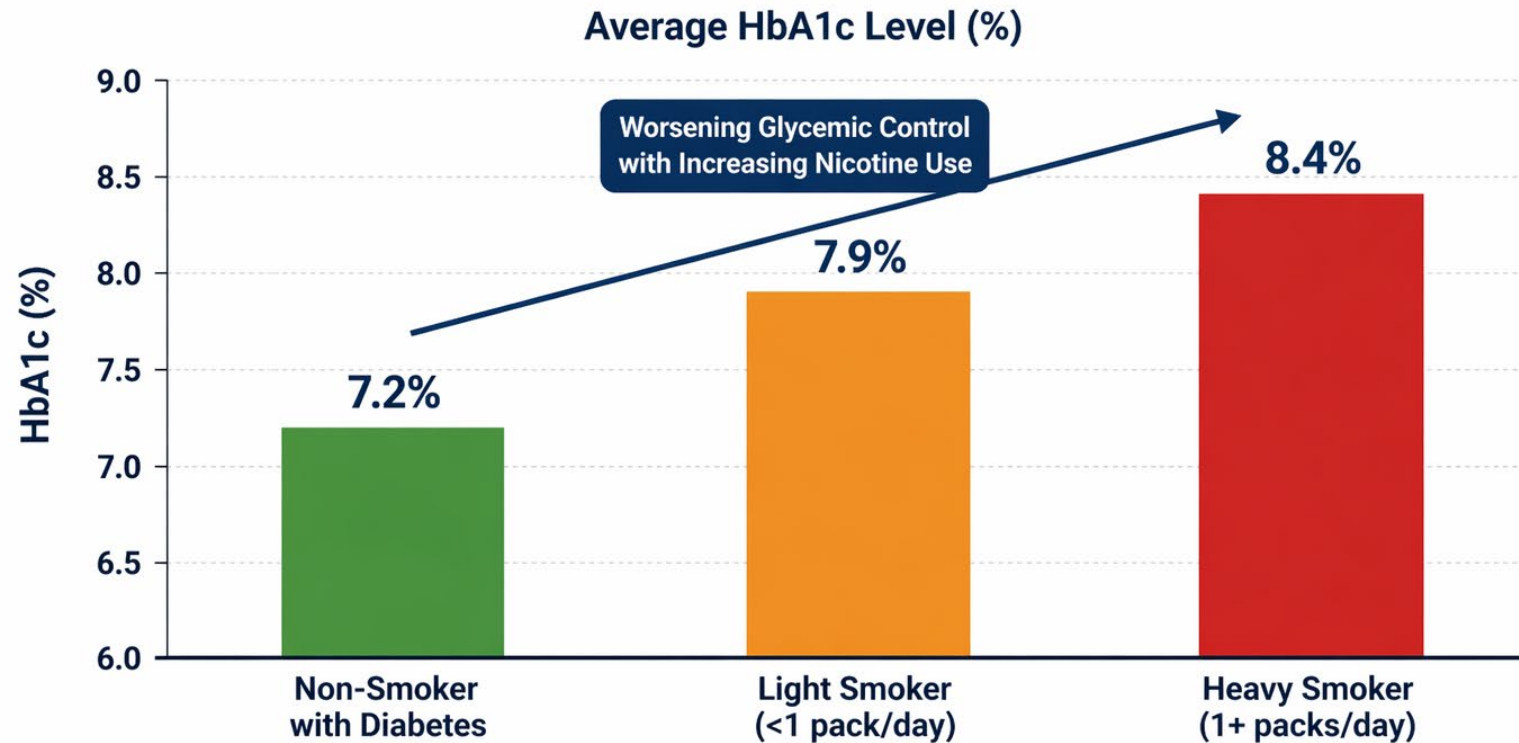
*Nicotine use worsens insulin resistance, making blood glucose harder to control.*

### References

- Xie XT, et al. Acta Pharmacol Sin. 2009;30(1):1-8.
- DeFronzo RA, et al. Diabetes Care. 2015;38(8):1407-1415.
- ADA Standards of Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S1-S298.

# Commercial Nicotine Use and Glycemic Control

*Higher Nicotine Use is Associated with Higher HbA1c Levels*



**Takeaway:** As commercial nicotine use increases, average HbA1c levels are higher, indicating poorer glycemic control among people with diabetes.

