Pharmacotherapy for the Treatment of Tobacco Use Disorder

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Objectives

- Describe various types of NRT and Non NRT medications available, how they work & general guidelines for use
- Describe and apply evidence-based medicine principles to pharmacological treatment for nicotine dependence
- Explain the anticipated effects of the available pharmacologic treatment in select medical conditions
- List additional special concerns and issues that affect the choice of pharmacologic treatment
- Apply knowledge of the use of pharmacotherapy to hypothetical cases

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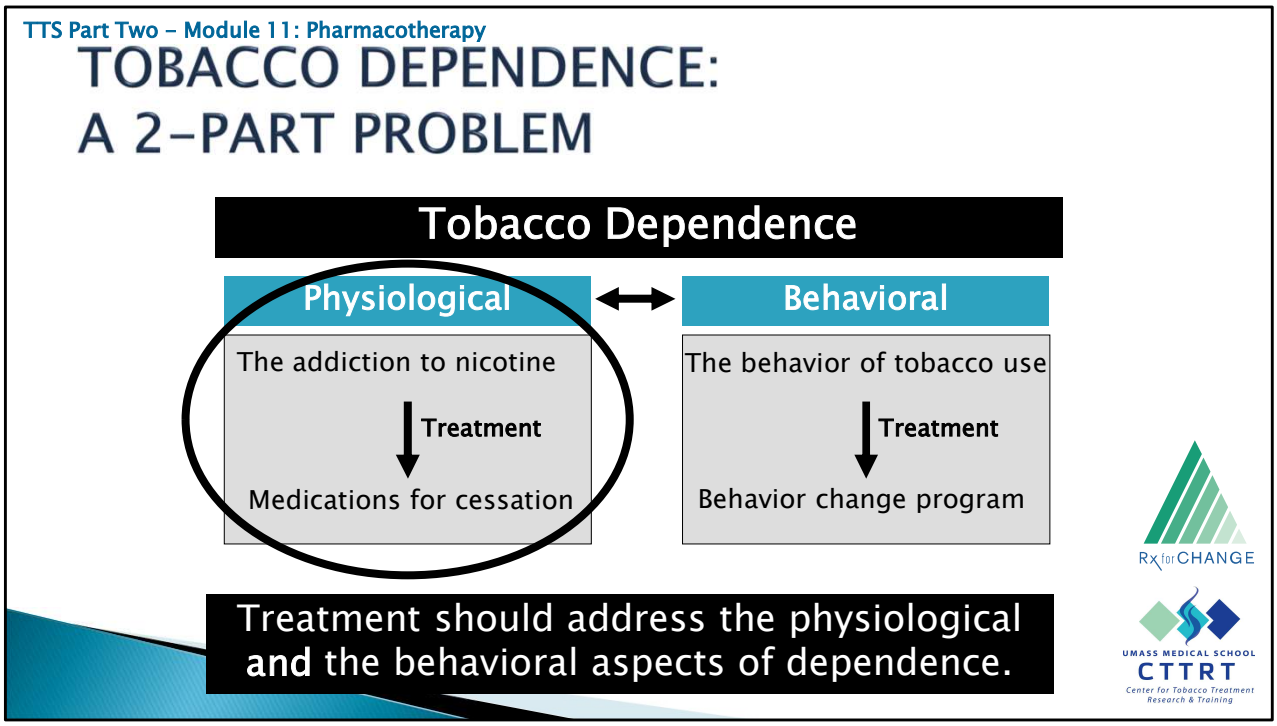
Consider a poll question after this –
Who can prescribe medications?
Comfort level with answering patients' questions?

Poll # 1 questions

1. Are you currently recommending over the counter or prescription medications at your place of work?
2. How comfortable are you with talking to your clients/patients about using medications to help them quit using tobacco?
3. What is you practice setting?
4. Are you a prescriber?



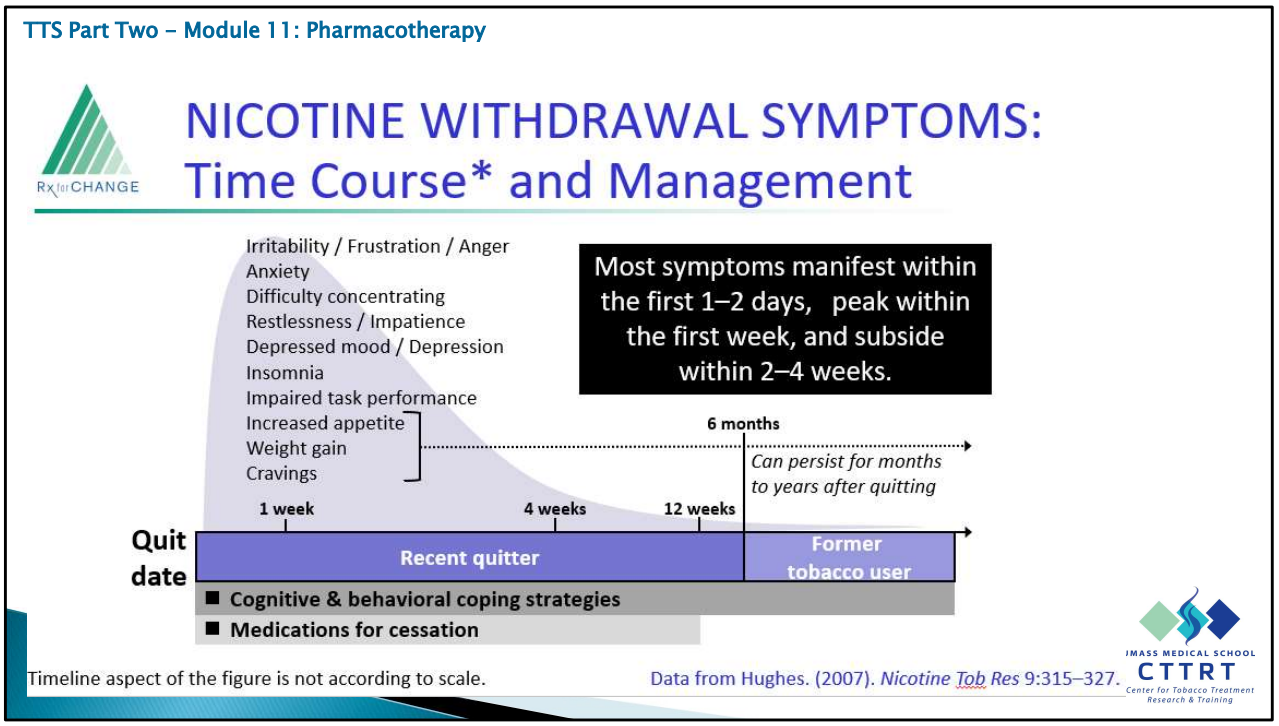
Tobacco dependence is a chronic condition that requires a two-prong approach for maximal treatment effectiveness (Fiore et al., 2008).

