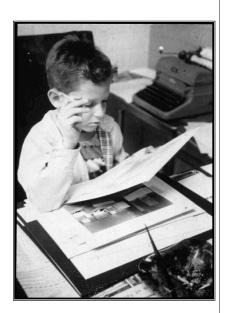
CSAM: Addiction Review Course Sept 6, 2014

Traditional to E-Cigarettes:
Nicotine Abuse and its
Treatments

Mitchell Nides, Ph.D.
President, Los Angeles Clinical Trials
Director, "Picture Quitting", The Entertainment
Industry's Quit Smoking Program



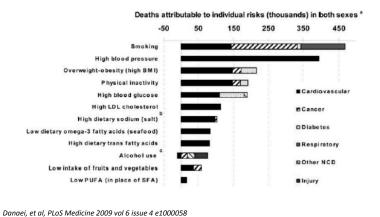
Disclosures

In the past 2 years:

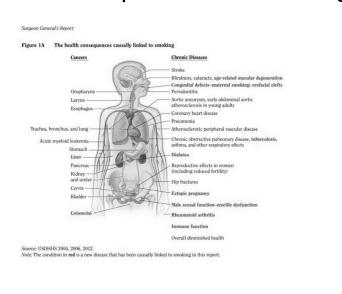
- I have received research grants from:
 - NJOY, Inc
 - GlaxoSmithKline
- I have received consulting fees from:
 - NJOY, Inc
 - GlaxoSmithKline
 - Pfizer, Inc
 - McNeil

The Problem

The morbidity and mortality from smoking related diseases is still the number one public health risk (Data:2003-2006)



Health Consequences of Smoking



SMOKELESS TOBACCO USE

- 9 million US users
 - Chewing tobacco, snuff, snus, dissolvables
- Periodontal effects
 - Gingival recession
 - Bone attachment loss
- Dental caries
- · Oral leukoplakia
- Cancer
 - Oral cancer
 - Pharyngeal cancer
- Swedish Snus has fewer Tobacco Specific Nitrosoamines



Oral Leukoplakia Image courtesy of Dr. Sol Silverman -University of California San Francisco

Use of alcohol in combination with moist snuff increases the risk of oral cancers.

Guess Which Identical Twin Smoked?



Smoking Related Mortality in U.S. (2005-2009)

Malignant Neoplasms (Cancer) Total	Male	Female	
Lung cancer	74,300	53,400	127,700
Other cancers ^a	26,000	10,000	36,000
Subtotal: Cancer	100,300	63,400	163,700
Cardiovascular Diseases and Metabolic Disearct	ases Male	Female	
Coronary heart disease	61,800	37,500	99,300
Other heart disease ^b	13,400	12,100	25,500
Cerebrovascular disease	8,200	7,100	15,300
Other vascular disease ^c	6,000	5,500	11,500
Diabetes mellitus	6,200	2,800	9,000
Respiratory Diseases Total	Male	Female	
Pneumonia, influenza, tuberculosis	7,800	4,700	12,500
COPDd	50,400	50,200	100,600
Subtotal: Respiratory	58,200	54,900	113,100
Total: Cancer, Cardiovascular, Metabolic Respiratory	254,100	183,300	437,400

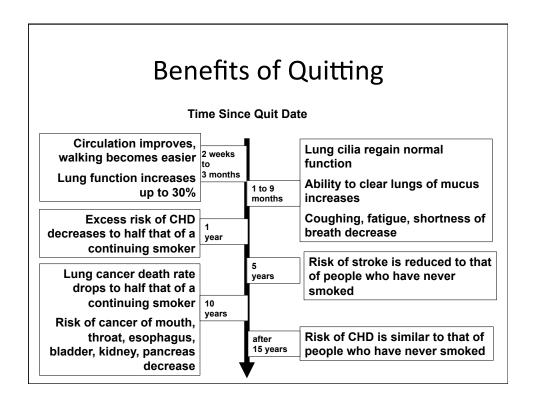
2014 Surgeon General's Report: The Health Consequences of Smoking—50 Years of Progress, Chapter 12, Table 12.4

Effects of 2nd Hand Smoke

- During 2007-2008, an estimated 88 million nonsmokers in the United States breathed other peoples' tobacco smoke.
- Each year, about 34,000 nonsmokers in the United States die from heart disease caused by secondhand smoke.
- Secondhand smoke exposure causes an estimated 7,300 lung cancer deaths annually among adult nonsmokers in the United States.