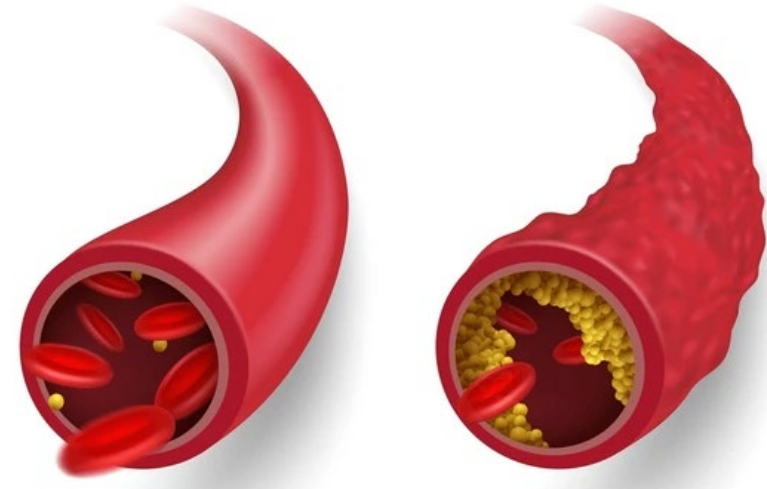


Data Source: Illustrative clinical data.

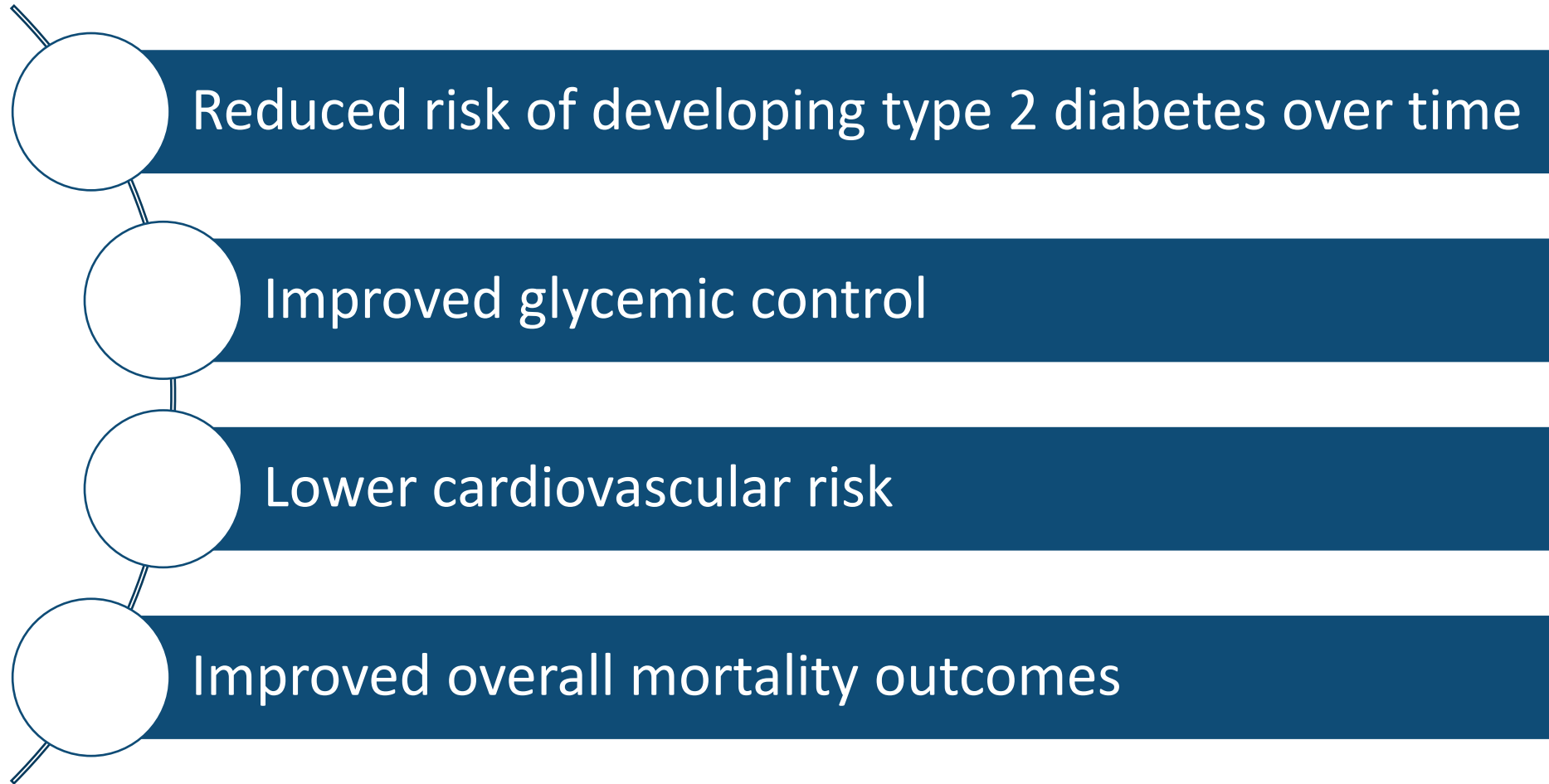
Pan A et al. *Diabetes Care*. 2015;38(4):574-586. (Meta-analysis of 88 studies; smokers had higher HbA1c by ~0.26%)

