

Neurobiology of Nicotine Addiction

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Outline

Addiction defined

- Nicotine absorption
- Nicotine neurophysiology
- Conditioning Cues
- Nicotine withdrawal
- Dealing with frustration

Frustration

- Patient viewpoint--ambivalence
 - 90% know cigarette smoking is harmful and want to quit.
 - Most smokers feel guilty and feel they have let themselves, their spouse, family and care provider down.
 - But most smokers are reluctant to quit and make only brief attempts to quit and often experience relapse if they do quit.

Frustration

- Health Care Provider viewpoint
 - Failure to help patient quit smoking may weaken care provider's resolve to try again
 - Tendency to “blame” the patient for “non compliance”
 - Failure to understand the addictive physiology and consequences of nicotine addiction which promotes relapse

Psychoactive Substance Dependence DSM_IV

Three or more of the following:

- Tolerance
- Substance taken in larger amounts or over a longer period than intended
- Persistent desire or unsuccessful efforts to cut down or control use
- Great deal of time spent in activities necessary to obtain or use the substance or recover from its effects

Dependence diagnosis criteria (continued)

- Important social, occupational, or recreational activities given up or reduced because of use
- Continued use despite knowledge of having had persistent or recurrent problems caused by the substance
- Withdrawal symptoms when attempt to discontinue

Cigarette smoking-not a “habit”

- Habits=automatic routine, repeated regularly and without thinking
- Addictions are compulsions characterized by subjective distress when routine behaviors are forbidden.

Nicotine “hard-wired”

- Nicotine creates a motivation for the “target” behavior (smoking) that is rendered undeniable by the abnormal amplified negative emotional consequences of unresolved compulsion.
- This association becomes “hard-wired” and persists over time

Addiction—alternative view

- “Continued smoking could no longer be considered a manifestation of motivation deficit, but instead must be considered a disorder of an abnormally amplified motivation “NOT to quit”
- Cessation treatment should focus less on the consequences of tobacco use and more on the amplified motivations NOT to quit

Nicotine absorption

Basically then the action is to prevent tobacco being

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.

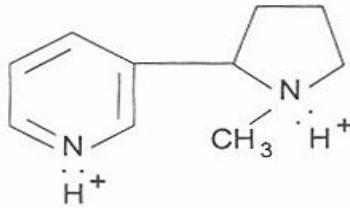
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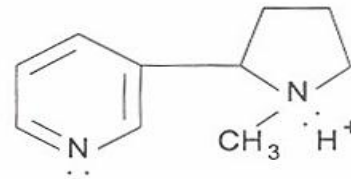
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of pH

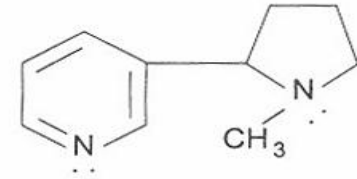
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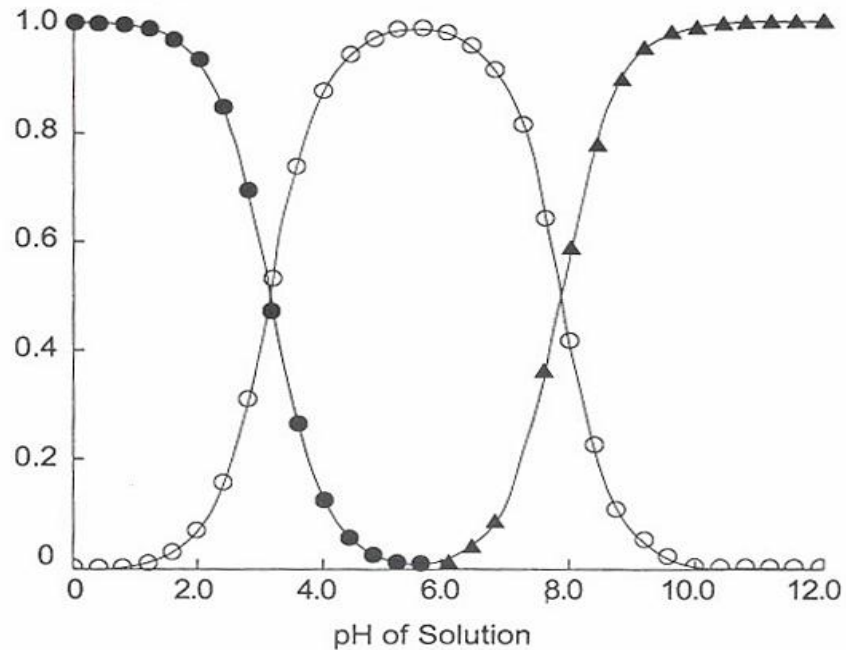
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▲▲▲ Unprotonated



Fraction of Each Species



Distribution of protonated and unprotonated nicotine in solution at various pH increments.

