

Tobacco Use Disorder:

... a history...

ENDS;

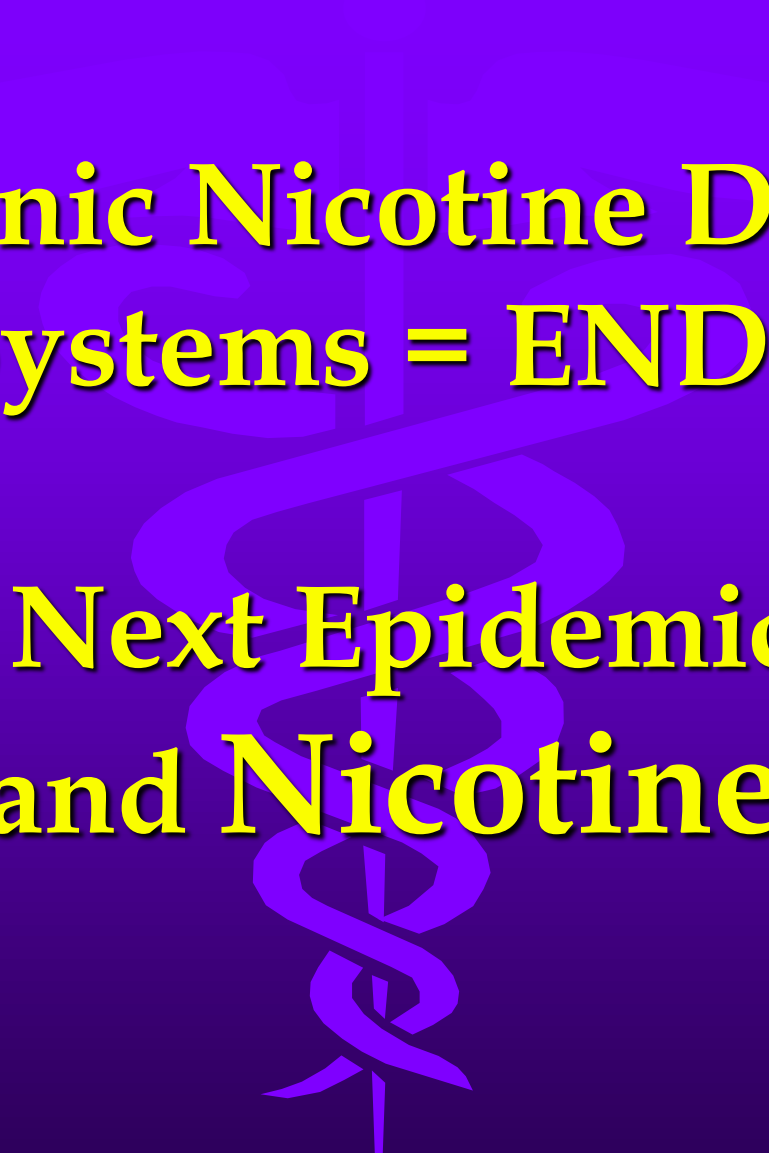
A Pediatric Disease;

A Chronic Disease;

Nicotine Dependence Disorder;

formerly... Smoking Cessation...

Albee Budnitz. MD, FACP, FCCP



Electronic Nicotine Delivery Systems = ENDS

The Next Epidemic? ... and Nicotine

This “Political Appliance” is passed down from Administration to Administration.

It is the only thing that passes Party lines without any argument



Tobacco Smoke Enema (1750s-1810s)

The tobacco enema was used to infuse tobacco smoke into a patient's rectum for various medical purposes, primarily the resuscitation of drowning victims. A rectal tube inserted into the anus was connected to a fumigator and bellows that forced the smoke towards the rectum. The warmth of the smoke was thought to promote respiration, but doubts about the credibility of tobacco enemas led to the popular phrase "blow smoke up one's ass."



Disclosures

- No financial disclosures...
- But I've had a lot of help!!
 - BNH (CVS Health grant summer, 2018 has resulted in “Vaping Unveiled” -TM)
 - Koop group, TFK, getoutraged.org
 - Stanford Univ on-line resources
 - NHDHHS, NNEPCC, stakeholders' collaboration

Déjà vu ... all over again - Yogi Berra

Nicotine – Replacement “Customers”

Other Tobacco products (OTP's), old and new

- Hookah's → “water” pipes
- Cigars/cigarillos → small flavored cigars
- Bidi's/snuff/chew →, sticks, dissolvable's...
- **ENDS**; e-cig's, tanks, mods, “heated” tobacco, iQOS, and JUUL's, JUUL's “2.0”

Conclusions.

- Electronic cigarettes are a constantly evolving class of products with great variability among members of the class in terms of electrical power, nicotine emissions, and design.
- In U.S. high school students, electronic cigarette use is more prevalent than tobacco cigarette use.
- Electronic cigarettes deliver the drug nicotine that causes dependence and can also alter brain development in adolescents.
- Evidence regarding ECIG effectiveness for smoking cessation is equivocal at best.
- While we know there are some toxicants in ECIG emissions, we have virtually no information about the long-term health effects of electronic cigarettes.

ENDS – what we will cover

- **Nicotine**
 - addiction;
 - gateway
- **ENDS – hx,**
 - what are they,
 - business; **customers**, marketing
 - what we know and don't know
 - what we need do now!
 - what we need look for – the future

Awareness/counter-marketing videos

YouTube - Real Teens Talk Vaping (2016)



AWARENESS/COUNTER-MARKETING VIDEOS



Real Teens Talk Vaping (2016)



Tobacco Free CA

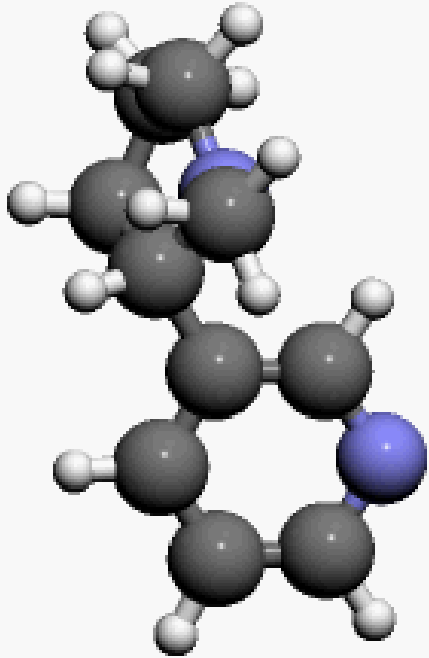
FDA -There's An Epidemic (2018)



The Real Cost

What is Nicotine?