# Amplification of Diabetic Complications

- Cardiovascular Disease (CVD):  
Smoking multiplies the elevated CVD risk in diabetes
- Nephropathy: Nicotine accelerates the progression of kidney function decline
- Neuropathy and Retinopathy:  
Reduced tissue oxygenation worsens nerve damage



# Benefits of Smoking Cessation



# Nicotine Cessation Fast Facts



- Nicotine dependence is a chronic, relapsing condition that often requires repeated intervention and long-term support.
- In 2022, 67.7% of adults who smoked said they wanted to quit smoking
- In 2022, 8.8% of adults who smoked were able to successfully quit smoking in the past year.
- Counseling + pharmacotherapy has the highest success rate

Source:

<https://www.cdc.gov/tobacco/hcp/patient-care-settings/clinical.html>

<https://www.cdc.gov/tobacco/php/data-statistics/smoking-cessation/index.html>

<https://pubmed.ncbi.nlm.nih.gov/25282429/>

# Nicotine Cessation Fast Facts (Cont.)

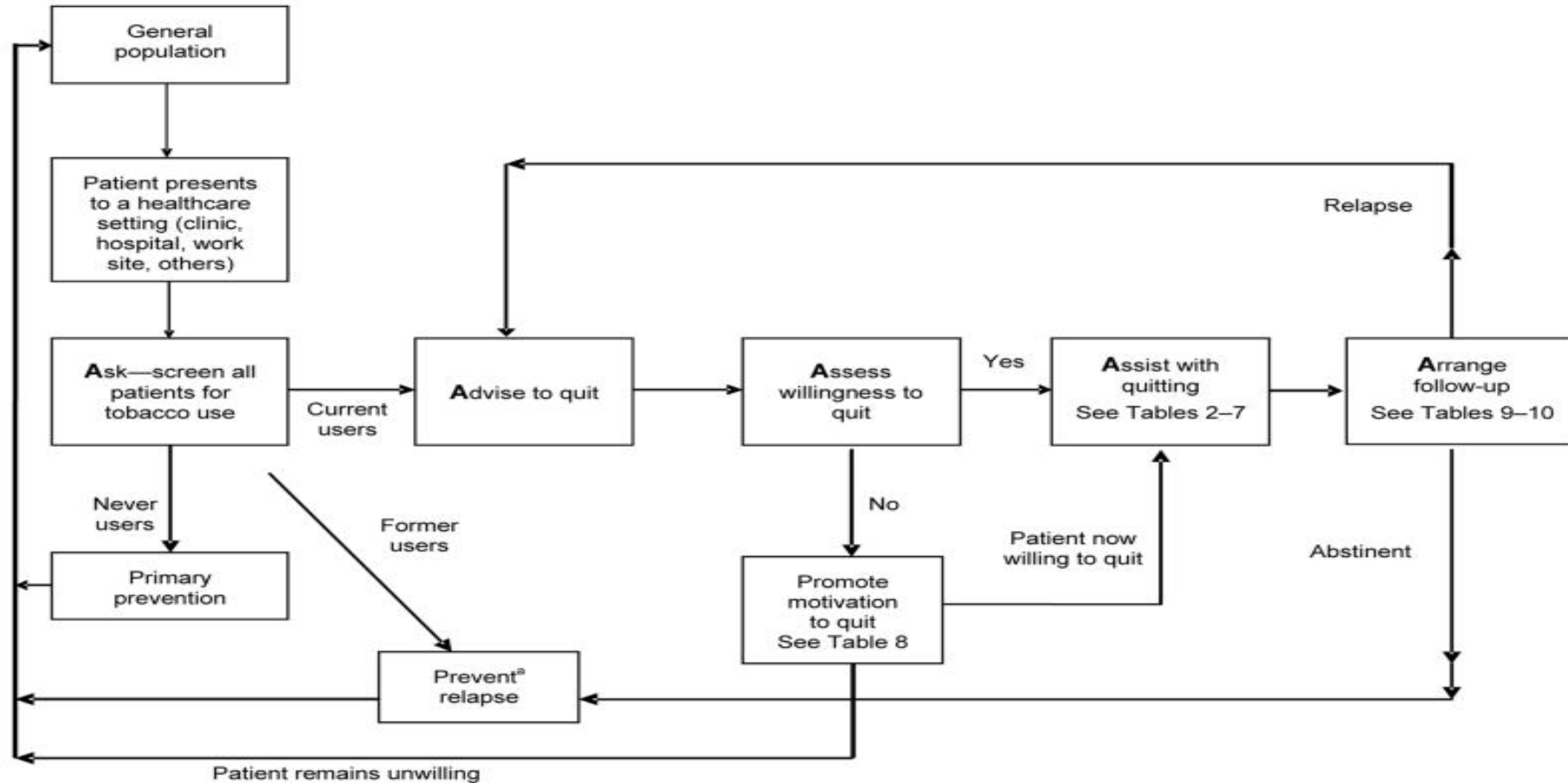