Nicotine state

- Protonated and free base
- Only the “free base” form can volatilize in gaseous form and be absorbed in the lungs
- Tobacco companies add ammonia to the tobacco leaf which by increasing pH increase nicotine conversion to “free base”

Cigarette-efficient nicotine delivery device

- Capable of producing very rapid peaks in the arterial concentration of nicotine
- Nicotine absorbed in alveoli of lung and circulates via pulmonary veins to Left heart. (bypasses the right heart)
- Nicotine circulates to brain within 7-10 seconds where nicotine receptors stimulate dopamine release

Cigarettes and Tobacco Dependence

- Cigarette is the most efficient delivery device for nicotine that exists- better than intravenous
- Cigarette manufacturers have modified cigarettes over the past decades to maximize nicotine delivery to the brain
- High doses of arterial nicotine cause upregulation of the nicotinic acetylcholine receptors
- Genetic factors influence tobacco dependence
- Left untreated 60% of smokers die from a tobacco-caused disease

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 ingenuity of man. Let me explain my conviction.

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

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 designing has brought in the way of nicotine packaging:

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

nicotine:

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

3) Dispensing is unobtrusive to most ongoing behavior.

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“Low Tar Low Nicotine” Cigarettes

FTC Method

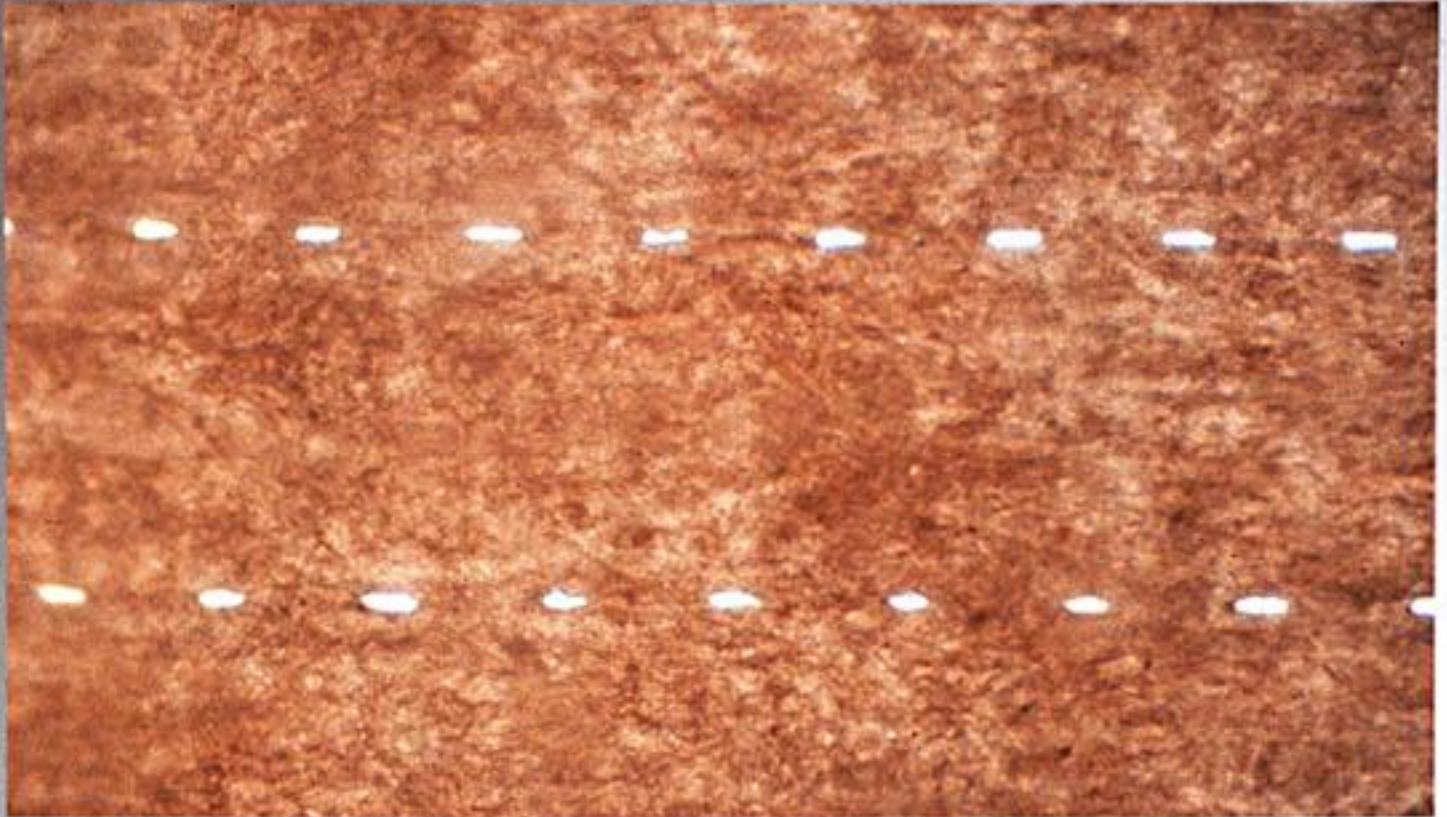
- Determines relative yield of individual cigarettes by smoking them in a smoking machine
- Machine draws 35ml puff of 2 seconds duration every minute
- Cigarette smoked down to 23mm butt length
- Cambridge filter collects the particulate matter
- Does not measure the gas phase “free nicotine”
- 2008 no longer used and as of June 2010 no longer can use “light” terminology

“Low Tar Low Nicotine” Cigarettes

Ventilation

- Ventilation holes one of key technologies to manipulate tar and nicotine yields
- Electrostatic or laser perforations of the filter or paper
- Ventilation holes in most brands are not visible
- 2/3's of U.S. smokers are unaware of ventilation holes or that blocking them increases tar/nicotine yield
- Many smokers block (consciously or not) the ventilation holes with their lips or fingers





Carcinogens Excreted by Smokers of Regular or “Light” Cigarettes

- 150 smokers of regular or “light” cigarettes
- Nicotine metabolites-Serum cotinine and urine NNAL, NNAL-Gluc, and 4 aminobiphenyl hemoglobin adducts measured
- Essentially the same concentrations of were present in “light” as in regular cigarette smokers.