Nicotine Molecule



- Drug
- Stimulant
- Highly Addictive
- Causes changes in brain chemistry
- Found in tobacco products

Where Can You Find Nicotine?



Nicotine

- A toxic colorless or yellowish oily liquid, **found naturally in tobacco**
- It acts as a **stimulant** in small doses, but in larger amounts blocks the action of autonomic nerve and skeletal muscle cells
- Repeated doses of nicotine alter the brain's activities
- Nicotine can also be a **sedative**
- Nicotine **is highly addictive**, as addictive as cocaine, heroin and more so than alcohol
- Nicotine is sometimes used in insecticides

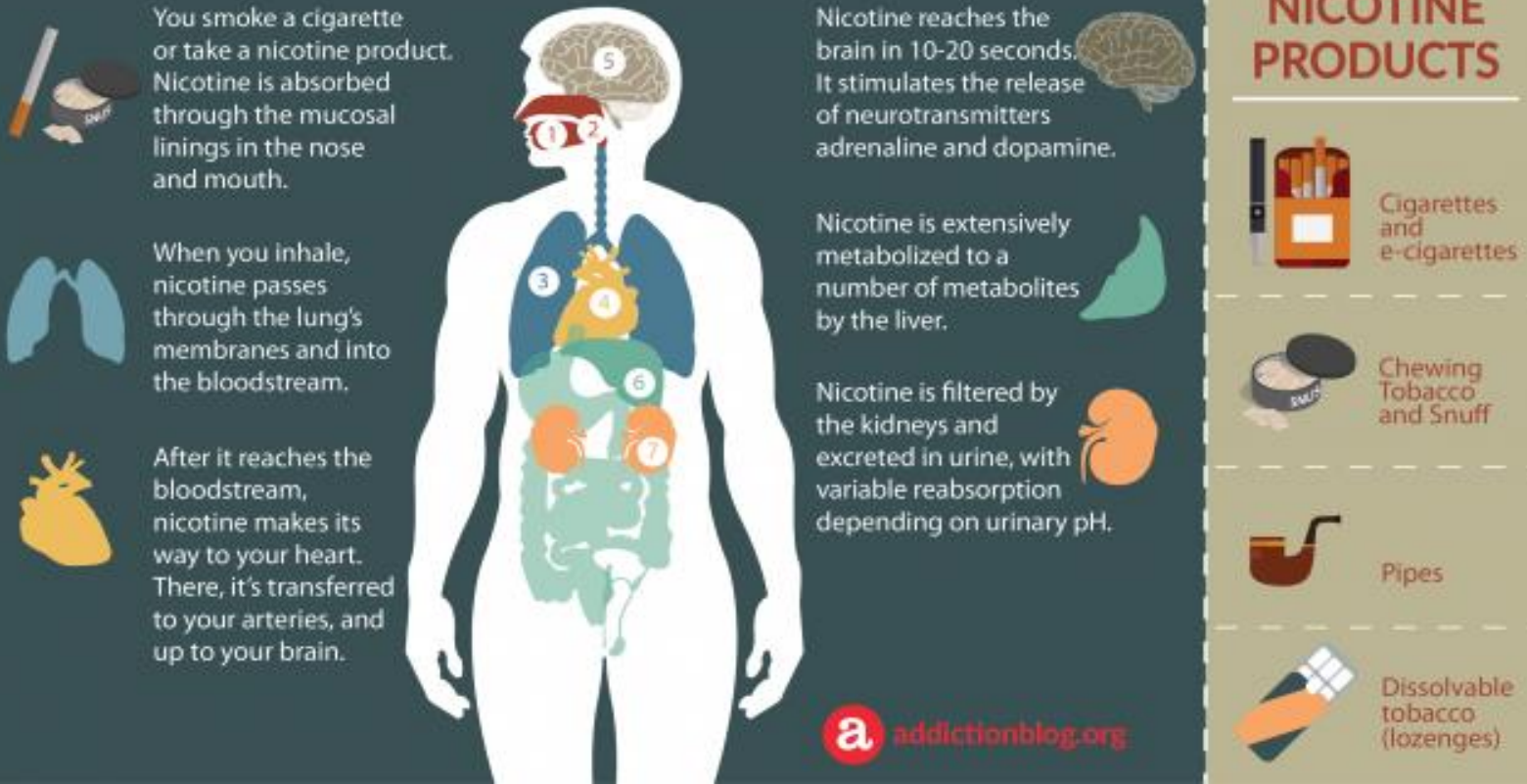


Nicotine

- Not a carcinogen
- Liquid in its native state
- Distilled from burning tobacco and carried on tar droplets
- Liquid nicotine plus entrained gas phase free nicotine
- Only free (unprotonated) nicotine crosses biological membranes
- Inhalation → peak arterial concentrations 2-4 X venous concentrations

Nicotine Effect on the Body

HOW DOES NICOTINE WORK IN THE BODY?



Effects of Nicotine and/or Smoking

Central Nervous System

- ↓ anxiety and stress
- ↑ well-being
- ↑ mental acuity on task performance
- As potent as cocaine and heroin**
- ↑ alertness

Cardiovascular

- ↑ heart rate acutely
- ↑ blood pressure acutely
- ↓ peripheral perfusion

Pulmonary

- ↑ risk of chronic obstructive pulmonary disease

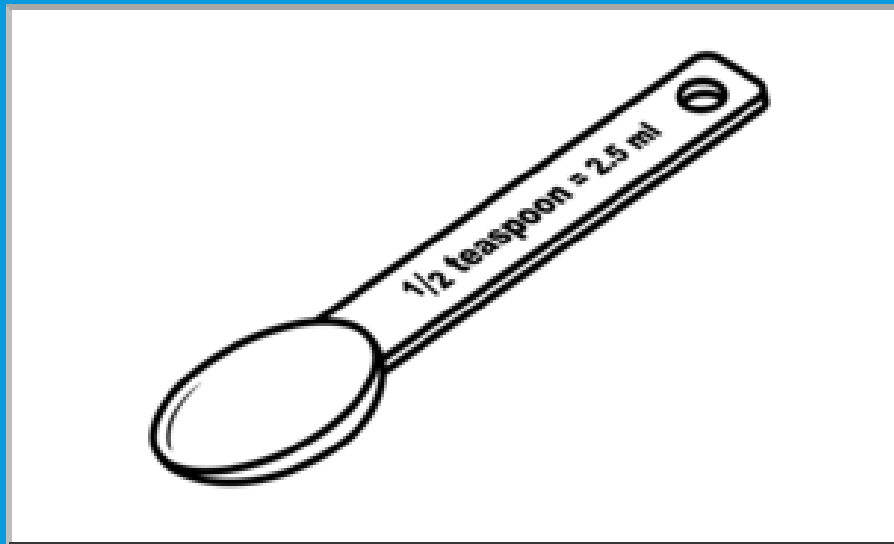
Other Systems

- ↑ basal metabolic rate and blood sugar levels
- ↑ peristalsis
- ↓ hunger pangs for 15–60 min

Does not cause cancer; not one of the > 70 carcinogens in combusted tobacco; “butt” ? co-carcinogen

NICOTINE EFFECT ON TODDLERS, SMALL PETS

Less than half a teaspoon of a nicotine containing e-cig/vape solution can be fatal to the average toddler and small pets.