A six-month prospective cohort study showed use of NRT alone without assistance may be worse than no intervention at all

| Smoking Cessation Treatment                             | Adjusted Odds of Abstinence |
|---------------------------------------------------------|-----------------------------|
| Prescription medication + specialist behavioral support | 2.58 (95% CI, 1.48-4.52)    |
| prescription medication + brief advice                  | 1.55 (95% CI, 1.11-2.16)    |
| NRT bought over the counter                             | 0.68; 95% CI, 0.49-0.94).   |

Kotz D, Brown J, West R. Prospective cohort study of the effectiveness of smoking cessation treatments used in the "real world". Mayo Clin Proc. 2014 Oct;89(10):1360-7.. PMID: 25282429.

# 5 A's Model – USPHS Clinical Practice Guidelines



Source: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4465757/>

# Treatment Strategies



## Biochemical Dependence

- Withdrawal Prevention
- *Target with medication*

## Psychosocial Conditioning

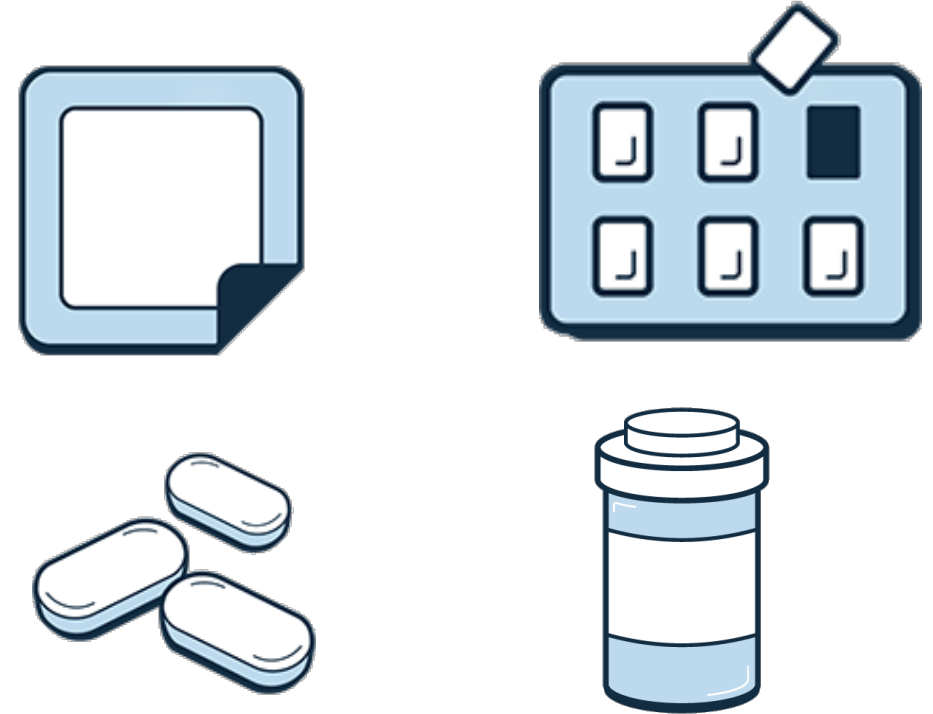
- Triggers
- Cues
- *Target with behavior change*