Nicotine neurophysiology

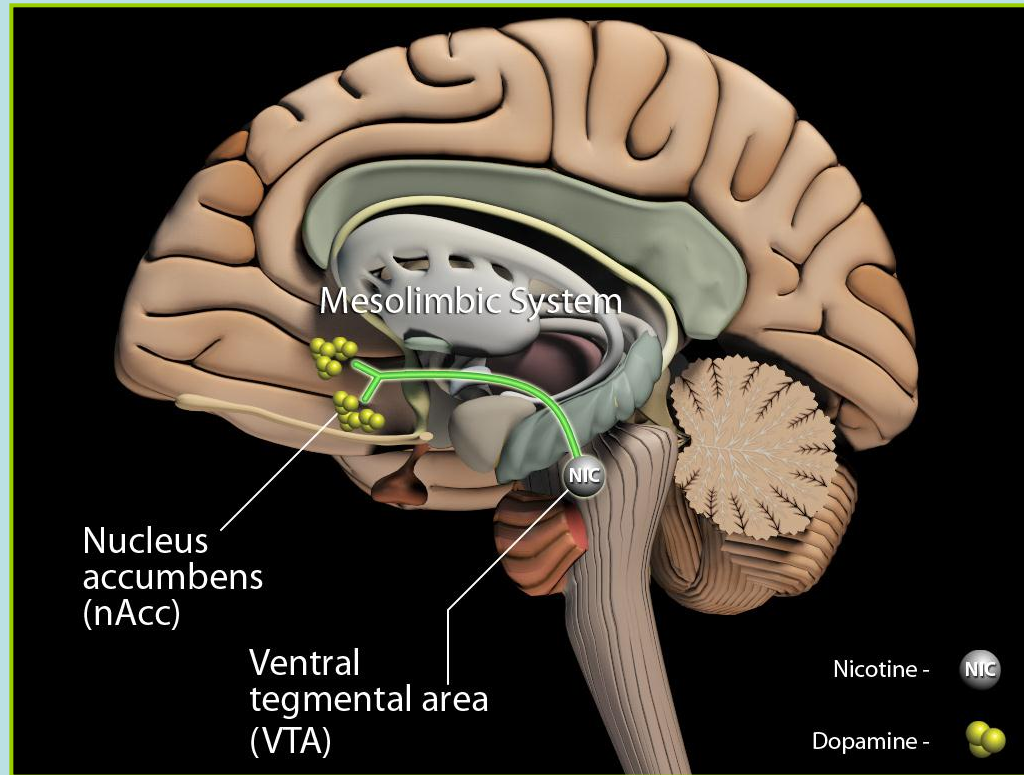
Nicotine effect on the brain

- Brain imaging studies show nicotine acutely increases activity in the prefrontal cortex, thalamus and visual system brain circuits—
- There is stimulation of central acetylcholine receptors (nAChRs) which results in release of several neurotransmitters most important -
Dopamine

Mesolimbic system

- Ventral Tegmental area (VTA)-collection of nerve cells located midline on the floor of the midbrain
- Neurons of the VTA send projections to target the Nucleus Accumbens in the prefrontal region of the brain
- The Nucleus Accumbens –reward center for most drugs of abuse

Central Nervous System “Reward Center”



Dopamine (DA) release in the nucleus accumbens is thought to be the “final common pathway” for the rewarding effects of most drugs of abuse