Prolonged tobacco use of tobacco results in tobacco dependence, which is characterized as a physiological dependence (addiction to nicotine) and behavioral habit of using tobacco. This module addresses the use of FDA-approved medications to treat tobacco dependence.

The Clinical Practice Guideline for treating tobacco use and dependence (Fiore et al., 2008), which summarizes more than 8,700 published articles, advocates the combination of behavioral counseling with pharmacotherapy in treating patients who smoke.

♪ **Note to instructor(s):** Specific methods for treating the behavioral aspects of tobacco use and dependence such as individualized counseling and group or online cessation programs are covered in detail in the *Assisting Patients with Quitting* module.

Fiore MC, Jaén CR, Baker TB, et al. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline.* Rockville, MD: U.S. Department of Health and Human Services. Public Health Service.



Nicotine replacement therapy, bupropion, and varenicline are used as aids for cessation in the management of the physiologic aspect of tobacco dependence. These agents work by alleviating the symptoms of nicotine withdrawal, which include (Hughes, 2007):

- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness/impatience
- Depressed mood/depression
- Insomnia
- Impaired task performance
- Increased appetite
- Weight gain
- Cravings for tobacco

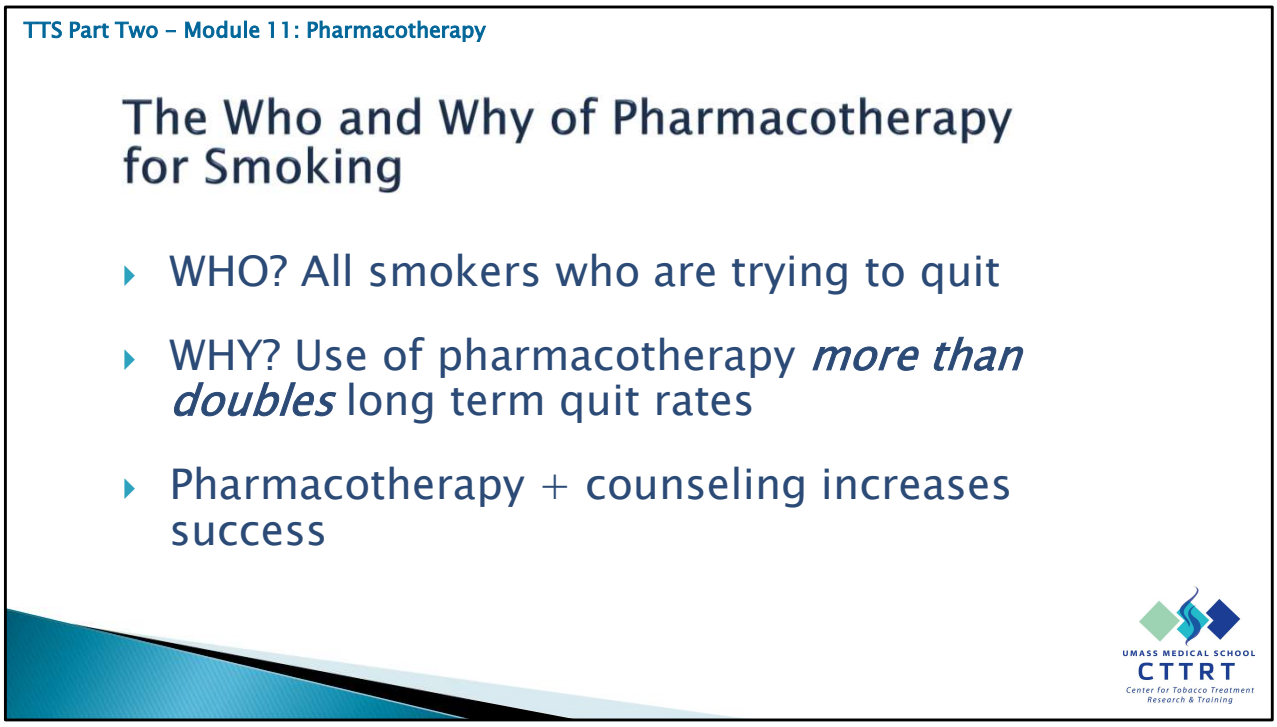
♪ **Note to instructor(s):** Other symptoms of quitting have been described in the literature. Please refer to Hughes, 2007 for further details.

This slide depicts the general time course for common nicotine withdrawal symptoms that is observed following the cessation tobacco use. **Most withdrawal symptoms manifest within the first 1–2 days, peak in intensity within the first week, and gradually subside within 2 to 4 weeks after cessation** (Hughes, 2007). In some individuals, prolonged appetite effects (e.g., hunger, weight gain) may occur continuously for 6 months or more (Hughes, 2007), and strong cravings for tobacco can persist for months to years after cessation (Benowitz, 1992).

For this reason, the typical recommended duration of therapy for pharmacotherapy is 6–12 weeks; this helps to alleviate the symptoms of nicotine withdrawal during the early stages of quitting. When patients are more comfortable, it's easier to address the habits and routines associated with tobacco use through use of cognitive and behavioral coping strategies. For additional information please refer to the *Assisting Patients with Quitting* module.

Benowitz NL. (1992). Cigarette smoking and nicotine addiction. *Med Clin N Am* 76:415–437.