Source:  
<https://www.ncbi.nlm.nih.gov/books/NBK493148/>  
<https://pmc.ncbi.nlm.nih.gov/articles/PMC2946180/>

# Pharmacotherapy



- Nicotine Replacement Therapy (NRT)
  - Short Acting
    - Nicotine Gum
    - Nicotine Lozenge
    - Nicotine Nasal Spray
    - Nicotine Inhaler (discontinued)
  - Long Acting
    - Nicotine Patch
- Oral Medication
  - Bupropion SR
  - Varenicline



Images: <https://www.cdc.gov/tobacco/about/how-to-quit.html>

Source: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4465757/>

# Principles of Oral Cessation Medication



## ❖ Bupropion SR

### Mechanism of Action

- Inhibitor of dopamine and noradrenaline reuptake
- May weaken the reinforcing properties of nicotine during withdrawal

## ❖ Varenicline

### Mechanism of Action

- An  $\alpha 4\beta 2$  receptors antagonist
- Blocks the ability of nicotine to activate and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking

## ❖ Clinical Pearl – patients should start medication prior to their quit date

Source:

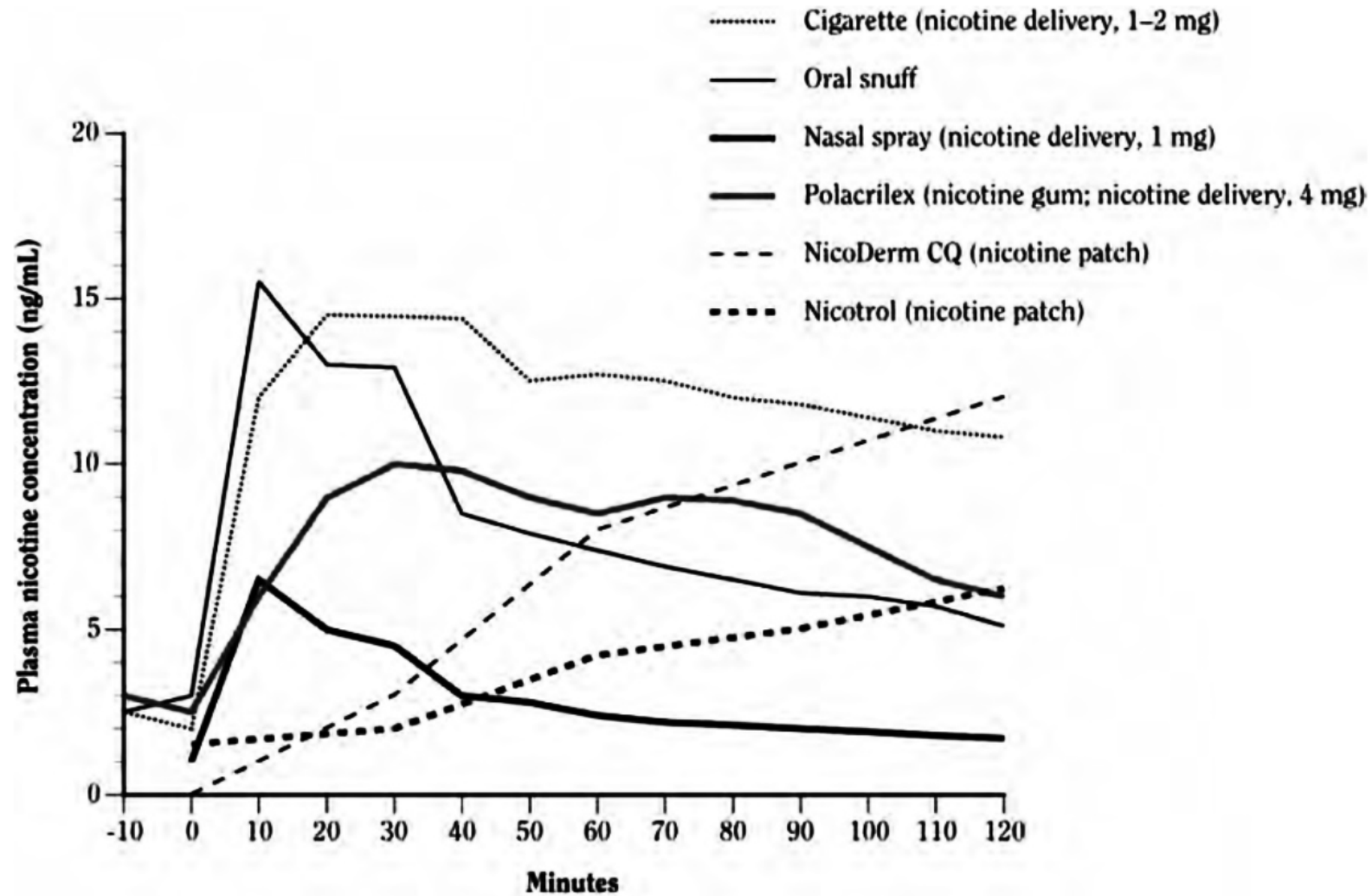
<https://pubmed.ncbi.nlm.nih.gov/16109583/>