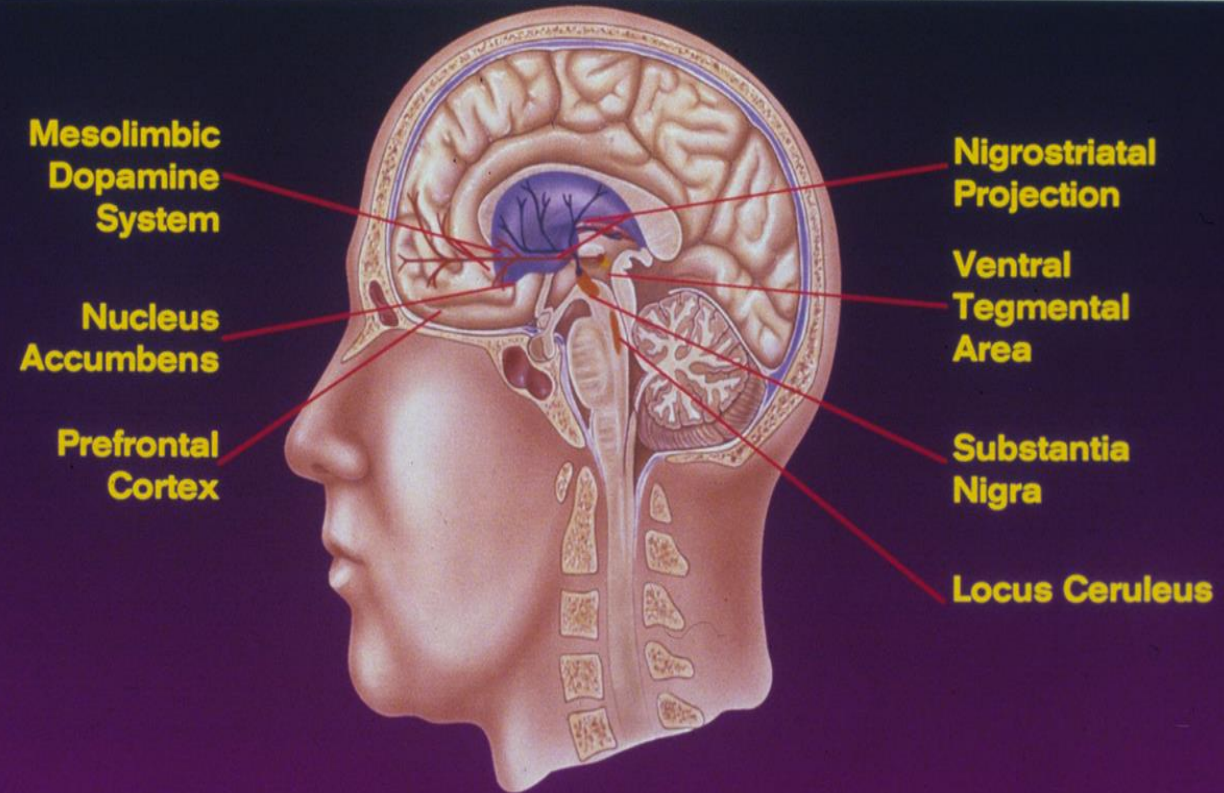


Nicotine is an addictive drug.