Second Hand Smoke (con't)

- Nonsmokers who are exposed to secondhand smoke at home or work increase their lung cancer risk by 20–30%.
- Secondhand smoke exposure is higher among persons with low incomes. For example, 60.5% of persons living below the poverty level in the United States were exposed to secondhand smoke in 2007–2008, compared with 36.9% of persons living at or above the poverty level.



Who Smokes?

Prevalence of Smoking by Demographics

Race/Ethnicity	Prevalence
American Indian/Alaska Natives (Non-Hispanic)	21.8%
Asians (Non-Hispanic)	10.7%
Blacks (Non-Hispanic)	18.1%
Hispanics	12.5%
Whites (Non-Hispanic)	19.7%
Multiple Races (Non- Hispanic)	26.1%

Sex	Prevalence
Men	20.5%
Women	15.8%

Age	Prevalence
18–24 years	17.3%
25-44 years	21.6%
45-64 years	19.5%
65 years and older	8.9%

Education Level	Prevalence
Less than high school	24.7%
GED	41.9%
High school graduate	23.1%
Some college	20.9%
Associate degree	17.9%
Undergraduate degree	9.1%
Postgraduate degree	5.9%

Income Status	Prevalence
Below poverty level	27.9%
At or above poverty level	17.0%

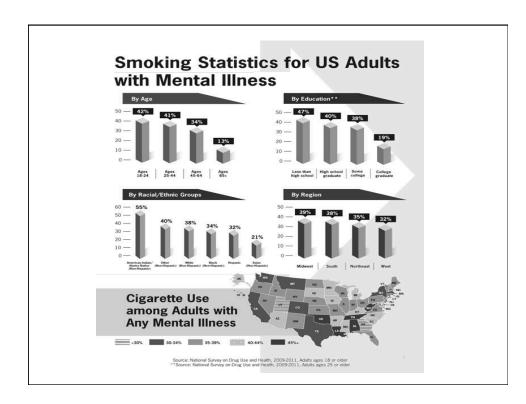
Sexual Orientation	Prevalence
LGBT	32.0%
Non-LGBT	19.5%

Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults—United States, 2005–2012. Morbidity and Mortality Weekly Report 2014;63(02):29–34 [accessed 2014 May 6].

Smoking Among those with Mental Illness/Substance Use Disorder

- 44% of cigarettes in the U.S. are smoked by people with substance use disorder/mental illness*
- Elevated rates of smoking among people with mental Illness/ substance use disorder
 - Drug/Alcohol Abuse (63 to 80%) (people with alcohol dependence more often die from tobacco-related causes than from alcohol-related causes)
 - Bipolar Disorder (60 to 69%) Schizophrenia (64 to 88%)
 - Major Depressive Disorder (44 to 60%)
 - Anxiety Disorders (32 to 55%)

*Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness - A population-based prevalence study. JAMA 2000:284:2606-2610



Most Smokers Want to Quit

- 70% say they want to quit
- 81% of smokers have tried to quit at least once
- 35-50% try to quit each year
- · Long-term success may require multiple attempts
 - Chronic relapsing disorder
- Only 3-5% of those quitting on own are still quit at the end of one year

Why is it so Hard to Quit?



All three aspects of addiction must be addressed for successful outcome

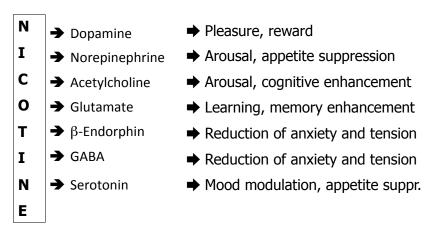
- Physiological
 - Pharmacotherapy
- Psychological
 - Cognitive behavioral therapy
 - Pharmacotherapy
- Behavioral
 - Behavioral therapy
 - Oral NRT can also be helpful as oral substitute