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/021928s008lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021928s008lbl.pdf)

# Principles of Nicotine Replacement Therapy (NRT)



- ❖ Mechanism of Action
  - Replicates the nicotine response typically experienced through smoking, thereby helping individuals manage cravings and withdrawal symptoms
- ❖ Clinical Pearls
  - Maintain same dose for 4-6 weeks and gradually taper
  - Can be used in combination with other medications



Source: <https://www.ncbi.nlm.nih.gov/books/NBK53018/figure/ch4.f1/>

# Nicotine Patch (OTC)

Starting Dose Range - 21mg vs 14mg

- Target 24-hour nicotine consumption and use for 6 weeks
- 1 cigarette = 1mg nicotine
- 1 Pack per day = 20 cigarettes

Duration – 8-10 weeks

Adverse Reactions

- Skin reaction (common)
- Hypertension (rare)
- Tachyarrhythmia (rare)
- Cardiac dysrhythmia (rare)

Warnings/Precautions

- Recent Myocardial Infarction
- Serious underlying arrhythmia
- Serious or worsening angina pectoris

Counseling Points

- Not recommended for patients with dermatologic conditions
- If impacting sleep, may remove patch before bed



21mg  
14mg  
7mg

# Nicotine Gum (OTC)



## Starting Dose 4mg vs 2mg

- Chew and park one piece every 1-2 hours while awake for 6 weeks

## Duration – 12 weeks

## Adverse Reactions

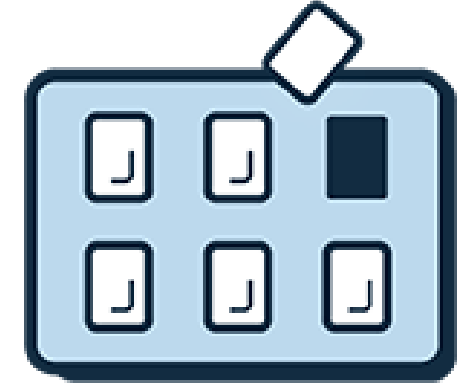
- Nausea, Mouth / Jaw Pain, Hiccups
- Dyspepsia, Hypersalivation

## Warnings/Precautions

- Temporomandibular Joint (TMJ) Disease
- Recent Myocardial Infarction
- Serious underlying arrhythmia
- Serious or worsening angina pectoris

## Counseling points

- Chew & Park between cheek and gum to achieve peppery / tingling sensation. Rotate to different areas of the mouth until sensation does not return.
- Improper technique may cause throat irritation and lightheadedness
- Do not exceed 24 pieces in 24 hours
- Do not eat or drink for 15 minutes before or during use



- Use 4mg – If time to first cigarette is 30 minutes or less after waking
- Use 2mg – If time to first cigarette is > 30 minutes after waking