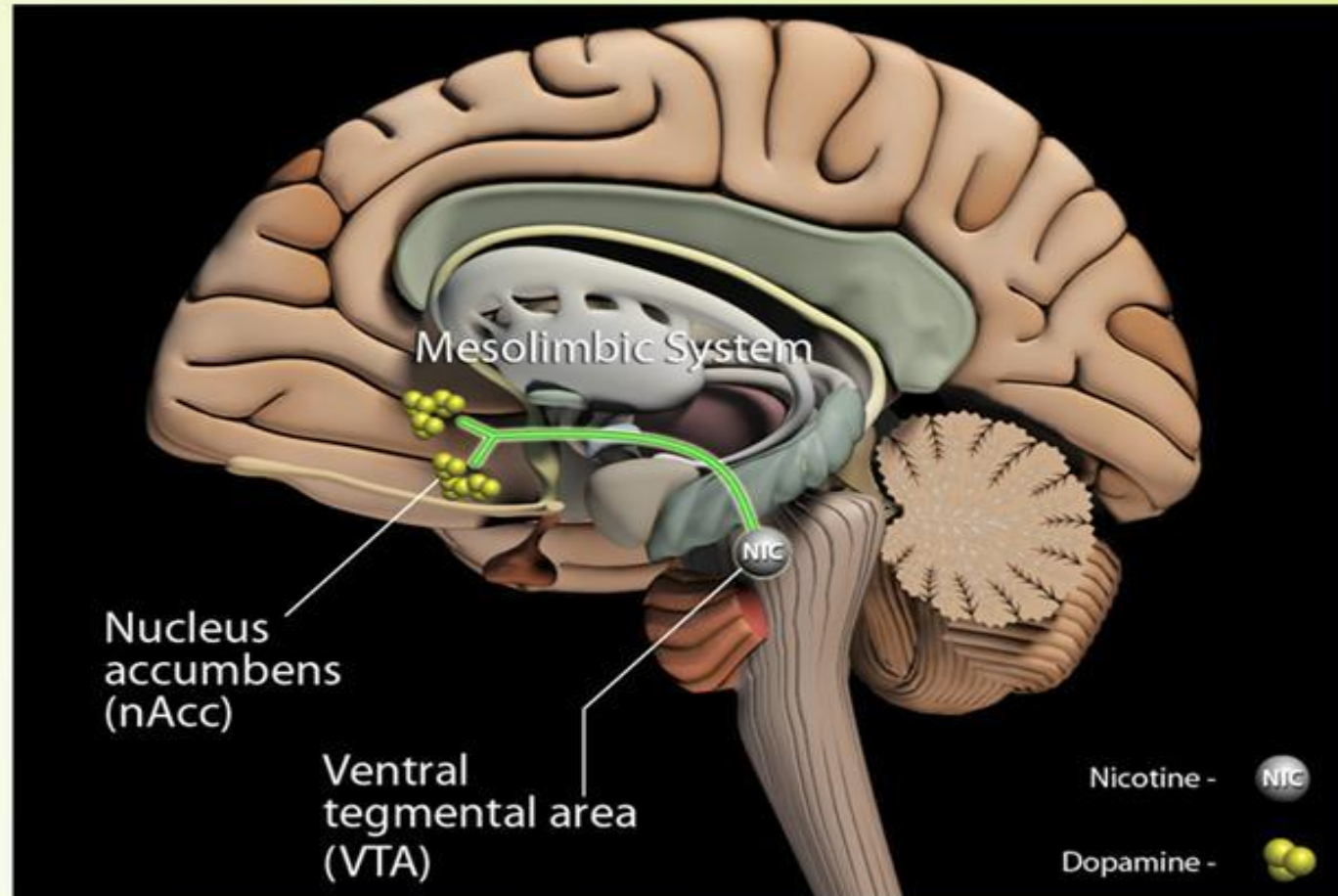
Physiologic Dependence

- Mesolimbic/reward, motivational behavior, feel good...
- Locus ceruleus/ vigilance, arousal-irritability...

Anatomy of Reward and Withdrawal



Mechanism of Action of Nicotine in the Central Nervous System

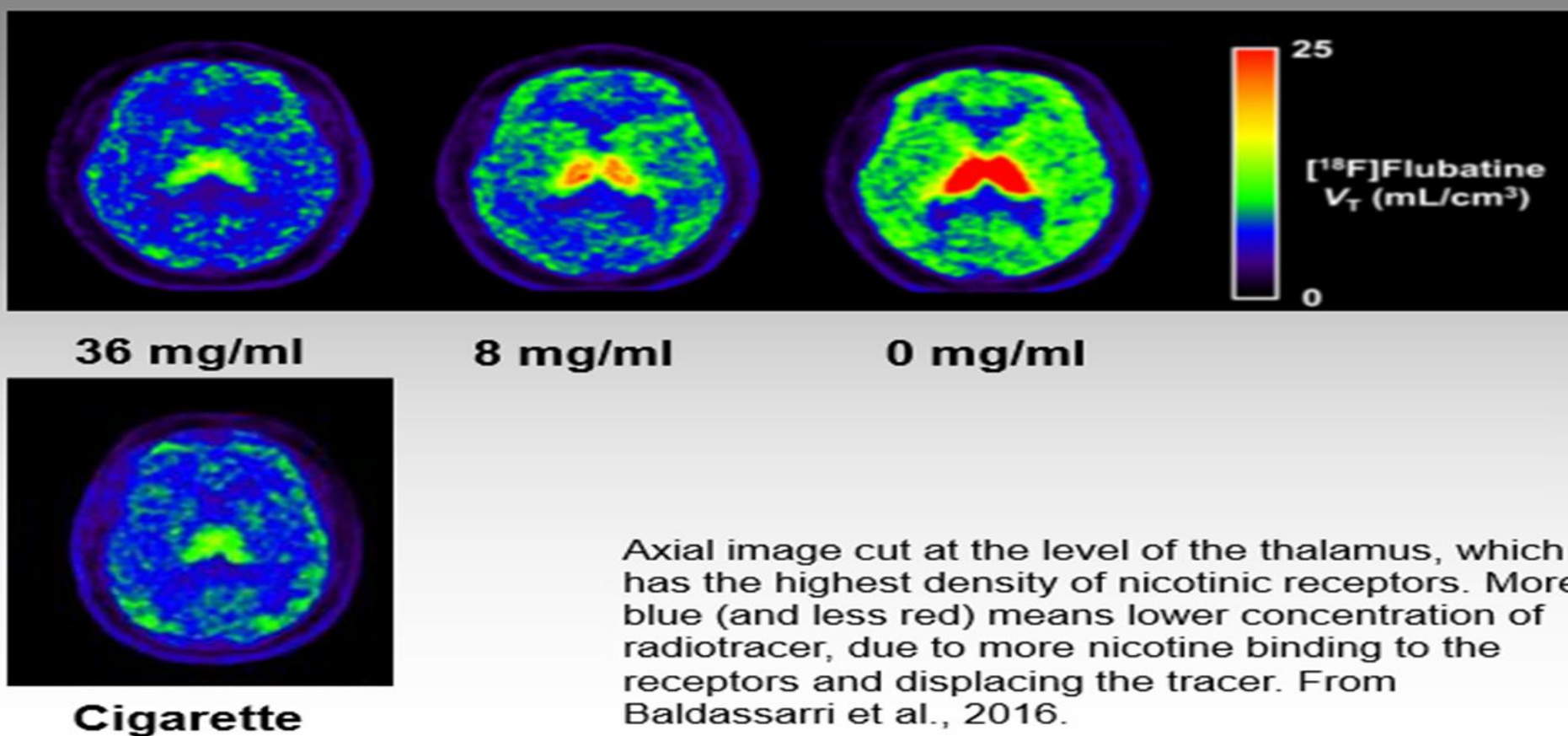


- Nicotine binds predominantly to nicotinic acetylcholine (nACh) receptors in the CNS; the primary is the $\alpha 4\beta 2$ nicotinic receptor in the Ventral Tegmental Area (VTA)
- After nicotine binds to the $\alpha 4\beta 2$ nicotinic receptor in the VTA, it results in a release of dopamine in the Nucleus Accumbens (nAcc) which is believed to be linked to reward

Tom Eissenberg, PhD, VCU, 9/2018, Koop Summit

Axial image cut at the level of the thalamus, which has the highest density of nicotinic receptors. More blue (and less red) means lower concentration of radiotracer, due to more nicotine binding to the receptors and displacing the tracer. From Baldassarri et al., 2016.

ECIG-delivered nicotine gets to the brain.