Nicotine Mechanism of Action

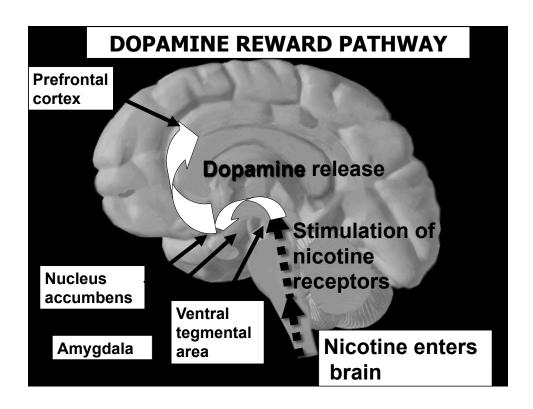
- Nicotine binding to α4β2* nAChRs in the ventral tegmental area of the midbrain leads to dopamine release in the ventral striatum/ nucleus accumbens (presumably leading to the pleasurable effects of smoking)
- In addition, nicotine inhibits the activity of monoamine oxidases A and B, leading to decreased breakdown of dopamine

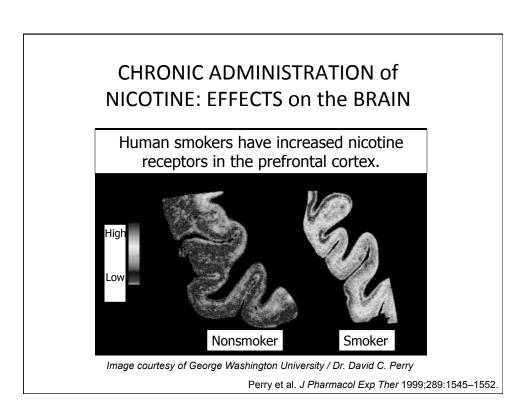
*Benowitz NL. Nicotine Addiction. N Engl J Med 2010; 362:2295-2303

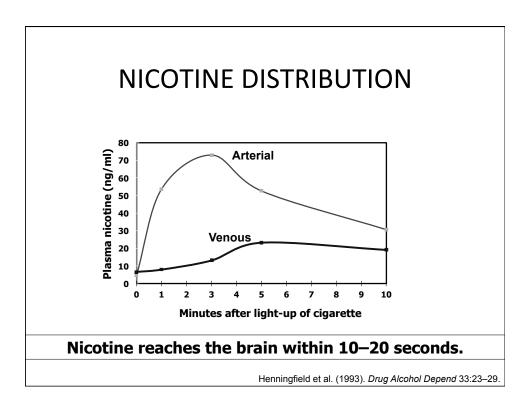
NEUROCHEMICAL and RELATED EFFECTS of NICOTINE

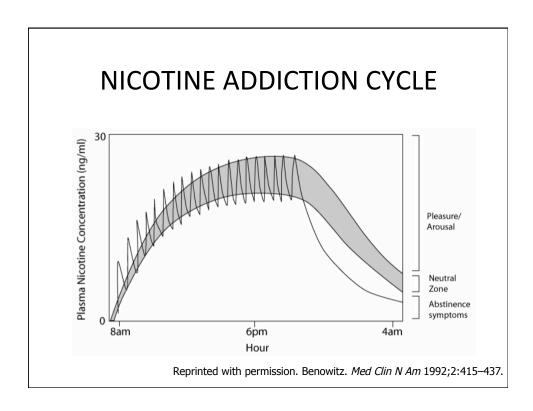


Benowitz. Nicotine & Tobacco Research 1999;1(suppl):S159–S163.









Withdrawal Symptoms

- · Half-life of nicotine is only 2 hours
- · For most smokers craving is the first sign of withdrawal
- Within a few hours or days other symptoms can include:
 - Dysphoric or depressed mood
 - Anxiety or nervousness
 - Irritability, frustration, anger
 - Restlessness
 - Insomnia or fatigue
 - Increased hunger and weight gain
 - Difficulty concentrating
- Most symptoms peak within 2-5 days and subside within 2-4 weeks
- It's these withdrawal symptoms that lead most smokers to relapse within a few weeks of a quit attempt

FDA Approved Smoking Cessation Medications

- Nicotine Replacement Therapy
- Short acting
 - Gum (2 and 4mg)
 - Up to 30 pieces per day
 - Lozenge (2 and 4mg)
 - Up to 30 pieces per day
 - Inhaler (Rx)
 - Recommend 8-16 cartridges per day. Each cartridge lasts 20 minutes of continuous puffing
 - Nasal Spray (Rx)
 - 1 spray each nostril (2 sprays = 1 mg nicotine) at least 8 times/day.
 Maximum 5/hour or 40 sprays per day
- Long acting
 - Patch (21, 14 and 7mg)
 - 16 hour and 24 hour products available
- Bupropion SR (150mg bid)
- Varenicline (1mg bid)
- Not FDA approved but shown effective in trials
 - Nortriptyline and clonidine