# Nicotine Lozenge (OTC)



Starting Dose – 4mg vs 2mg

- Use one piece every 1-2 hours while awake for 6 weeks

Duration – 12 weeks

Adverse Reactions

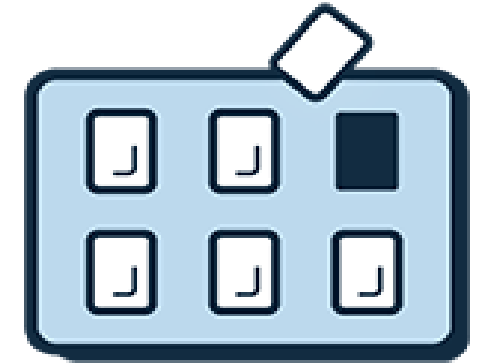
- Nausea, Hiccups, Cough,
- Heartburn, Headache, Insomnia

Warnings/Precautions

- Recent Myocardial Infarction
- Serious underlying arrhythmia
- Serious or worsening angina pectoris

Counseling points

- Do NOT chew or swallow
- Rotate to different areas of the mouth and allow to slowly dissolve
- May feel a tingling sensation as nicotine is released
- Do not exceed 20 lozenges in 24 hours
- Do not eat or drink for 15 minutes before or during use



- Use 4mg – If time to first cigarette is 30 minutes or less after waking
- Use 2mg – If time to first cigarette is > 30 minutes after waking

# Nicotine Nasal Spray (Rx)



## Starting Dose

- Use one spray in each nostril per hour 1-2 hours while awake for 6 weeks

Duration – 3 to 6 months

## Adverse Reactions

- Hot, peppery, or burning sensation in the nose or throat
- Rhinitis, Tearing, Sneezing, Cough, Headache

## Warnings/Precautions

- Severe reactive airway disease
- Underlying chronic nasal disorders
- Recent myocardial Infarction
- Serious underlying arrhythmia
- Serious or worsening angina pectoris

## Counseling points

- Recommend initially using 8 doses (16 sprays) daily
- Do not sniff, swallow, or inhale while dose is being administered
- Do not exceed 5 doses (10 sprays) per hour or 40 doses (80 sprays) per day

# Nicotine Inhaler (Rx, Discontinued)



**US Manufacturer discontinued product in 2023 due to shortage of raw materials**

## Starting Dose

- 1 cartridge every 1-2 hours (6-16 cartridges per day)

Duration – 3 to 6 months

## Adverse Events

- Mouth and/or throat irritation
- Cough, Headache, Rhinitis, Dyspepsia, Hiccups

## Warnings/Precautions

- Bronchospastic disease
- Recent Myocardial Infarction
- Serious underlying arrhythmia
- Serious or worsening angina pectoris

## Counseling Points

- Do not inhale like a cigarette to deliver to lungs. Puff in short breaths or inhale into back of throat
- Cartridges may be less effective in cold environments (less than 60F)

# Bupropion SR (Rx)



## Starting Dose

- 150mg daily for 3 days, then increase to 150mg twice daily

Duration – 7 to 12 weeks or longer in selected patients

## Adverse Events

- Insomnia, dry mouth, nervousness/difficulty concentrating, Nausea
- Dizziness, Constipation, Rash, Seizures, Neuropsychiatric Symptoms

## Contraindications

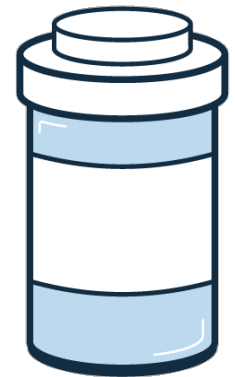
- Seizure disorder, concomitant bupropion therapy, current or history of bulimia or anorexia nervosa, simultaneous abrupt discontinuation of alcohol or sedatives/benzodiazepines, MAOI inhibitors the last 14 days or concurrent use of reversible MAO inhibitors

## Warnings/Precautions

- **Boxed warning** - suicidality
- Concomitant use with medications that lower the seizure threshold
- Hepatic impairment

## Counseling Points

- Start medication 1 to 2 weeks prior to goal quit date
- If insomnia occurs, afternoon dose can be taking 8 hours after morning dose



# Varenicline (Rx)



## Starting Dose

- 0.5mg daily for 3 days, 0.5mg twice daily for 4 days, then 1mg twice daily

Duration – 3 to 6 months

## Adverse Events

- Nausea, sleep Disturbances (insomnia/vivid dreams), Constipation
- Flatulence, Vomiting, Neuropsychiatric Symptoms

## Warnings/Precautions

- Renal dose adjustment

## Counseling Points

- Start medication 1 week prior to goal quit date
- Take dose after eating and with a full glass of water