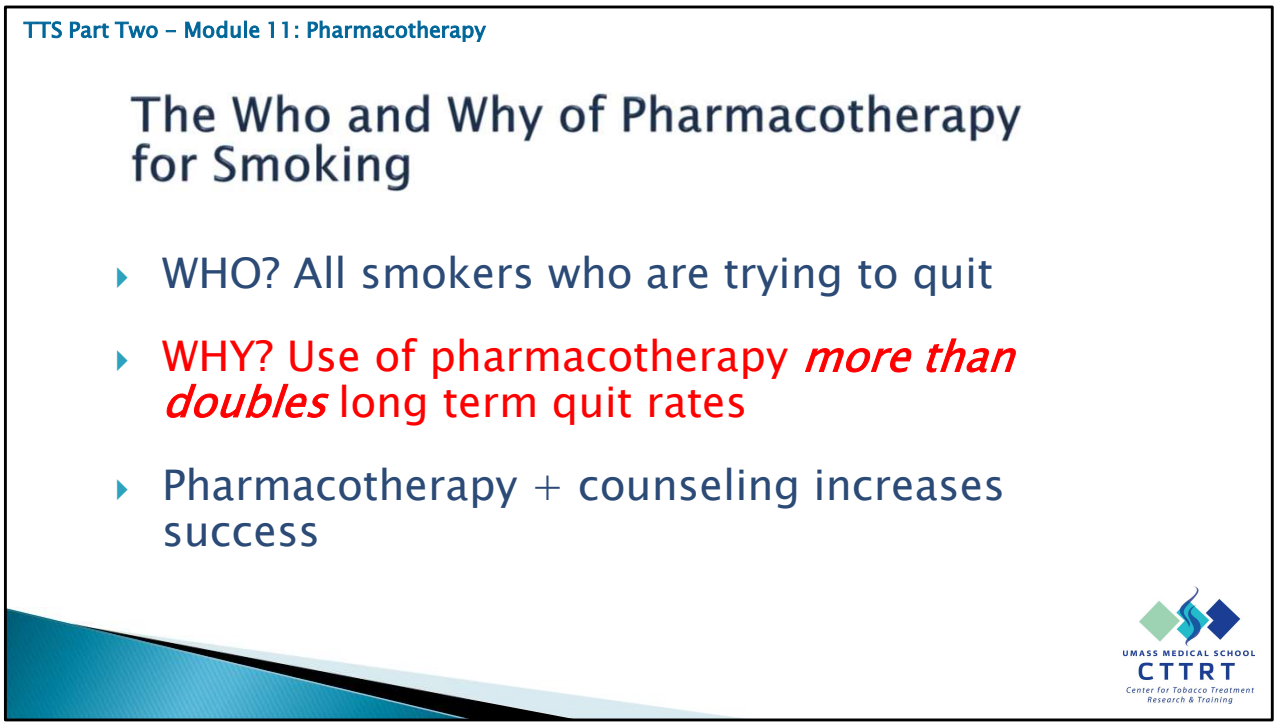
Hughes JR. (2007). Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res* 9:315–27.



KEY POINTS:

- Smokers who quit cold turkey (no pharmacotherapy) have a 5-15% (avg 7%) chance of long term success
- In general, pharmacotherapy more than doubles the chances of success
- Furthermore, adding counseling to meds (the "Gold Standard") will increase potential for success even more
- Smokers <10 CPD were not included in clinical trials therefore recommendations have only included those smoking 10 or more cigs/day
- Consider today's changing landscape of smoking restrictions. The manner in which many smoke has changed i.e., many "relight" (e.g. reporting smoking 5 cigs/day but smoking 10-12 x/day). Re-lighters smoke differently in than they tend to have deeper and more complete inhalations each time they smoke.
- Using TFC (time to first cig/use) may be more helpful indicator of degree of dependence. Those who smoke within the first 30 mins. upon waking being more heavily dependent and therefore need more pharmacotherapy rather than less

REFERENCES: FAGERSTOM (FTC); Stead, 2012.



KEY POINTS:

Let's start by talking about pharmacotherapy efficacy.

FDA-Approved Pharmacotherapy Options

Nicotine Replacement (NRT)	Non-Nicotine Medications
Patch	Bupropion SR
Gum	Varenicline
Nasal Spray	
Inhaler	
Lozenge	

Fiore et al, 2008; Ebbert et al, 2014

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- Current FDA-approved pharmacotherapy options include using a single medication or combining two medications

KEY POINTS:

- Published studies suggest that all 7 first line meds are effective, with varenicline being most effective and combination therapy being more effective than solo NRT
- Combination NRT therapy or NRT and bupropion is rapidly becoming a standard of treatment and is recommended in the PHS Guidelines. Provides long-acting medication with ability to use short acting as needed
- There is controversy regarding the use of Chantix as part of combination therapy. We will discuss this in detail later on in the presentation after we review the individual agents.

REFERENCES: Steinberg, 2009; Ebbert, 2014; Kozlowski, 2007; Schnieder, 2001; Shiffman, 2005; Sweeney, 2005; Koegelenberg, 2014

The Who and Why of Pharmacotherapy for Smoking

- WHO? All smokers who are trying to quit
- WHY? Use of pharmacotherapy *more than doubles* long term quit rates
- Pharmacotherapy + counseling increases success

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We will spend most of this talking about pharmacotherapy, but don't forget the importance of counseling. Pharmacotherapy and counseling has been proven in multiple studies to be better than either modality alone. It is also recommended by the PHS guidelines due to such evidence. We will discuss it further on the next slide.

Combine Medications and Counseling

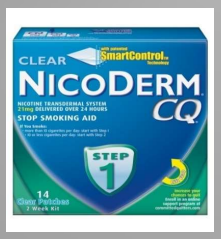
Type	% increase in smoking cessation compared to no treatment or placebo
NRT + Behavior Therapy	70–100%
NRT Alone	53–68%
Bupropion SR Alone	49–76%
Varenicline Alone	102–155%*
Behavioral Therapy Alone	18–96%
Without treatment ~ 5% of smokers will quit over the course of a year	

Patnode et al, 2015

- According to a review by Patnode and colleagues, a combined intervention with both pharmacotherapy and behavioral intervention increases cessation success by 70 to 100%
- Behavioral support provided in the study's review included tailored self-help materials; brief, practical counseling by physicians; and more intensive counseling by specialists through quitlines or in-person tobacco treatment programs. Evidence for mobile phone applications, internet-based interventions and alternative or complementary therapies was limited.
- Literature regarding minimal interventions show that of those who go "cold turkey", about 5% of smokers will quit over a 12 month period (Slade, 1993).
- Appropriate and proper use of NRT, varenicline or bupropion has been found in many studies to double these numbers.
- What's the take home message? Whenever possible, provide both behavioral counseling AND pharmacological support!
- *"Trials with pharmaceutical funding have been shown to have slightly higher effect sizes than nonindustry funded studies; given the number of included trials funded by pharmaceutical companies (particularly for varenicline) the magnitude of the effects may be smaller than estimates suggest" (Patnode, 2015).