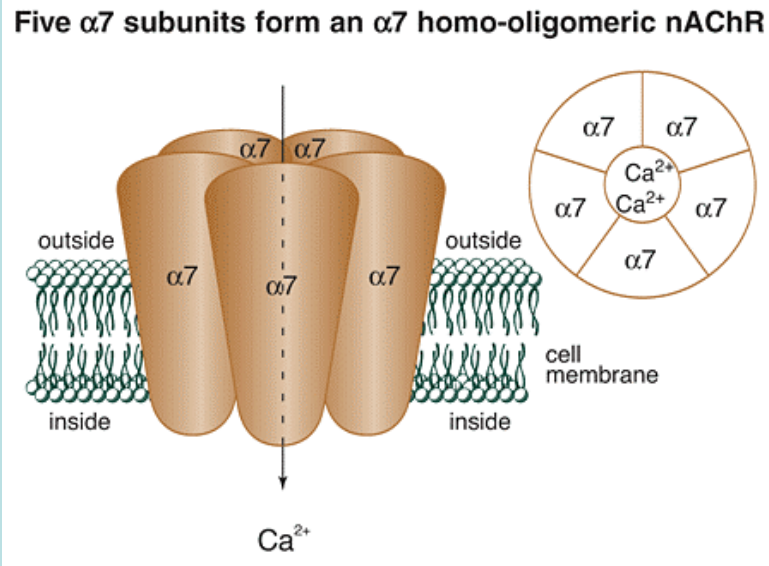
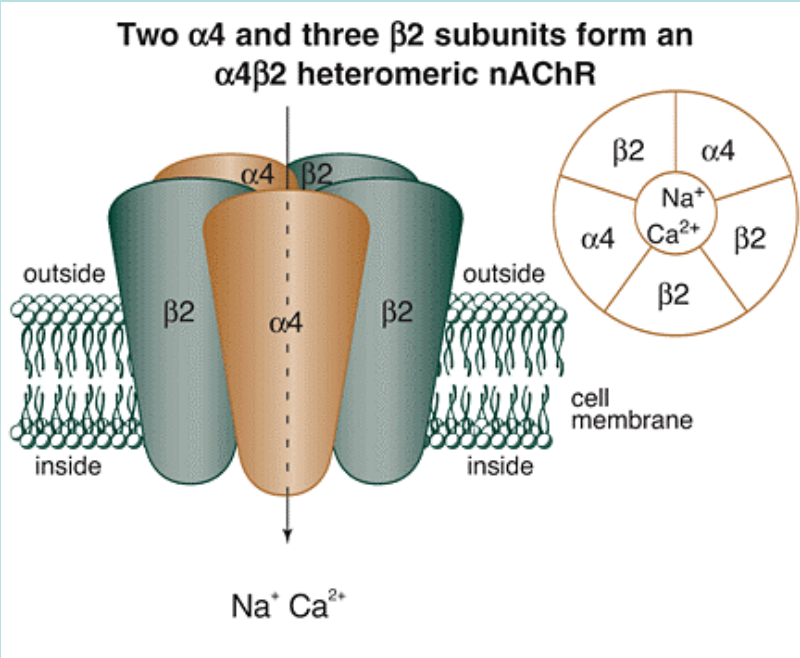
Mesolimbic system

- VTA contains “dopaminergic neurons” that respond to external rewarding stimuli such as food, sex and social interaction as well as aversive stimuli and stress.
- VTA stimulation promotes a generalized behavioral arousal under both positive and negative stimuli.
- “seeking of safety”

Neurophysiology of nicotine

- VTA's inputs are transmitted by cholinergic pathways and receptors.
- Nicotine “hijacks” these receptors and compels them to produce dopamine, creating a powerful but artificial “safety” signal.
- Most potent drug—more potent than cocaine, amphetamine and morphine to compel repetitive behavior