# Combination Therapy



Opportunity exists to increase smoking abstinence rates and decrease withdrawal symptoms by using combinations of pharmacotherapies that have been proven to be effective as monotherapies:

- Long Acting NRT + Short Acting NRT
- Long Acting NRT + Bupropion SR
- Long Acting NRT + Short Acting NRT + Bupropion
- Varenicline + Bupropion SR

Source: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3164516/pdf/nihms-318611.pdf>

# Motivational Interviewing (MI)



- Collaborative conversation style
- Seeks to motivate patients who are ambivalent about a change towards making the behavior change
- Seeks to call forth a patient's own motivation and commitment
  - Partnership – Not Confrontation
  - Acceptance – Not Judgement
  - Compassion – Not Indifferent
  - Empowerment - Not Giving Advice
- Avoidance of “Sustain Talk” and utilization of “Change Talk”

# Motivational Interviewing (cont.)



## Tools of MI

- **O**pen Ended Questions
- **A**ffirmations
- **R**eflections
- **S**ummaries

## Recognizing

- **D**esire to change
- **A**bility to change
- **R**eason to change
- **N**eed
- **C**ommitment
- **A**ctivation
- **T**aking steps

# Patient Case



- ☐ TW is a 54-year-old male, member of a local tribal community with a diagnosis of Type 2 Diabetes (diagnosed 6 years ago) and Hypertension.
- ☐ He smokes 1 pack of commercial cigarettes per day (30-pack-year history). Uses traditional tobacco occasionally for prayer and ceremonial purposes.
- ☐ Current Medications: Metformin 1000mg BID, Insulin glargine 10 units daily, Lisinopril 10mg daily.
- ☐ Chief Complaint / Motivation: TW is visiting the clinic for a routine diabetes check. He mentions his feet have been "tingling" more frequently at night. He recently welcomed his first grandchild and states, "I want to be around to teach him how to fish, but I know these cigarettes are slowing me down. I think I'm ready to quit."

# Patient Case

| Metric            | Current Reading                       | Clinical Context (Nicotine's Role)                                                                                                               |
|-------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| HbA1c             | 8.6% (Elevated)                       | Chronic catecholamine release from commercial nicotine is inducing systemic insulin resistance, making his Metformin and insulin less effective. |
| Blood Pressure    | 142/88 mmHg                           | Nicotine causes acute vasoconstriction, exacerbating his baseline hypertension and putting severe strain on microvascular networks.              |
| Neuropathy Screen | Decreased sensation in bilateral toes | Reduced tissue oxygenation (hypoxia) from smoking is accelerating his peripheral neuropathy.                                                     |

# Patient Case



1. Acknowledge &  
Differentiate

2. Connect the Dots  
(Neuropathy)

3. Prepare for Glycemic  
Shifts

4. Harm Reduction &  
NRT

5. Coordinated Follow-  
Up

# Strategies for Smoking Cessation

- Integrate smoking status checks into every visit
- Tailor cessation strategies to respect cultural differences
- Monitor for glycemic fluctuations during quit attempts



Medical Check Up

# Nicotine and the Cardiovascular System



## *Sources*

<https://nida.nih.gov/research-topics/parents-educators/mind-matter-series/nicotine-tobacco-vaping>

[https://pmc.ncbi.nlm.nih.gov/articles/PMC8505064/#:~:text=Tobacco%20smoke%20is%20an%20established,aneurysms%20and%20dissections%20\(TAAD\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC8505064/#:~:text=Tobacco%20smoke%20is%20an%20established,aneurysms%20and%20dissections%20(TAAD))

<https://pubmed.ncbi.nlm.nih.gov/32473788/>

[https://pmc.ncbi.nlm.nih.gov/articles/PMC8505064/#:~:text=Tobacco%20smoke%20is%20an%20established,aneurysms%20and%20dissections%20\(TAAD\)](https://pmc.ncbi.nlm.nih.gov/articles/PMC8505064/#:~:text=Tobacco%20smoke%20is%20an%20established,aneurysms%20and%20dissections%20(TAAD))

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<https://pmc.ncbi.nlm.nih.gov/articles/PMC3711704/>

<https://pmc.ncbi.nlm.nih.gov/articles/PMC6077562/>

<https://pmc.ncbi.nlm.nih.gov/articles/PMC9871277/>

<https://pubmed.ncbi.nlm.nih.gov/39323358/>