Cigarettes and Tobacco Dependence

- Cigarette smoke – complex mixture of 7,000 chemicals with >60 known carcinogens
- Most efficient delivery device for nicotine that exists- better than I.V.
- Cigarette manufacturers modified cigarettes over the past decades to maximize nicotine delivery to the brain
- High doses of arterial nicotine → upregulation of the nicotinic acetylcholine receptors
- Genetic factors influence tobacco dependence
- Left untreated >60% of smokers die from a tobacco-caused disease

Nicotinic Acetylcholine Receptors

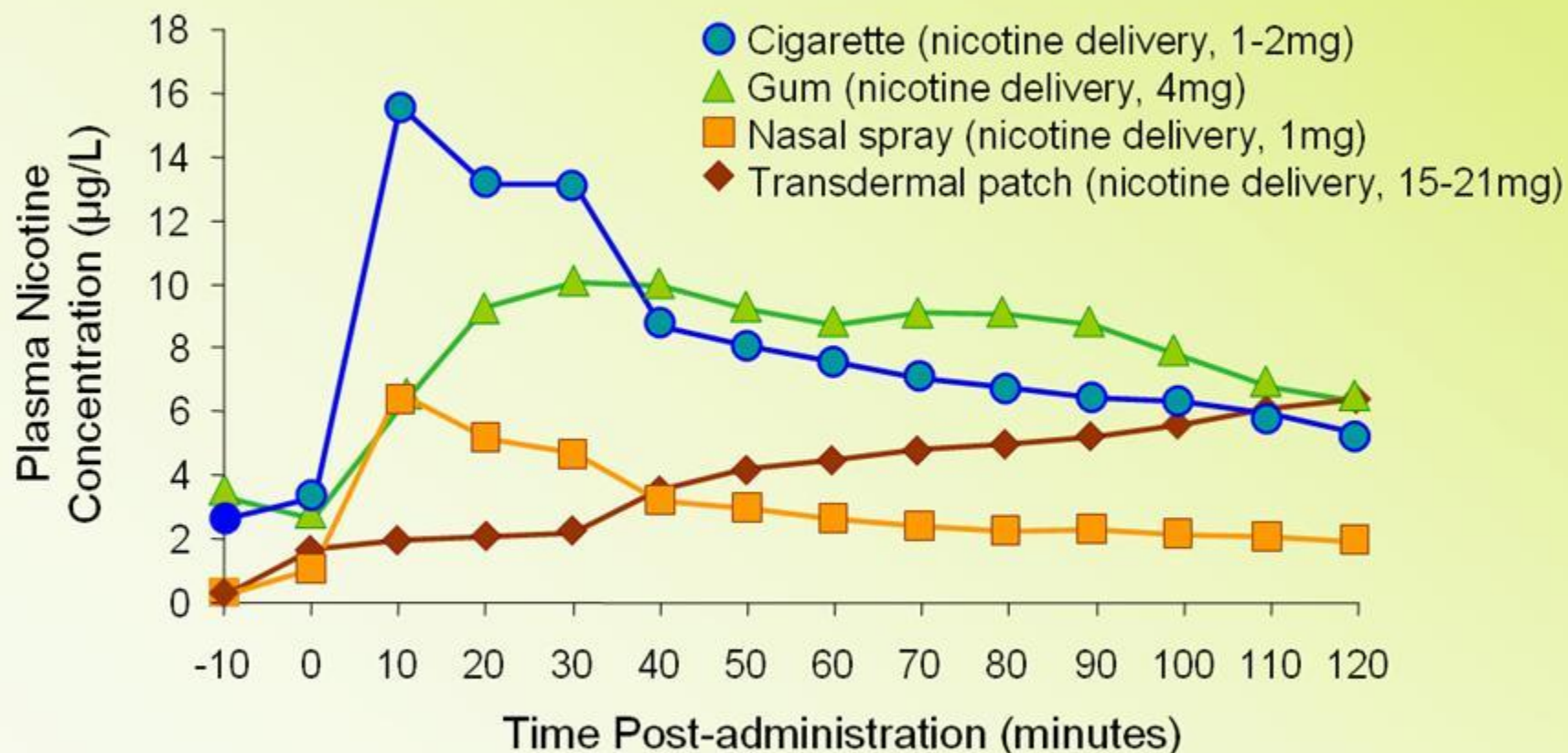
Unique in Biology

- **Up-regulated by high arterial doses of nicotine**
- **Nicotine resets sensitivity of brain reward systems to ↑'d levels**
- **Indelible “memory” of its effect on reward systems**
- **Down-regulation takes months of smoking abstinence**
- **This indelible “memory” evoked by external cues → craving**

Nicotine Effect on Brain

- Nicotine increases levels of the neurotransmitter - dopamine
- Dopamine is released normally when experiencing something pleasurable: good food, fun activity, spending time with people you enjoy
- Typical smoker takes 10 puffs on lit cigarette over 5 minutes. Smoking one pack (20 cigarettes)/day = 200 “hits”.
- “Hits” ... the brain within 10 seconds!!

Nicotine Delivery by Cigarettes and Nicotine Replacement Therapy (NRT)