How Nicotine Replacement Works

- Relief of withdrawal symptoms
- Positive Reinforcement (arousal, stress relief)
- Desensitization of Nicotinic Cholinergic Receptors (mood stabilization)

NRT Quick Facts

- Efficacy of all nearly the same so choice is up to preference and past experience of smoker
- Inhaler and Nasal Spray are Rx and cost can be high unless covered by Insurance
- Contraindicated if unstable angina, pregnant or nursing
- Most common side effects/toxicity (flushing, dizziness, headache, skin irritation [patch], insomnia/vivid dreams [patch], jaw ache [gum])

NRT Tips to Maximize Effectiveness

- For oral products rinse mouth with water after drinking acidic beverages or else little nicotine will be absorbed through oral mucosa.
- Nasal spray good for heavy smokers but takes approx. 3 days to get used to nasal irritation.
- Inhaler delivers very little nicotine per puff so many puffs in succession are often required to feel satisfied
- Use enough short-acting to feel comfortable. Most smokers under-dose.
- For gum, make sure to "chew and park". If constant chewing much of nicotine will be swallowed and metabolized by liver.
- Rotate site of patch administration over a 7 day period to reduce skin irritation. Hydrocortisone cream may be helpful for irritation
- For 24 hour patch, remove 1-2 hours before bedtime to reduce sleep disturbances and vivid dreaming
- Use all long enough to reduce chance of relapse. At least 3 months.

FDA Change to NRT Labeling (2013)

- Allows use of NRT while still smoking or chewing or using another form of NRT
- Allows for longer use of NRT

	Previous Drug Facts Labeling	New Drug Facts Labeling
Warnings:		
Do n	ot use if you continue to smoke, chew tobacco, use snuff, or use [a different NRT product] or other nicotine containing products	None. The "Do not use" statement would be deleted.
Direc	ctions:	
	stop smoking completely when you begin using [the NRT product]	begin using [the NRT product] on your quit day
•	it is important to complete treatment. Stop using [the NRT product] at the end of [a specified number of] weeks. If you still feel the need to use [the NRT product], talk to your doctor	it is important to complete treatment. If you feel you need to use [the NRT product] for a longer period to keep from smoking, talk to your health care provider

Bupropion

Mechanism of Action is still uncertain

- Reuptake inhibitor of dopamine in the nucleus accumbens and noradrenaline in the locus ceruleus
- May also act as weak antagonist of α4β2 nicotinic receptors

Dosing

- 300 mg (150 mg BID) with titration during the first week
- · Begin therapy while still smoking
- · Smoking Quit Date usually set for Day 8 of use

Side effects

- · Dry mouth and insomnia
- Risk of seizure: approximately 1 in 1,000
 - Contraindicated for patients with seizure disorder or predisposing factors that increase seizure risk (head injury, active substance abuse, eating disorder)

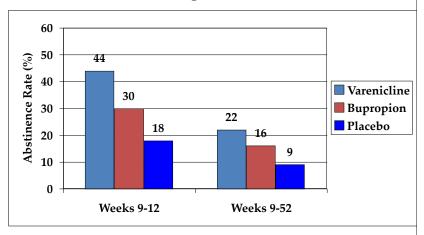
Bupropion prescribing information, 2006

Varenicline

- Non-nicotine medication
- Has both agonist and antagonist properties at the $\alpha 4 \mbox{\ensuremath{\mbox{\footnotesize R2}}}$ nicotine receptor
- Initial treatment period of 12 weeks
 - 1mg bid with titration during first week
 - Quit smoking date usually set for Day 8
- If not smoking at week 12, an additional 12 weeks of 1mg bid is recommended for relapse prevention

Varenicline prescribing information, 2013

Varenicline vs. Bupropion for Smoking Cessation



Nides, et al. American Journal of Health Behavior 2008;32(6):664-675

Boxed Warning for Varenicline and Bupropion

- All patients being treated with varenicline or bupropion should be observed
 for neuropsychiatric symptoms including changes in behavior, hostility,
 agitation, depressed mood, and suicide-related events, including ideation,
 behavior, and attempted suicide. These symptoms, as well as worsening of
 pre-existing psychiatric illness and completed suicide have been reported in
 some patients attempting to quit smoking while taking varenicline or
 bupropion in the post-marketing experience.
- Advise patients and caregivers that the patient should stop taking varenicline
 or bupropion and contact a health care provider immediately if agitation,
 hostility, depressed mood, or changes in behavior or thinking that are not
 typical for the patient are observed, or if the patient develops suicidal ideation
 or suicidal behavior. In many post-marketing cases, resolution of symptoms
 after discontinuation of varenicline or bupropion was reported, although in
 some cases the symptoms persisted; therefore, ongoing monitoring and
 supportive care should be provided until symptoms resolve.