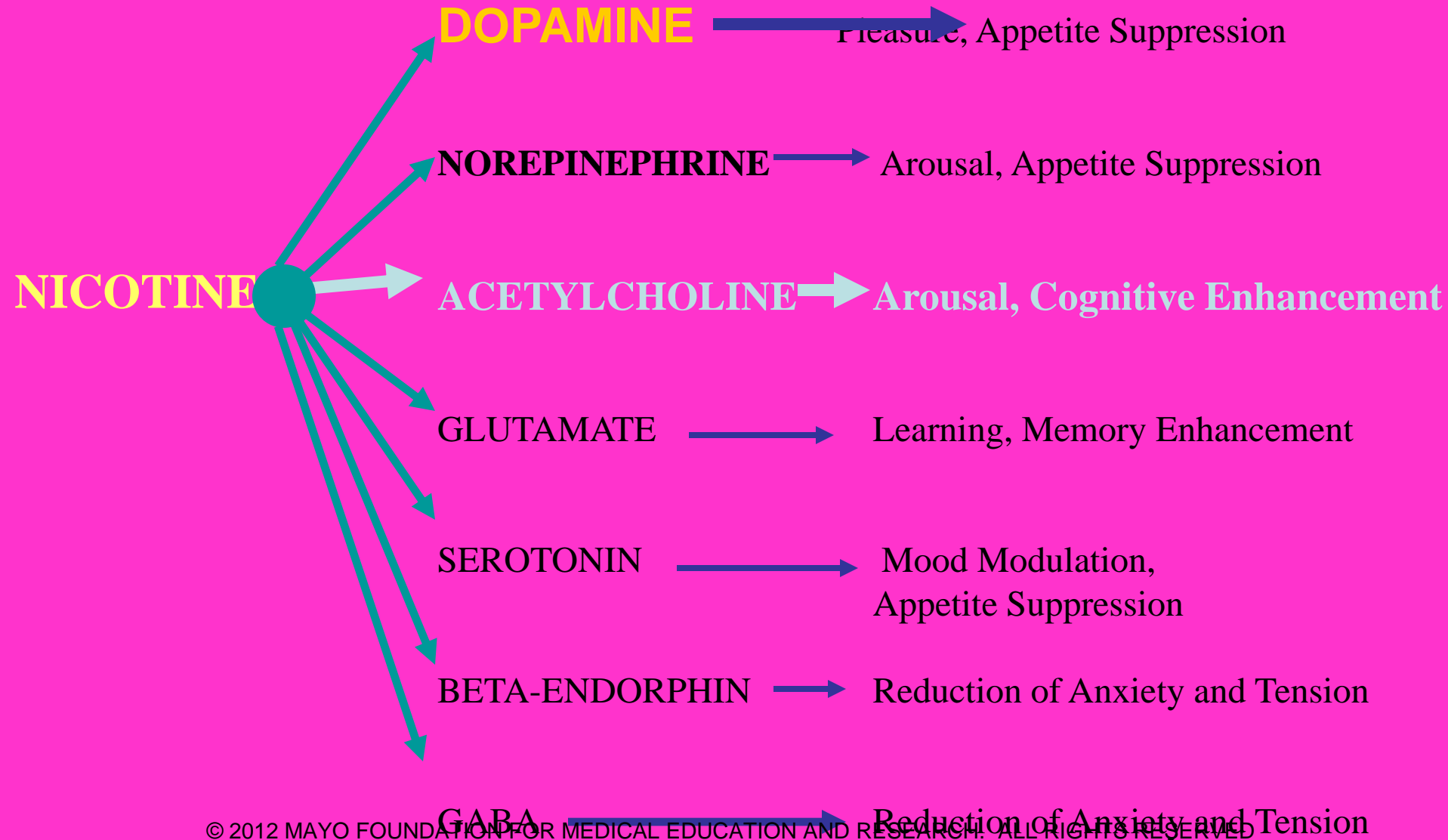
Different types of nAChR



Nicotine addiction-animal study

- Powerful motivator of behavior
- Animal studies
 - Prolonged “foot shock” behavior extinction
 - Lever pressing of nicotine exposed monkeys

Nicotine Stimulates Release of Many Different Neurotransmitters



Nicotine actions

- Induces stimulation and pleasure
- Reduces stress/anxiety
- Improves concentration, reaction time and task performance
- Prevents withdrawal symptoms by keeping nAChRs in desensitized state

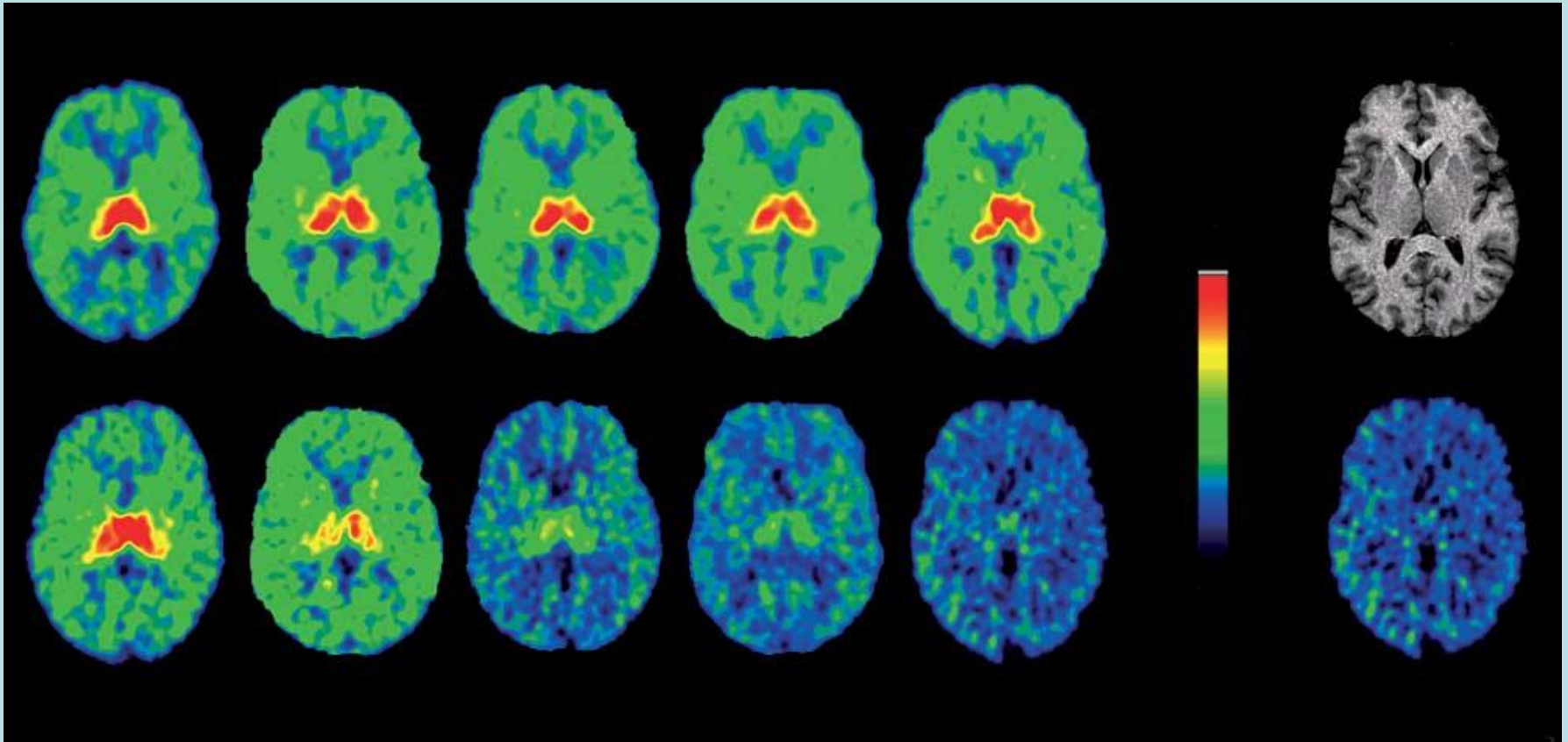
Smoking Saturates Nicotinic Receptors

- Radioligand allows for visualization of $\alpha 4\beta 2$ nAChRs
- Position Emission Tomography (PET) Scans
- 11 smokers had 14 PET scan sessions
- Smoked: none, 1 puff, 3 puffs, 1 cigarette or 2-3 cigarettes (satiety)