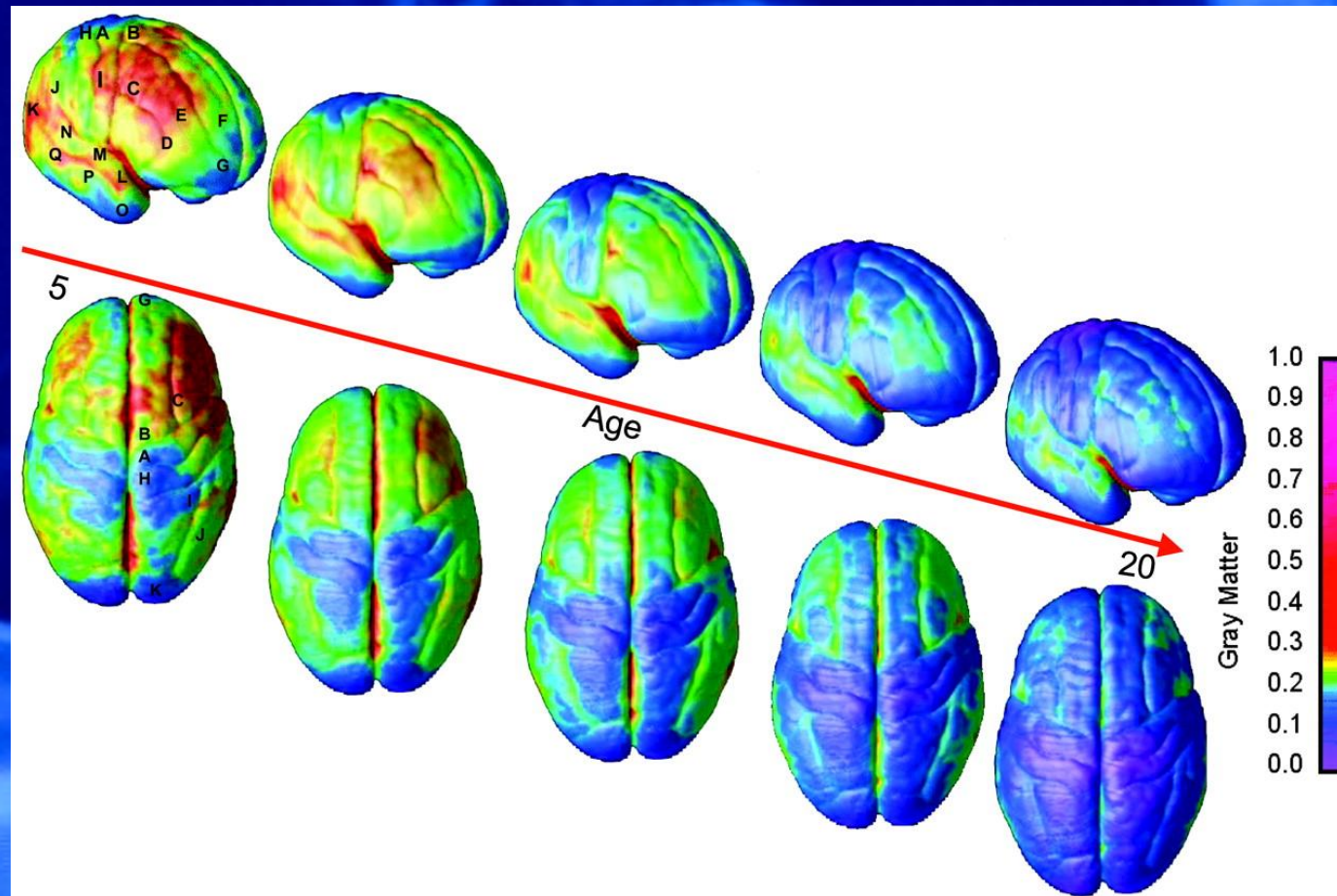


- NRT has rates of delivery which are all less than that of cigarette smoking
- NRT acts as an agonist alone, mimicking nicotine in its mechanism of action
- Peak levels achieved by NRT are about 30-50% of those achieved by smoking

Nicotine, the brain, youth/teens

- The brain continues to develop until about **age 25**.
It is the last organ in the body to develop fully
- Nicotine exposure during this time can **disrupt the growth of the brain circuits** that control attention, cognition, learning, susceptibility to psychiatric disorders, the reward system, and susceptibility to addiction to other substances - alcohol, opioids, marijuana
- Adolescent brain appears to be **uniquely susceptible to nicotine addiction - 80% of kids who try 2 cigarettes go on to battle a lifetime of addiction = one of MOST addictive substances**

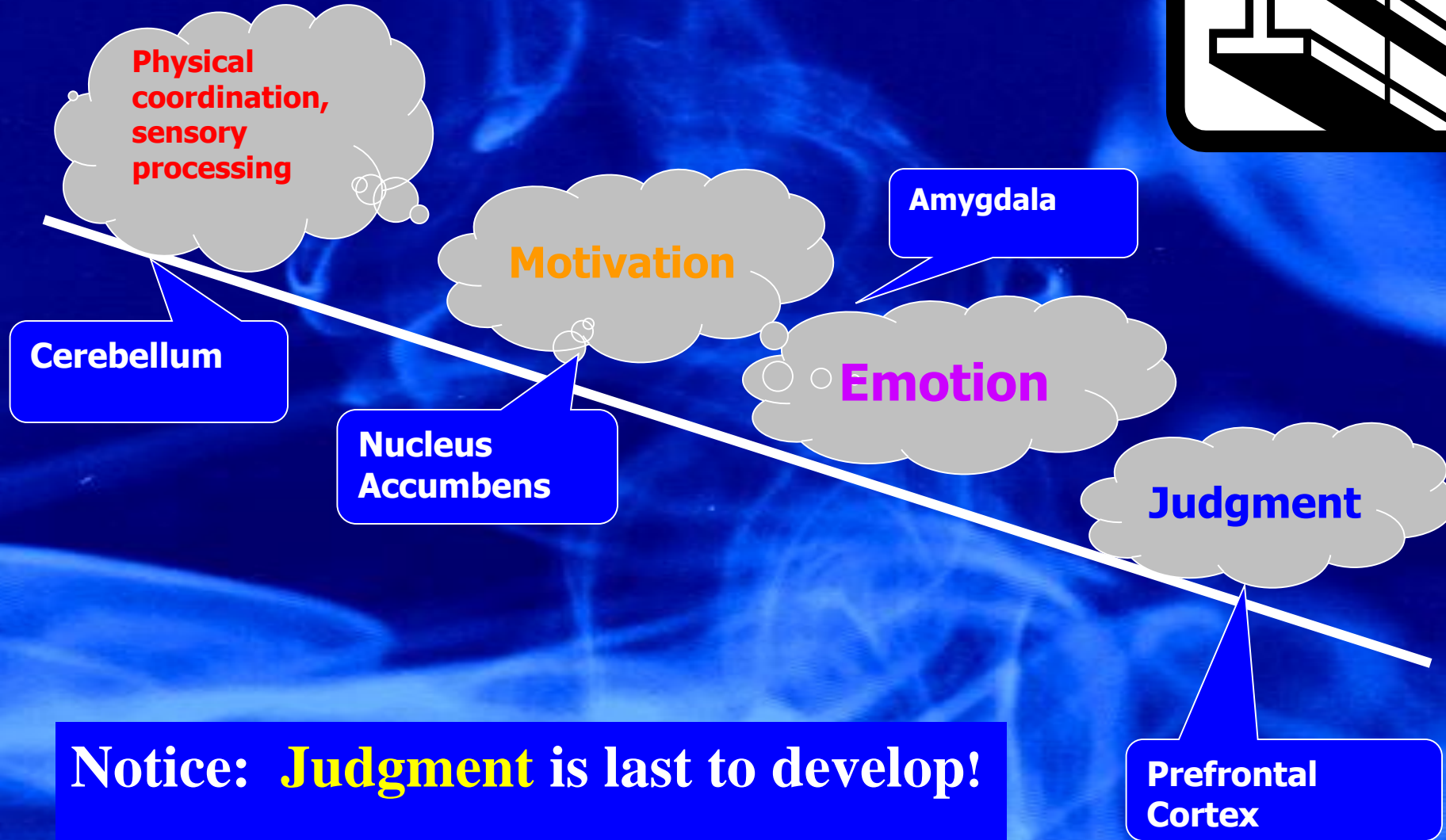
Dynamic Sequence of Gray Matter Maturation Over the Cortical Surface



Source: Gogtay, Nitin et al. (2004) *Proc. Natl. Acad. Sci. USA* 101, 8174-8179

Copyright ©2004 by the National Academy of Sciences

Maturation starts at the back of the brain ... and moves to the front



Notice: **Judgment** is last to develop!