Combination Therapy

- Nicotine patch plus short-acting NRT (gum, nasal spray) more effective than monotherapy
- Bupropion plus the nicotine patch may be more effective than monotherapy
 - Also bupropion plus the nicotine patch plus shortacting NRT has been used
- Varenicline plus bupropion
 - Several trials show increased efficacy

Efficacy of Mono and Combination therapy

Medication	Estimated Odds Ratio (95% C.I.)
Nicotine Patch (reference group)	1.0
Varenicline (2 mg/day)	1.6 (1.3-2.0)
Nicotine Nasal Spray	1.2 (0.9-1.6)
Nicotine Inhaler Bupropion SR	1.1 (0.0-1.5) 1.0 (0.0-1.2)
Nicotine Gum	0.8 (0.6-1.0)
Patch (>14 weeks) + Short-Acting NRT	1.9 (1.3-2.7)
Patch + Bupropion SR	1.3 (1.0-1.8)

PHS Clinical Guidelines. Treating Tobacco Use and Dependence: 2008 Update

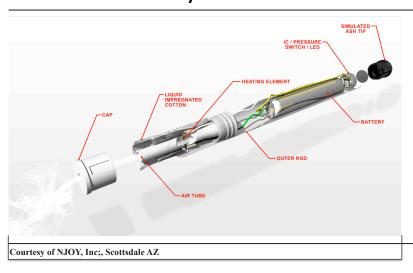
Electronic Nicotine Delivery Systems (ENDS)

- Commonly called electronic cigarettes or e-cigs
- Heat, rather than combustion used to create an aerosol of nicotine in a vehicle of propylene glycol and/or vegetal glycerin, and flavorings. No carbon monoxide
- More closely mimic sensory and behavioral characteristics of cigarettes than NRT
- Studies have shown 5 minute blood nicotine levels ranging from negligible to close to cigarettes
- Not currently regulated by FDA, but process in place

Popularity of ENDS

- Current US sales of \$2 billion
- Projected to overtake sales of combustible tobacco by 2020
- Tobacco Industry has entered market in a big way.
 - Blu (Lorillard) has over 40% of the "cigalike" market
 - MarkTen (Philip Morris), Vuse (RJ Reynolds) are in process of rolling out their products nationally

Anatomy of an ENDS



Types of ENDS

- "Cigalikes" resemble cigarettes and are either disposable or have replacement cartridges
- "Pen type" tank models are typically refillable and offer more flavors and more vapor
- "Mod" units are larger tank or drip models with many user adjustable features. Popular with enthusiasts



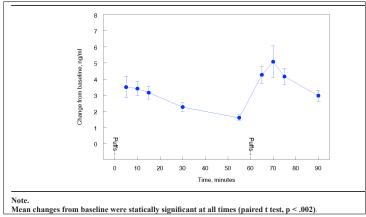
- Users often start with "cigalikes" and move on to tank models although more are starting with tanks
 - The market for "cigalikes" actually fell in the 2014 Q1

ENDS—Factors that Affect Nicotine Intake

- · Nicotine in e-liquid
 - Ranges from 0-24 ng/ml
- Factors that will increase vapor production per puff
 - Higher battery voltage, dual or quad vs.
 single coil, lower resistance coils, dripping
 e-liquid directly on coils.
- Puff topography, particularly puff duration.