Smoking Saturates Nicotinic Receptors Results

- 1-2 puffs of a cigarette → 50% occupancy of $\alpha 4\beta 2$ nAChRs for 3 hours after smoking
- One cigarette → 88% receptor occupancy and ↓ cigarette craving

Smoking Saturates Nicotinic Receptors



Neuroadaptation

- Repetitive Nicotine exposure
 - Upregulation -Increase in nAChRs
 - Response to nicotine-mediated desensitization of receptors which may lead to tolerance/dependence
 - Daily smoking maintains near-complete saturation and desensitization of nAChRs
 - Avoids withdrawal

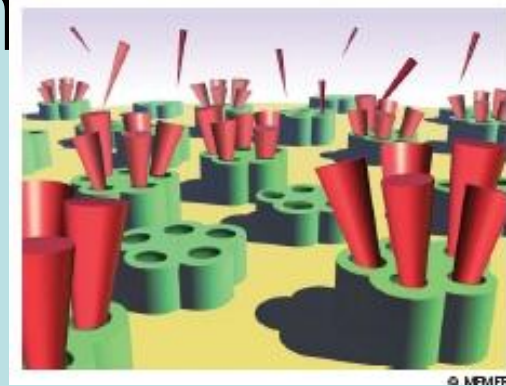
Conditioning

environmental factors (cues) contribute to urge to smoke (after meals, with coffee, with friends)

Cue often is to avoid “irritability

- Association between cues and anticipated drug effect drives urge
- May maintain nicotine use while nAChRs are desensitized

Nicotine Addiction



- Physical Dependence

- Psychological Dependence:

- “Conditioned Response” to Cues

- The Five Senses
- Emotions (positive and negative)

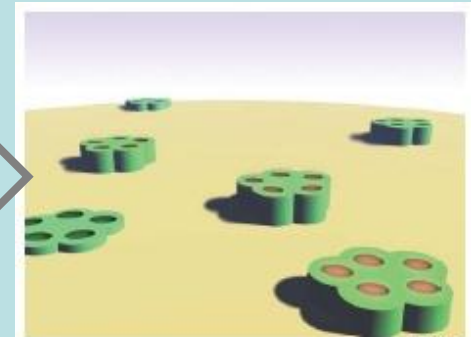
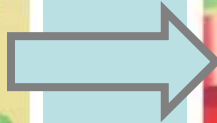
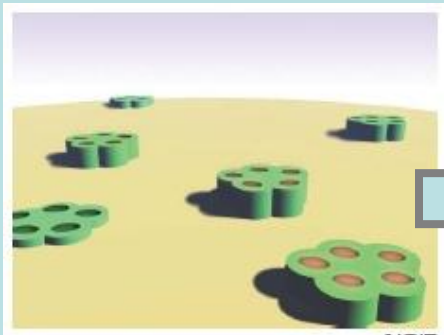
- Cues trigger neurotransmitter release

- Anticipation of Nicotinic receptor activation and Dopamine release



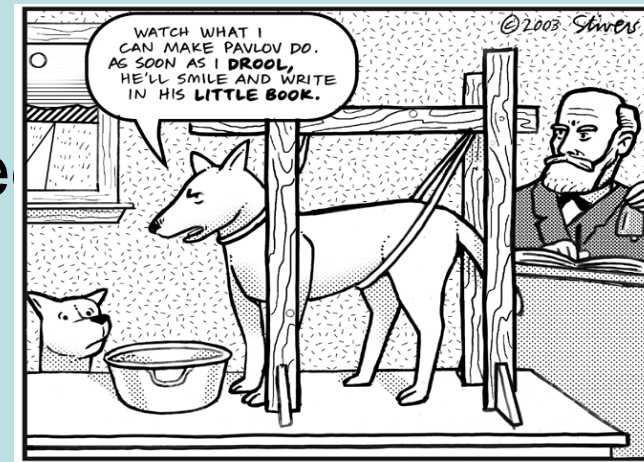
Withdrawal Syndrome or "Abstinence Syndrome"

Pathophysiologic disturbances which result when a drug to which an organism is physically dependent is stopped.



Craving

- An intense desire to fulfill an unsatisfied state
 - As opposed to ‘like’
- Positively correlated with relapse in two ways
 - Intensity during early quit
 - Momentary craving associate relapse long after initial quit



The experience: Withdrawal symptoms

- Insomnia
- Restlessness
- Anxiety, Irritability, Frustration, Anger
- Difficulty concentrating
- Sad, depressed mood, anhedonia
- Increased appetite
- Decreased heart rate