-8-
Why then is there not a market for nicotine per se, to be eaten, sucked, drunk, injected, inserted or inhaled as a pure aerosol? The answer, and I feel quite strongly about this, is that the cigarette is in fact among the most awe-inspiring examples of

The cigarette should be conceived not as a product but as a package. The product is nicotine.

which contains the cigarette, which contains the smoke. The smoke is the final package. The smoker must strip off all these package layers to get to that which he seeks.

But consider for a moment what 200 years of trial and error

Think of the cigarette pack as a storage container for a day's supply of nicotine:

Think of the cigarette as a dispenser for a dose unit of nicotine:

2) Its rate of combustion meters the dispensing rate, setting an upper safe limit for a substance that can be toxic in large doses.

3) Dispensing is unobtrusive to most ongoing behavior.

2024273963

MEMORANDUM:

In a sense, the tobacco industry may be thought of as being a specialized, highly ritualized and stylized segment of the pharmaceutical industry. Tobacco products, uniquely, contain and deliver nicotine, a potent drug with a variety

In a sense, the tobacco industry may be thought of as being a specialized highly ritualized and stylized segment of the pharmaceutical industry.

His choice of product and pattern of usage are primarily determined by his individual nicotine dosage requirements and secondarily by a variety of other considerations including flavor and irritancy of the product.

of attractive dosage forms of nicotine, and our company's position in our Industry is determined by our ability to produce dosage forms of nicotine which have more overall value, tangible or intangible, to the consumer than those of our competitors.

The habituated user of tobacco products is said to derive "satisfaction" from nicotine. Although much studied, the physiological actions of nicotine are still poorly understood and appear to be many and varied. For example, in different situations and at different dose levels, nicotine appears to act as a stimulant, depressant, tranquilizer, psychic energizer, appetite reducer, anti-fatigue agent, or energizer, to name but a few of the varied and often

But again, the picture is not quite all that clear. Critics of tobacco products increasingly allege that smoking is dangerous to the health of the smoker. Part of this alleged danger is claimed to arise from ingestion of nicotine and part is claimed to arise from smoke components or smoke "tar". If, as proposed above, nicotine is the sine qua non of smoking, and if we meekly accept the allegations of our critics and move toward reduction or elimination of nicotine from our products, then we shall eventually

If, as proposed above, nicotine is the sine qua non of smoking, and if we meekly accept the allegations of our critics and move toward reduction or elimination of nicotine from our products, then we shall eventually liquidate our business.

to humanity because of their overriding beneficial effects. Might we not take a leaf from that book in our approach to nicotine? Unless we do, our long-term prospects become unattractive.

Our critics have lumped "tar" and nicotine together in their allegations about health hazards, perhaps because "tar" and nicotine are generated together in varying proportions when tobacco is smoked. An accompanying Research Planning Memorandum suggests an approach to reducing the amount of "tar" in cigarette smoke per unit of nicotine. That is probably the most realistic approach in today's market for conventional cigarette products. However, another more futuristic approach is possible which goes more directly to the fundamentals of the alleged problem.

There seems no doubt that the “kick” of a cigarette is due to the concentration of nicotine in the blood-stream and this is a product of the Nicotine is in the smoke in two forms as free nicotine base (think of ammonia) and as a nicotine salt (think of ammonium chloride) and it is almost certain that the free nicotine base is absorbed faster into the blood-stream.

HDA/MDP/46C
7.8.64.

c.c. R. and D. E. ✓

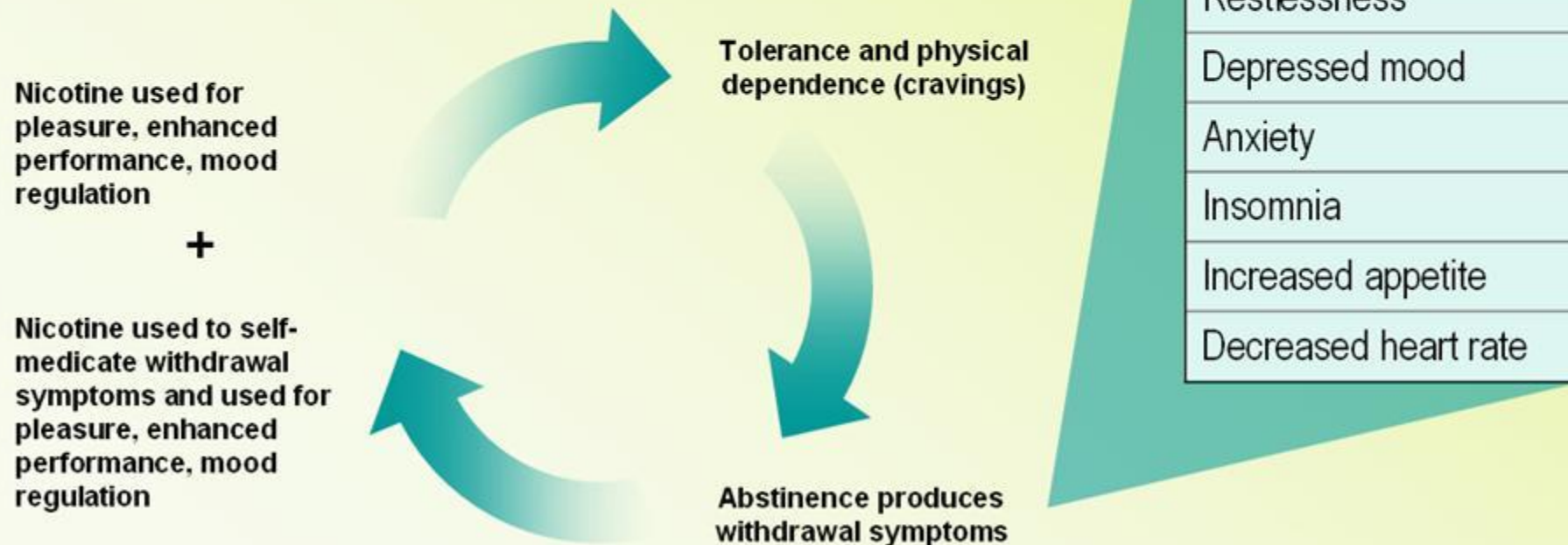
109059067

Nicotine Effect on Brain

- Youth who use nicotine are at risk of long-term health effects
- Nicotine affects the development of the brains reward system
- Nicotine affects the development of brain circuits that control attention and learning
- As **tolerance** builds, more nicotine is required
- Continued use of nicotine can lead to addiction and **raise the risk for addiction** to other drugs, **especially opioids and alcohol**

The Cycle of Nicotine Addiction

- The half-life of nicotine is only 2 hours. This along with its rapid clearance from the CNS results in withdrawal symptoms occurring quickly. Withdrawal symptoms, combined with cravings for tobacco, result in relapses that reinforce the reward and satisfaction from nicotine- starting the addiction cycle over again



1. Foulds J. *Int J Clin Pract.* 2006;60:571-576.

2. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed.1994:242–247.