ENDS Blood Nicotine Levels

Two series of 10 puffs over 5 minutes, each series spaced 1 hour apart. Subjects were 12 hours abstinence from all nicotine. ENDS used was NJOY King Bold ("cigalike" 4.5% nicotine) N=25



Nides M, Leischow S, et al. Am Jr Health Behav. 2014;38(2):265-274

Risks of ENDS

- Although a number of toxicants have been identified in e-cigarette vapors, the levels of these toxicants are orders of magnitude lower than those found in cigarette smoke, although higher than those found in NRT¹
 - The chance of formaldehyde production may increase with increasing temperature of vapor²
- Nicotine Addiction
- Poison center calls from child ingestion of e-liquid have increased need for childproofing of e-liquid used for refillable models
- May be some 2nd hand exposure to nicotine, but probably too low for any pharmacological effect³

¹Goniewicz M, et al., [published online March 6, 2013]. Tob Control. doi:10.1136/tobaccocontrol-2012-050859 ²Kosmider L, Sobczak A, Fik M, et al published online May 15, 2014]. *Nicotine Tob Res.* doi:10.1093/ntr/ntu078. ³. Hajek P, Etter J-F, Benowitz N, McRobbie H (2014) Addiction in press

Risks of ENDS (con't)

- Youth uptake of ENDS
 - CDC¹ reports that number of middle and high school youth that have ever tried ENDS doubled from 4.7% in 2011 to 10.0% in 2012
 - 76% are dual users with cigarettes
 - 20% of middle school ever users report never smoking cigarettes
- Gateway to smoking combustible cigarettes
 - Too soon for there to be any direct evidence

¹MMWR September 6, 2013 / 62(35);729-730

Is There any Evidence that ENDS can be used to Help Cigarette Smokers Quit?

- Two studies of ENDS with N's of 300¹, and 657², using early models that did not deliver much nicotine, did not show a difference in quit rates between active and placebo ENDS. The 2nd study ² also did not show a difference compared with active nicotine patch
- In an English surveillance study³:
 - "Smokers who use e-cigarettes in a quit attempt are more likely to remain abstinent from cigarettes for at least a few months than those who try to quit unaided or using a licensed nicotine product bought from a store, but probably less likely than those who attend high quality specialist stop-smoking support of the kind available in England"

FDA Deeming Regulations

- Proposed regulations published April 2014
- Would regulate a variety of non-cigarette tobacco products including e-cigs
- E-cig manufacturers will need to file comprehensive new product applications for each product, but will be allowed up to two years after final approval of regulations to file.
- After FDA approval any changes to products would need to go back to FDA for approval
- Proposed regulations would also prohibit sales to minors, but would not restrict flavors, advertising or marketing, or internet sales
- MY OPINION: Prohibitive costs will result in market consolidation, fewer products, less innovation and greater market share for the tobacco industry due to deep pockets

¹Caponnetto P, et al. (2013). PLoS ONE 8(6): e66317. doi:10.1371/journal.pone.0066317

² Buellen, et al., www.thelancet.com **Published online September 7, 2013** http://dx.doi.org/10.1016/S01406736(13)61842-5

³ Brown J, Beard E, Kotz D, Michie S, West R (2014) Addiction. doi: 10.1111/add.12623. Epub May 20.

Motivating Smokers to Make a Quit Attempt

- · Consistently ask about smoking status
- Motivational Interviewing techniques can be effective
- Individualize advice to quit based on the patients risk factors
- Carbon monoxide monitoring shows immediate effects of smoking
- Accentuate the benefits of quitting as much if not more than the risks of continued smoking
- Most smokers want to quit but don't think they can.
 Emphasize that we have very effective treatments that can make it so much easier to quit

Counseling Options

- Counseling improves chances of quitting over medication alone
- Telephone Counseling 1-800-QUIT NOW
 - Connects smokers to state's quitline
 - · California Smoker's Helpline was first in country
 - Behavioral Counseling free of charge
 - Often offer free NRT through mail (usually patch)
 - Well trained counselors
- · Online programs
 - Quitnet.com
 - Pharmaceutical companies with smoking cessation medications offer primarily web-based behavioral program
- Variety of quit-smoking apps for smartphones

DRUG INTERACTIONS with SMOKING

Clinicians should be aware of their patients' smoking status:

- Clinically significant interactions result from the combustion products of tobacco smoke, not from nicotine.
- Constituents in tobacco smoke (e.g., polycyclic aromatic hydrocarbons;
 PAHs) may enhance the metabolism of other drugs, resulting in an altered pharmacologic response.
- Changes in smoking status might alter the clinical response to the treatment of a wide variety of conditions.
- Drug interactions with smoking should be considered when patients start smoking, quit smoking, or markedly alter their levels of smoking.