Other Common Withdrawal Symptoms

- Headache
- Mouth ulcers
- Nausea
- Constipation
- Diarrhea



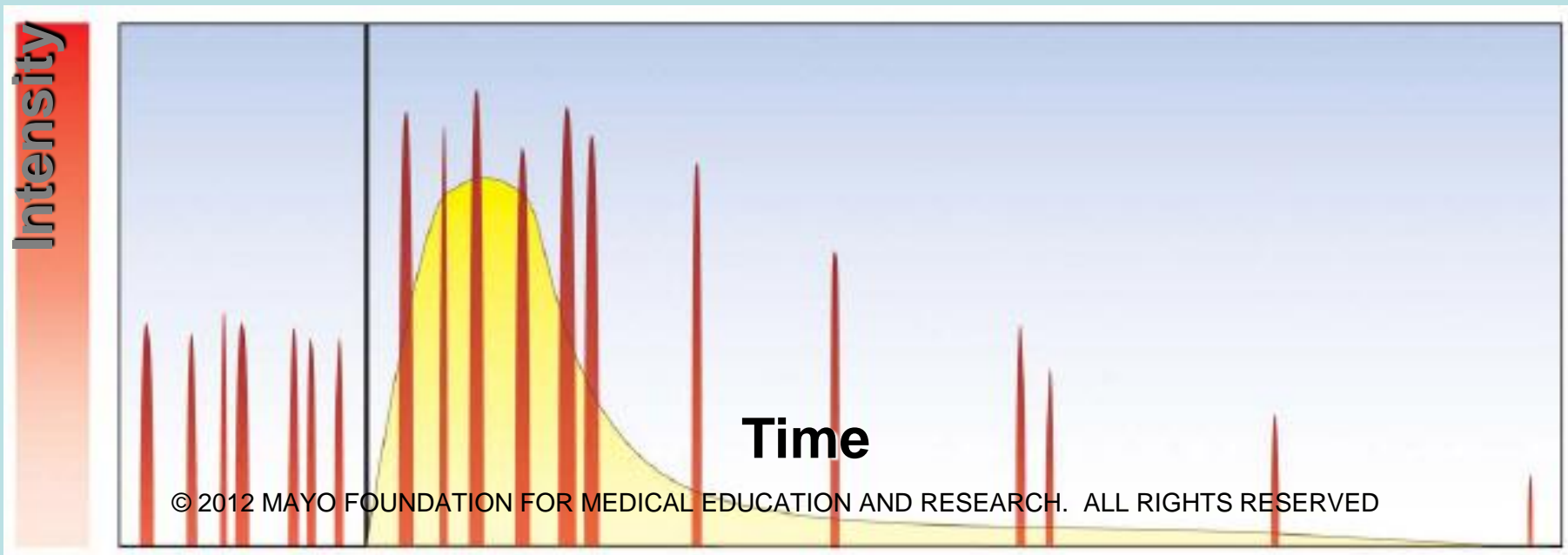
Timeline of Nicotine Withdrawal

For most smokers, withdrawal symptoms last for a few weeks and then resolve.

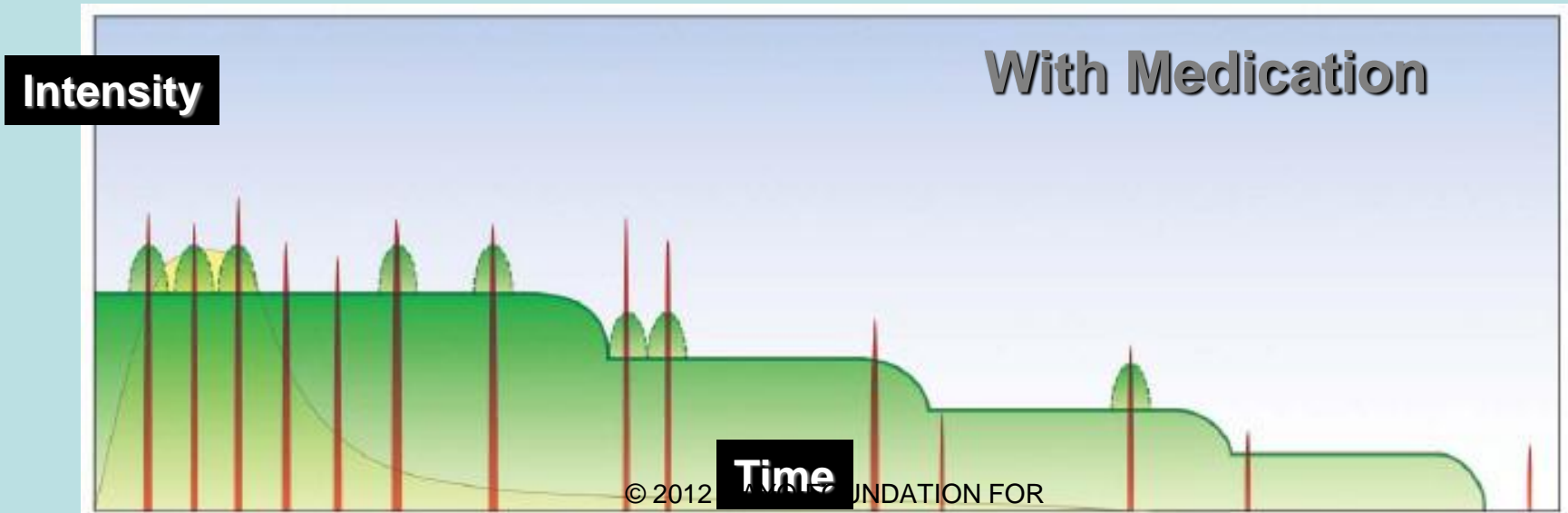
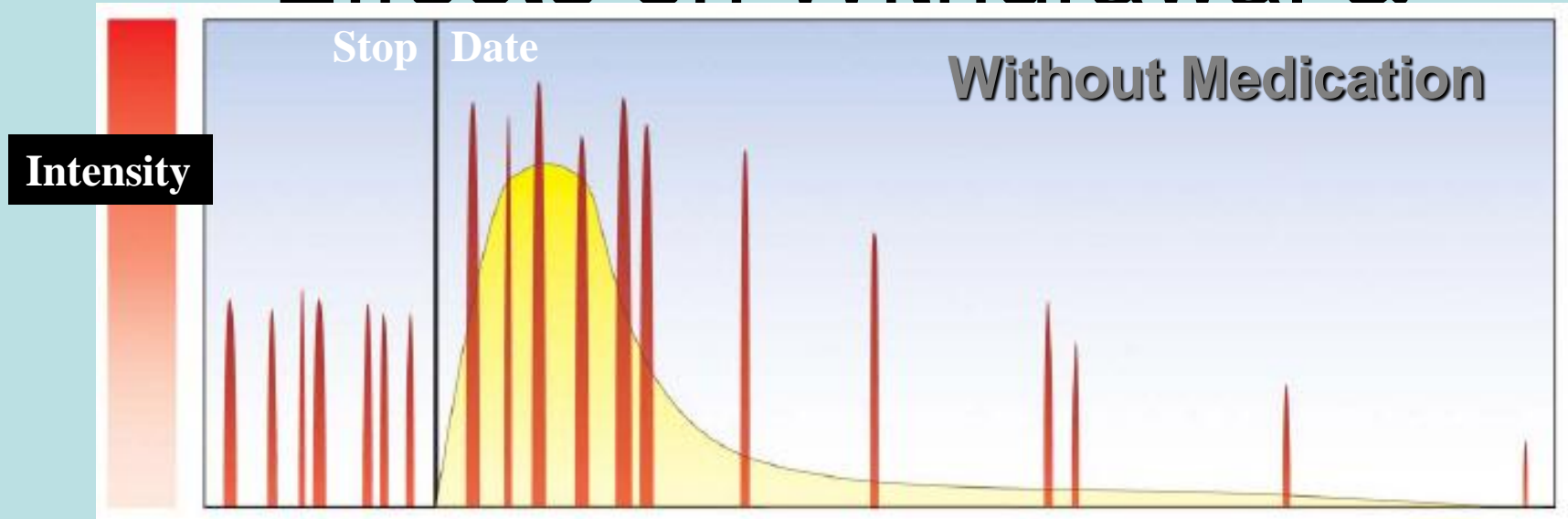
Cravings can be frequent and intense early, but become less intense and less frequent