Now we will review each of the 7 first line medications beginning with the 5 nicotine replacement therapy (NRT) products.

Types of Nicotine Replacement

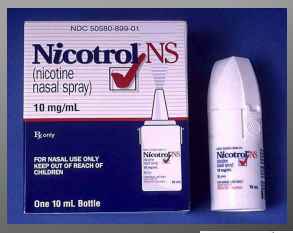


PATCH

GUM

LOZENGE

INHALER



SPRAY

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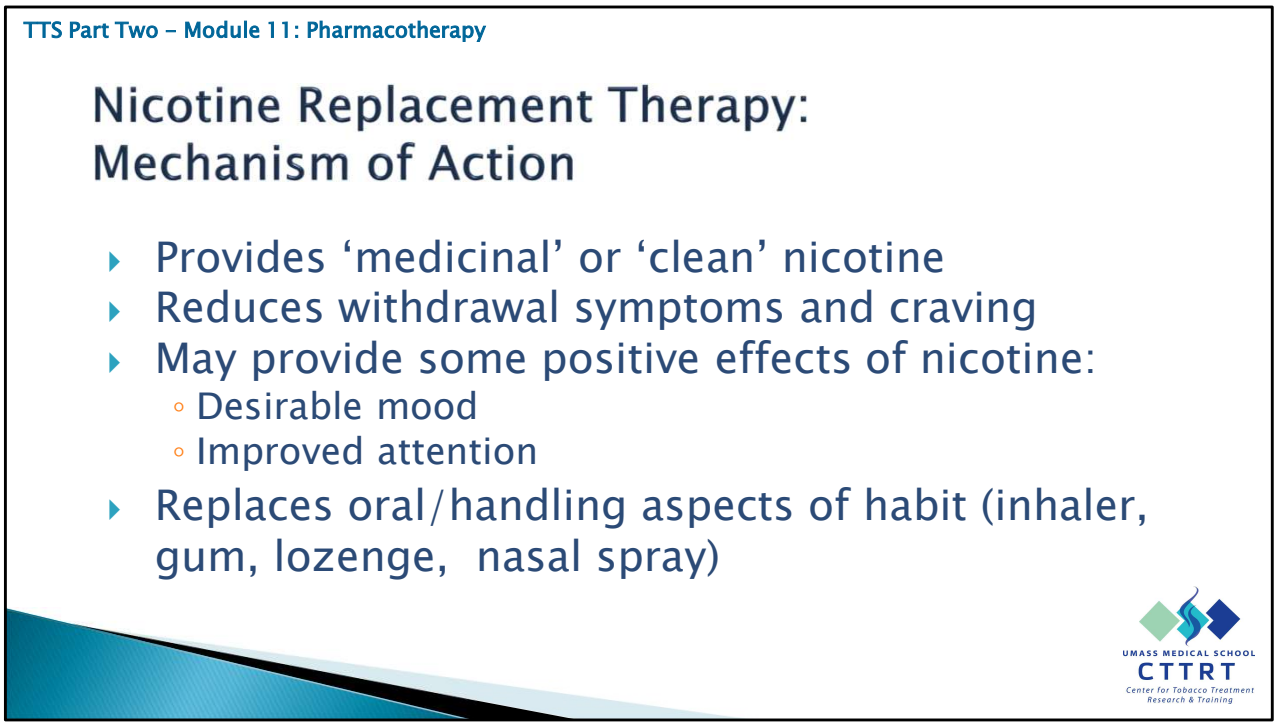
- Current forms of FDA-approved nicotine replacement therapy (NRT) include gum, patch, lozenge, inhaler and nasal spray. In addition to these name brands, generic products are also available.
- Other nicotine products that have been developed include nicotine water, lollipops and straws. NONE have received FDA approval.
- Electronic cigarettes that contain nicotine are NOT approved by the FDA as a cessation aid.

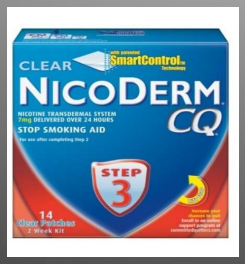


KEY POINTS:

- Cigarettes use the best drug delivery system in our body (i.e., our lungs). Reaches the brain/reward pathway within 8 seconds.
- NRT is slower, does not access the reward pathway in the same manner.
- NRT will reduce both withdrawal symptoms and cravings which will allow the smoker to focus on changing behavior without the intense distraction of symptoms.

REFERENCES: Stead, 2012

Nicotine Patch



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- Transdermal nicotine patches came on the market in 1991 as a prescription medicine. In 1996, the FDA approved a switch to over-the counter (OTC) status for both nicotine patches and gum.
- The NicoDerm CQ patch is available in 21, 14, and 7 mg doses. It is designed to be worn for 16 or 24 hours and then replaced with a new patch every day.
- Generic patches are available at most large pharmacy stores and are comparable to the name brand patches.

Patch – Dosing Guideline

PATCH	
21 mg, 14 mg or 7 mg	
Dose:	1 patch every 24 hrs
Start:	21 mg patch if $\geq$ 10 cig/day 14 mg patch if < 10 cig/day
Duration:	~8 weeks to up to 6 months

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- Patches deliver nicotine very gradually, over a period of 16- 24 hours, in doses ranging from 7 to 21 mg, depending on the particular patch. It takes about 5 hours for blood levels to reach peak plasma levels. The patch is not reinforcing and there are no reports of addiction to the patch.
- A step-down dosing approach is recommended, which gradually weans patients off nicotine. For example use Step 1 (21 mg) for weeks 1- 4, step 2 (14 mg) for weeks 5 and 6, and step 3 (7 mg) for weeks 7 and 8. However, the number of weeks for each step should be determined on an individual basis depending upon the client's experience of withdrawal and cravings.

- Apply a new patch every morning and wear it for 24 hours . For some people, wearing the patch while sleeping causes sleep disturbances; these people should remove any patch at bedtime. For people who crave a cigarette upon waking, they are advised to wear the patch for 24 hours.
- The patch should be applied as soon as a person awakes on their quit day, and be placed on a relatively hairless location between the neck and waist.
- Some people (20 - 50%) will develop local skin irritation while on the patch. Application of 1% over the counter hydrocortisone cream should help minor irritation. It is usually mild and goes away by itself. In case of a severe reaction, patch use should be discontinued.
- In some cases patches do not adhere as well. If this is the case, first aid adhesive tape may be used to help the patch stay in place.