PHARMACOKINETIC DRUG INTERACTIONS with SMOKING

Drugs that may have a *decreased effect* due to induction of CYP1A2:

- Bendamustine - Olanzapine

CaffeineRopinirole

- Clozapine - Tacrine

Erlotinib
 Theophylline

Fluvoxamine

 Irinotecan (clearance increased and systemic exposure decreased, due to increased glucuronidation of its active metabolite)

Smoking cessation will reverse these effects.

The 5 A's ASK ADVISE ASSESS ASSIST ARRANGE

READY to QUIT Discuss Key Issues

- Reasons/motivation to quit
- Confidence in ability to quit
- Triggers for tobacco use
 - What situations lead to temptations to use tobacco?
 - What led to relapse in the past?
- Routines/situations associated with tobacco use
 - When drinking coffee
 - While driving in the car
 - When bored or stressed
 - While watching television
 - While at a bar with friends
- After meals or after sex

Fiore et al. (2008). Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: USDHHS, PHS, May 2008.

- During breaks at work
- While on the telephone
- While with specific friends or family members who use tobacco

READY to QUIT Discuss Key Issues (cont'd)

Stress-Related Tobacco Use

THE MYTHS

- "Smoking gets rid of all my stress."
- "I can't relax without a cigarette."

THE FACTS

- There will always be stress in one's life.
- There are many ways to relax without a cigarette.

Smokers confuse the relief of withdrawal with the feeling of relaxation.

STRESS MANAGEMENT SUGGESTIONS:

Deep breathing, shifting focus, taking a break.

READY to QUIT Discuss Key Issues (cont'd)

Concerns about Weight Gain

- Discourage strict dieting while quitting
 - Encourage healthful diet and meal planning
 - Suggest increasing water intake or chewing sugarless gum
 - Recommend selection of nonfood rewards
- When fear of weight gain is a barrier to quitting
 - Consider pharmacotherapy with evidence of delaying weight gain (bupropion SR or 4-mg nicotine gum or lozenge)
 - Assist patient with weight maintenance or refer patient to specialist or program

READY to QUIT

Facilitate Quitting Process (cont'd)

Cognitive Coping Strategies

- Review commitment to quit
- Distractive thinking
- Positive self-talk
- Relaxation through imagery
- Mental rehearsal and visualization



READY to QUIT

Facilitate Quitting Process (cont'd)

Behavioral Coping Strategies

- Control your environment
 - · Tobacco-free home and workplace
 - Remove cues to tobacco use; actively avoid trigger situations
 - Modify behaviors that you associate with tobacco: when, what, where, how, with whom
- -Substitutes for smoking
 - Water, sugar-free chewing gum or hard candies (oral substitutes)
- Minimize stress where possible, obtain social support, take a break, and alleviate withdrawal symptoms

READY to QUIT

Facilitate Quitting Process (cont'd)

- Provide medication counseling
 - Promote compliance
 - Discuss proper use, with demonstration
- Discuss concept of "slip" versus relapse
 - "Let a slip slide."
- Offer to assist throughout quit attempt
 - Follow-up contact #1: first week after quitting
 - Follow-up contact #2: in the first month
 - Additional follow-up contacts as needed
- Congratulate the patient!

Smoking Cessation Apps

Benefits may include:

- Self monitoring of cravings and cigs
- Programmed gradual reduction to quitting
- Targeted motivational messages
- Instant rewards for meeting goals
- Coping strategies including games for distraction
- Support community
- Low cost
- Automatic tracking of cigs not smoked, health benefits and money saved

Smoking Cessation apps (con't)

- Reality Check—Content Analysis of 400 apps¹
 - Popular apps have low level of adherence to Clinical Practice Guidelines (mean=12.9 out of 42)
 - Not one recommended calling a Quitline
 - Only 4% recommended using FDA approved meds
- Check out Livestrong My Quit Coach
 - Free, and access to Livestrong community for support

¹Abroms, et al. Am J Prev Med. 2013 Dec;45(6):732-6. doi: 10.1016/j.amepre.2013.07.008.

Summary

- Tobacco use is a complex addiction with physical, psychological and behavioral components
- Consistently talk to your smokers about treatment options
- When used appropriately NRT and bupropion double success rates while varenicline triples success rates vs placebo in clinical trials
- Combination therapies increase efficacy vs monotherapy
- Medication plus counseling has the highest rate of success
- ENDS have promise but more research is needed
- Don't ever give up on your smokers. They can quit