Stop Date

over time



Medication: Effects on Withdrawal &



High Relapse

- Most people who smoke want to stop
- 80% of smokers who try to quit on their own relapse within 1 month
- Only 3% remain abstinent at 6 months
- Nicotine addiction=chronic disease

Dealing with frustration

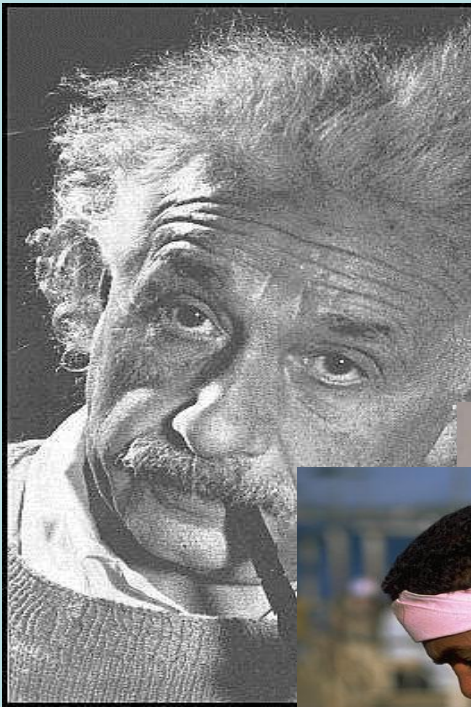
- Patient's internal conflict → ambivalence
- Our responsibility is to help patients resolve ambivalence
 - Motivational interviewing which enhances motivation to change through reflective listening without confrontation or judging
 - Elicit trust by demonstrating
 - Empathy-develop a sense of “shared experience”
 - Joining –develop shared goals

Dealing with Frustration

- Validation –confirm that the patient’s experience/frustration with quitting has a “biologic/physiologic basis”, but don’t undermine “self-efficacy” by over emphasizing “how difficult quitting can be”
- Hope-hopelessness is a common barrier to behavior change in addiction.

Dealing with frustration

- Hope –Work to reinvigorate hope by maintaining a positive non judgmental attitude, emphasizing creative solutions to common problems.



It Is A Disease

“Not a Bad Person with a Bad Habit, but a Good Person with a Difficult Disease”

--Tom Gauvin, NDC Counselor

References

- 1. “Neurobiology of Nicotine Addiction: Implications for smoking cessation Treatment” Neal L Benowitz, MD
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- 2. Leone, FT et al; “Developing a Rational Approach to Tobacco use Treatment in Pulmonary Practice: A review of the Biological Basis of Nicotine Addiction”; Clinical Pulmonary Medicine, Vol 19, No. 2, March, 2012

Association for the Treatment of Tobacco Use and Dependence

An organization of providers
dedicated to the promotion of and
increased access to evidence-based
tobacco treatment for the tobacco user.

www.attud.org