Nicotine Gum

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- Nicotine gum was developed in response to concerns by a Swedish submarine commander about nicotine withdrawal among his crew members when they were not able to smoke. It was first marketed in the US in a 2 mg dosage form, by prescription only, as an adjunct to behavioral treatment of smoking.
- Nicotine gum is commonly used in combination with the nicotine patch.

Gum – Dosing Guideline

GUM	
2 mg or 4 mg	
Dose:	1 piece every 1–2 hrs
Start:	2mg if > 30 min to first cig 4 mg if ≤ 30 min to first cig
Max:	24 pieces/day
Duration:	Up to 6 months

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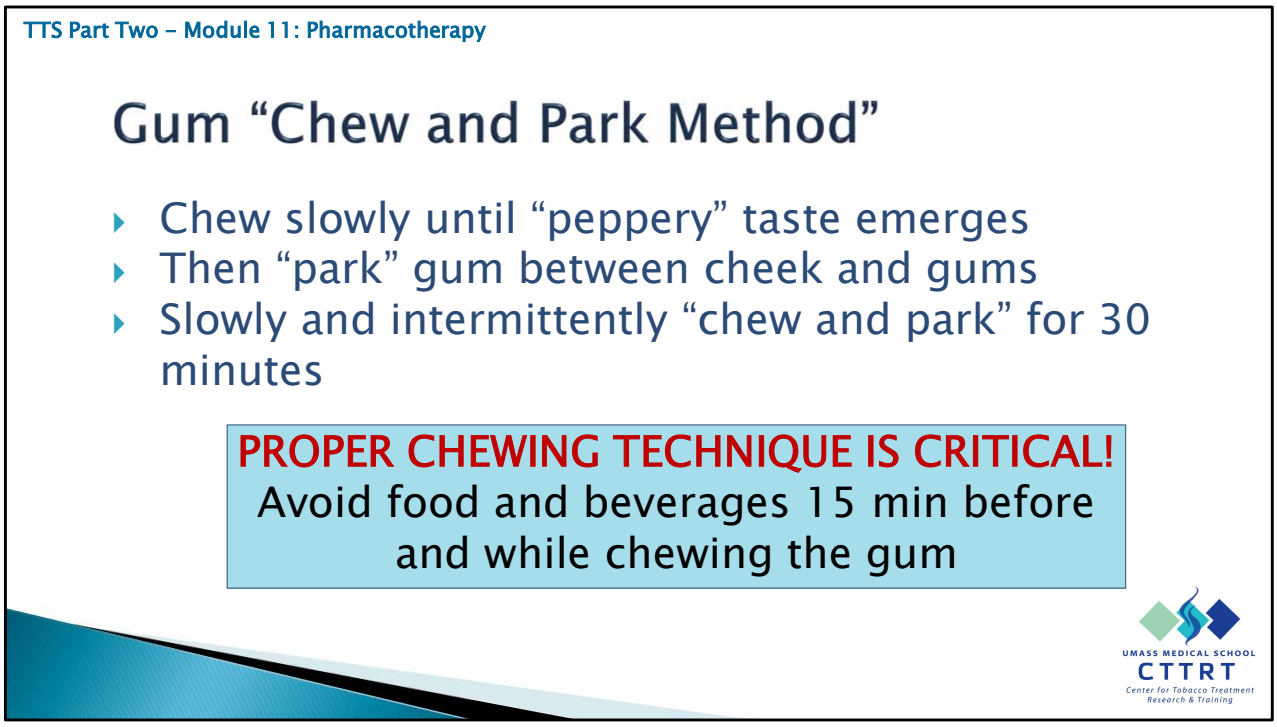
- With optimal use, the gum delivers about 0.8 mg from the 2 mg product and about 1.5 mg from the 4 mg product, over about half an hour. This time course is far slower than the nicotine delivery from a cigarette, cigar or even moist snuff.
- If using nicotine gum as the main form of NRT when quitting, the user should be encouraged to chew the gum on a regular schedule (see above). This will help to maintain sufficient blood nicotine levels and help avoid relapse.
- If nicotine gum is used as an adjunct to the patch a regular schedule may also be helpful, especially before any times known to be difficult, such as first thing in the morning). Or, chew a piece whenever withdrawal symptoms seem to be breaking through or when experiencing cravings.
- Nicotine gum can be used effectively in response to cravings, cues and triggers to smoke. Some people find the gum to be mildly reinforcing and there are reports of people becoming dependent upon the gum.



- Proper chewing technique, called "chew and park", is critical! Patients must be instructed in how to chew correctly:
- Chew slowly until "peppery" taste emerges, about 1 minute.
- Then "park" gum between cheek and gum, until peppery taste goes away, about 1 or 2 minutes. This is when the nicotine is being absorbed by the oral mucosa.
- Slowly and intermittently "chew and park" for 30 minutes.
- Do not drink acidic beverages or foods while chewing the gum. This will diminish its effectiveness.
- Do not eat or drink 15 minutes before using or while the gum is in mouth
- Nicotine gum is difficult to use with dentures, braces or jaw problems.

Nicotine Lozenge

Different flavors available

Mini lozenge – dissolves 3 times faster

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- The nicotine lozenge is the most recent NRT product to be approved for use in the US.
- It is available in the original full size and the mini-lozenge. The mini is preferred by many since it dissolves faster.
  The mini lozenges come in flavors such as mint and original.

Lozenge – Dosing Guideline

LOZENGE or MINI-LOZENGE	
2 mg or 4 mg	
Dose:	1 lozenge every 1-2 hrs
Start:	2mg if > 30 min to first cig 4 mg if ≤ 30 min to first cig
Max:	20 pieces/day
Duration:	Up to 6 months

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- Like the gum, the dose for the lozenge is calculated by the time to first cigarette, so those who smoke within the first 30 minutes of waking should use the higher, 4 mg dose, and those who wait more than 30 minutes before smoking their first cigarette should use the 2 mg dose.
- The lozenge is a popular choice to use as needed in combination with the nicotine patch. If used alone the schedule above should be followed.
- As with other forms of NRT, it may be beneficial for the patient to taper off use.