NICOTINE

Highly addictive chemical derived from tobacco plants

- **Psychoactive effects** (Stimulates, relaxes)
- **Drug-reinforced behavior** (feels good, fun)
- **Physical dependence and tolerance** (the more you smoke, the more you need/want to get relief) ...leading to...
- **Compulsive use** (the urge to smoke when you wake, before bed, after class)
- **Abrupt quitting causes physical and emotional distress**
- **Relapse after abstinence**

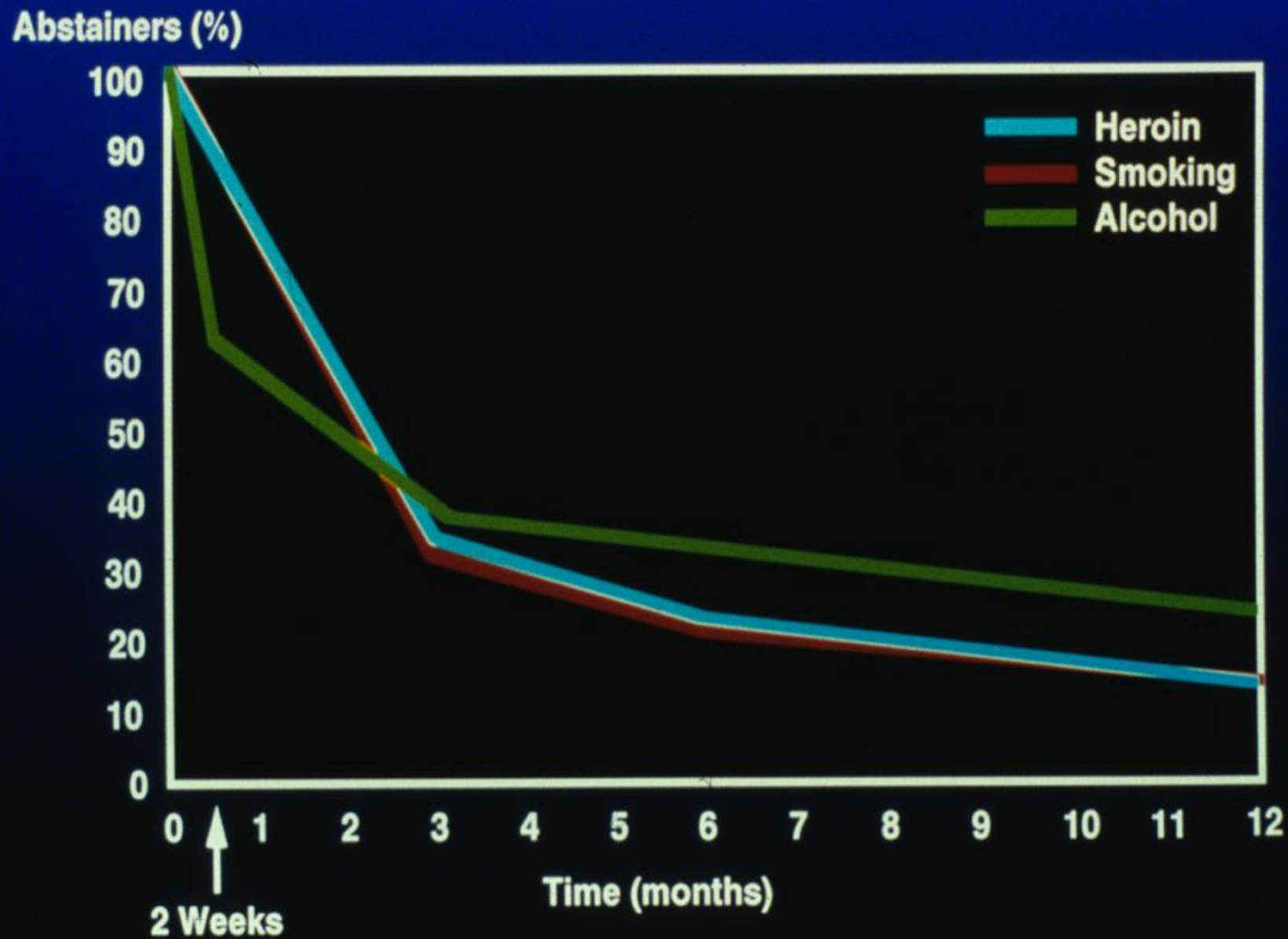
HALLMARKS OF ADDICTIVE DRUGS

- 1. Psychoactive**
- 2. Create dependence and lead to compulsive use**
- 3. Abrupt quitting causes emotional and physical distress**
- 4. Strong tendency for quitters to relapse**

"The addictive nature of cigarette smoking is why cigarette sales continue year after year in spite of the health hazards of smoking."

Source: U.S. Department of Health and Human Services

RELAPSE RATES OVER TIME





Nicotine and Youth/Teens

- 2015 CDC Report: **99% of e-cigarettes** sold in U.S. convenience stores, supermarkets and similar outlets contained nicotine.



Nicotine Content

- Traditional Cigarette: Can contain up to **30 mg**, but usually has less
- A JUUL pod contains nicotine = to a traditional pack of 20 cigarettes
- **JUUL, 5%/50mg; 3%/30mg**
- Electronic Cigarette: Up to **24 mg** per e-cigarette
- Refill Bottle of E-Juice: Up to **240 mg** in each bottle of liquid nicotine



NICOTINE CONTENT

Typical smoker takes 10 puffs on a lit cigarette over about 5 minutes.
Smoking 1 pack (20 cigarettes)/day = 200 nicotine “hits”



1 JUUL Pod - 200 puffs contain amount of nicotine equal to one pack of cigarettes

NICOTINE CONTENT



=