Lozenges – Instructions

- Allow to dissolve slowly
- Do not bite or chew
- "Park" between cheek and gum, and move around with tongue periodically

Avoid food and beverages 15 min before and while using the lozenge

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- Use of the lozenge is less complicated than the gum. Unlike the gum the lozenge should NOT be chewed.
- Similar to the gum it is important to avoid acidic foods and beverages, which alter the pH of the mouth and interfere with absorption of the nicotine.
- Do not eat or drink 15 minutes before using or while the gum is in mouth

FDA Consumer Update: NRT OTC Labeling

Drug Facts Labeling (2013)	Current Labels
Warnings	
Do not 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 has been deleted**
Directions	
• 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 longer period to keep from smoking, talk to your health care provider**

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm
https://www.federalregister.gov/documents/2013/04/02/2013-07528/modifications-to-labeling-of-nicotine-replacement-therapy-products-for-over-the-counter-human-use

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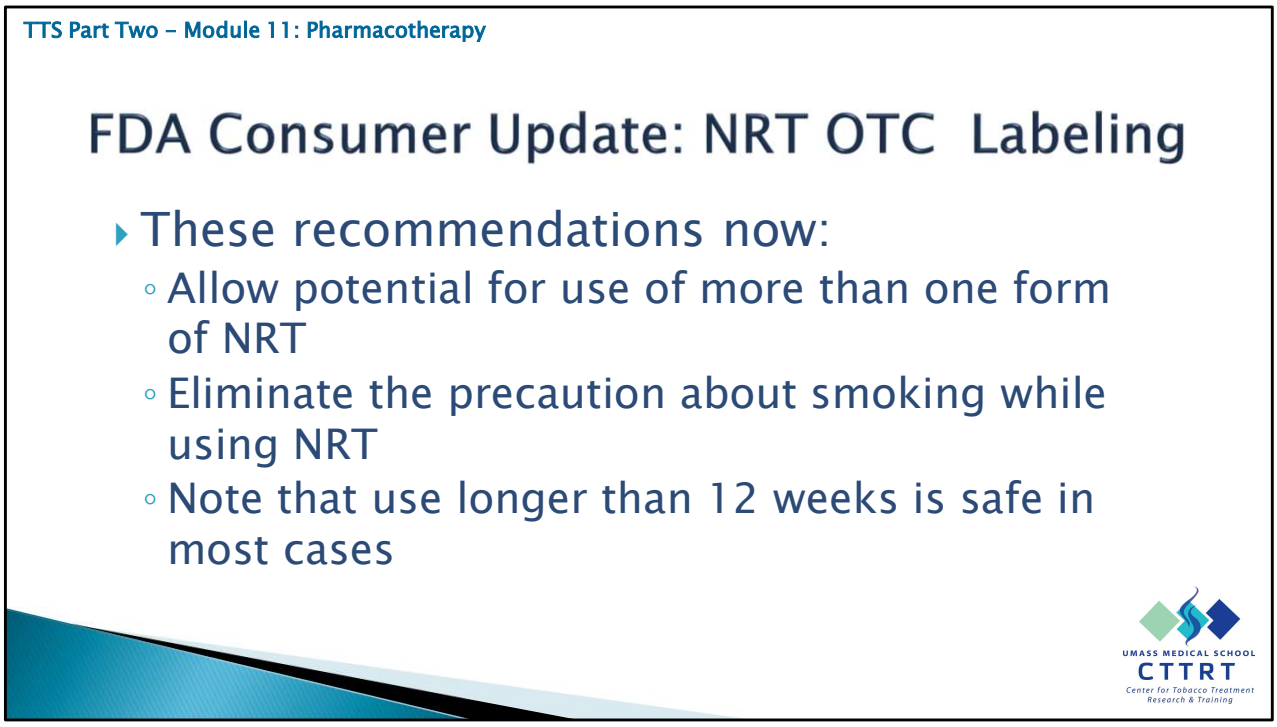
KEY POINTS:

- Initial labelling was from an abundance of caution. There were further recommendations that labels be amended to include recommendations for combination therapy, but that has not been put into action.
- When the PHS update was published in 2008 it included strong evidence to support combining medications – Patch plus short acting NRT especially
- In 2013 the FDA responded to a citizens request from organizations like SRNT and ATTUD to change the labeling on NRT
- The nicotine gum and patch products were originally approved through the new drug application (NDA) process between 1984 and 1992. Both the gum and the patch were initially available by prescription only; these products were switched from prescription to OTC status between 1996 and 2002. The nicotine lozenge and mini-lozenge were approved directly for OTC use in 2002 and 2009, respectively.
- Over that 20 plus year period, additional evidence from studies and use in practice have shown that patients may benefit from tapering down cigarettes, combination NRT and longer duration of use, all of which we will discuss today.
- In order to make the changes, the drug companies did have to submit an application for a label change to the FDA.



KEY POINTS:

- These recommendations now :
  - Allow for the use of more than one form of NRT → does not specifically recommend for or against; this is a good option for counseling. That being said, the patch does say not to wear more than 1 patch at a time. Again, this is a good option for counseling and explanation for nicotine levels attained from tobacco products.
  - Eliminate the precaution about smoking while using NRT
  - Note that use longer than 12 weeks is safe to do so in most cases.
- *Ask "*What does this tell you about the safety of NRT?"

Nicotine Inhaler

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- The nicotine inhaler was approved in 1998 on a prescription basis as an adjunct in the management of tobacco dependence. It continues to be available by prescription only.
- It is the only form of NRT to address both the physical and behavioral aspects of nicotine dependency.

Inhaler – Dosing Guideline

INHALER (Nicotrol® Inhaler)	
Dose:	6 –16 cartridges/day as needed
Max:	16 cartridges/day
Duration:	3 – 6 months

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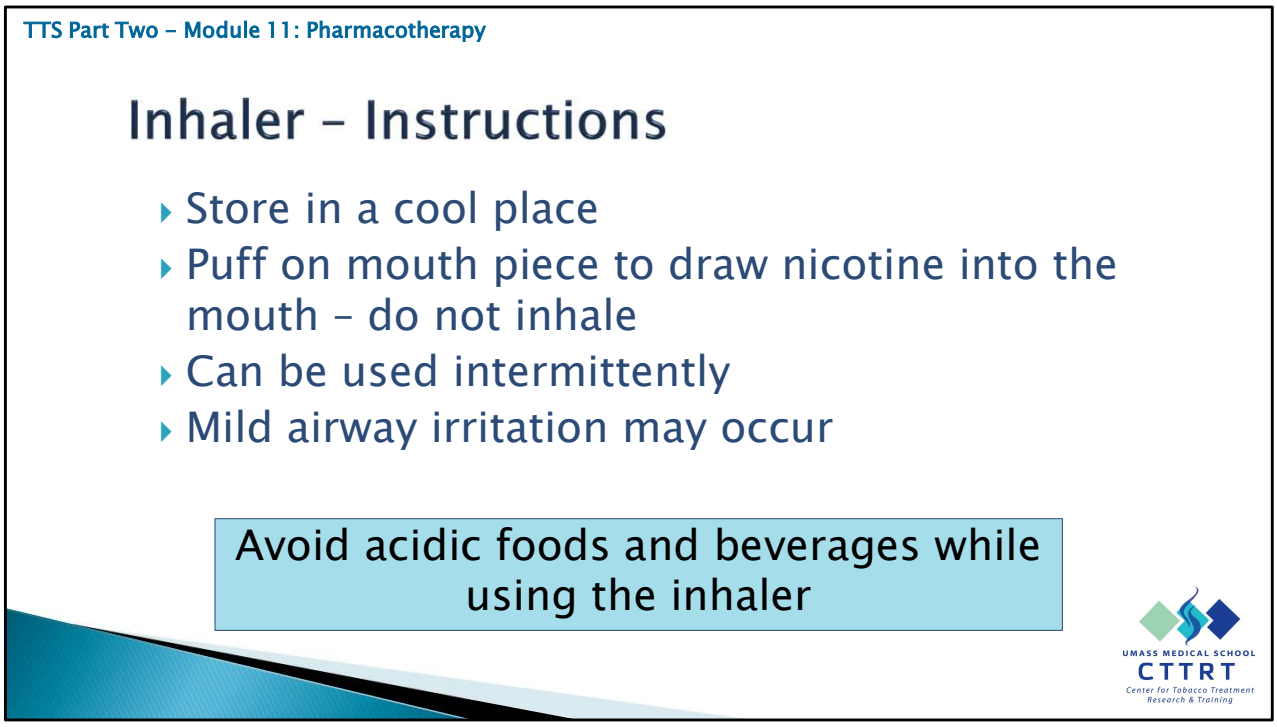
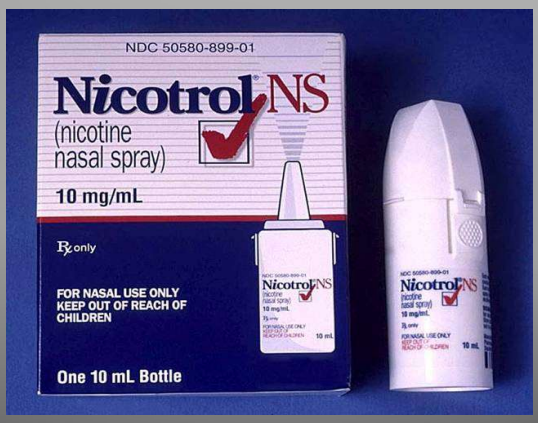
- Recommended dose for monotherapy: 6 - 16 cartridges per day for the first 6 weeks. In actual use, it appears that the lower dose is sufficient for most smokers/tobacco users.
- Can also be used as needed in combination with nicotine patches.
- Approximately 2 mg (the equivalent of about 2 cigarettes) are absorbed from one cartridge.
- Start tapering by 3 months. Use for longer than 6 months may indicate dependence.



- Despite its name, nicotine is delivered only to the mouth and throat, not to the lungs, via a plastic cartridge - a "nicotine puffer" which accurately describes it.
- Puff in short breaths for about 20 minutes (1 cartridge); the nicotine is absorbed in the mouth and upper airways. It can be used for about 10 minutes (1 cigarette worth), set down, and resumed later for the final 10 minutes.
- Start tapering by 3 months; do not use longer than 6 months.
- The most common side effects are throat and mouth irritation and coughing, which usually go away after a while.

Nicotine Nasal Spray



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- Of all NRT products on the market, the nicotine nasal spray delivers nicotine to the blood stream the most rapidly. Because of this, the dependency potential is greater with the spray than with other forms of NRT. It is available by prescription only.

Nasal Spray – Dosing Guideline

NASAL SPRAY (Nicotrol® NS)	
(1 dose= 1 mg= 2 sprays)	
Dose:	1 – 2 dosages per hr
Max:	5 doses/hr or 40 doses/day
Duration:	3 – 6 months

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- The usual dose is two sprays, one in each nostril; each spray delivers about 0.5 mg of nicotine.
- The solution concentration is 10 mg/ml
- For monotherapy start at 1 - 2 doses/hour; the maximum dose is 5 doses/hour or 40 doses/day.
- The manufacturer recommends treatment for up to 8 weeks then stopping or tapering dose for another 4 - 6 weeks. The PHS Clinical Guideline recommends use for up to 6 months.
- The nasal spray also can be used as needed in combination with nicotine patches.

Nasal Spray – Instructions

- Most rapid delivery of nicotine
- Dose = 1 spray in each nostril
- Nasal irritation may occur, but may resolve with continued use

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- The spray has not been widely used because many find it irritating and uncomfortable to use initially.
- The irritation subsides after about one week of use.
- In clinical trials, some subjects found the spray to be reinforcing.

Nicotine Delivered by Tobacco Products

Nicotine Delivery Device – TOBACCO	Nicotine In Product	Approximate Amount of Nicotine Delivered to User	Comments
Marlboro Red	13 mg	1 to 3 mg	Also delivers a wide range of carcinogens and other toxins
Marlboro Light	13 mg	1 to 3 mg	
Cigars	10 to 400 mg	Highly variable	
Moist Snuff	3 to 12 mg/gm	Varies depending on pH & other characteristics	

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- This slide reviews the nicotine content in various tobacco products. Note that the light cigarette delivers just as much nicotine as the regular cigarette, or about 1 - 3 mg per cigarette.
- Moist Snuff and other smokeless products deliver a wide range of nicotine.
- It is important to remember that in addition to nicotine, tobacco products deliver irritants, toxins and carcinogens.

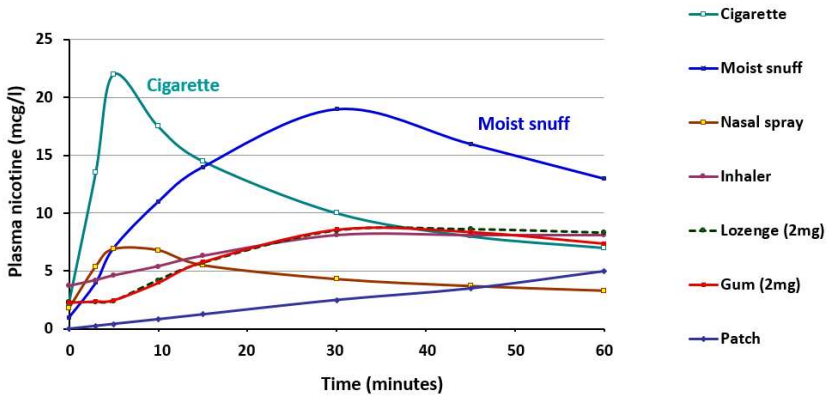
Nicotine Delivered by Nicotine Replacement Products

Nicotine Delivery Device – NICOTINE REPLACEMENT	Nicotine in Product	Approximate Amount of Nicotine Delivered to User	Comments
Nicotine Gum	2 mg/piece	Up to 0.8 mg	Only delivers nicotine to the consumer
Nicotine gum	4 mg/piece	Up to 1.2 mg	
Nicotine patch (Habitrol)	17 mg	7 mg/24 hours	
Nicotine patch (Habitrol)	35 mg	14 mg/24 hours	
Nicotine patch (Habitrol)	52 mg	21 mg/24 hours	
Nicotine nasal spray	10 mg/ml	0.5 mg/1 spray	
Nicotine inhaler	10 mg/cartridge	Up to 4 mg/cartridge	

- In contrast to tobacco products, NRT products only deliver nicotine to the user. There are no carcinogens, no carbon monoxide, no formaldehyde, no benzene, etc., ingested with nicotine from the patch, gum, spray, lozenge or inhaler.
- Nicotine replacement products contain higher levels of nicotine than what is delivered to the patient. As with all medications, caution should be used to protect children and pets from accidental exposure to nicotine.
- Remember that nicotine replacement products provide only partial replacement of the nicotine that had been delivered by tobacco products.

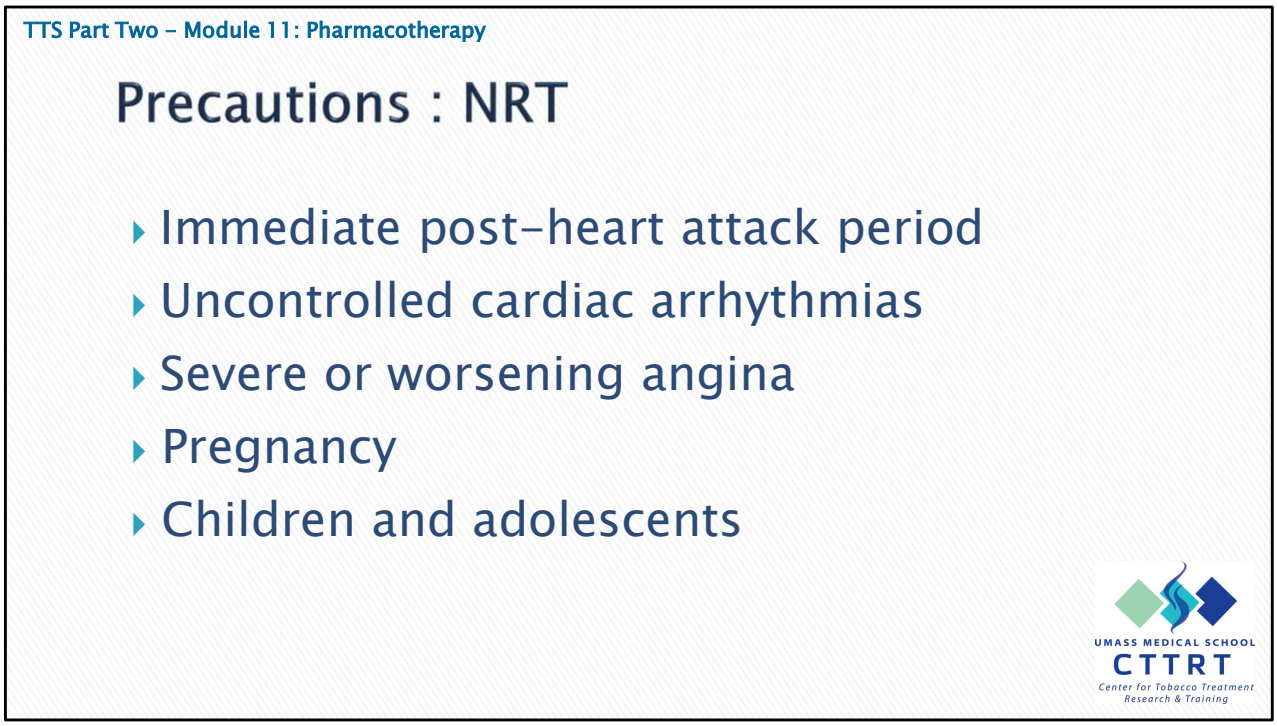
Comparing Nicotine Levels

PLASMA NICOTINE CONCENTRATIONS for NICOTINE-CONTAINING PRODUCTS



- This graph is used with permission from Rx for Change:
- It depicts the plasma venous nicotine concentrations achieved with the various nicotine delivery systems.
- The concentration time curves in this slide depict levels achieved after administration of a single dose of nicotine following a period of overnight abstinence (Cigarette smoked- 5", Snuff placed in cheek-30", Inhaler was puffed over 20", Gum chewed – 30", Lozenge in cheek - 30").
- "I'm sure you may notice by this graph…what is our best drug delivery system? The CIGARETTE, OF COURSE!!. Which uses the lungs and rapidly reaches the reward pathway in the brain.
- Peak plasma concentrations are higher and are achieved more rapidly when nicotine is delivered via cigarette smoke compared to the available NRT formulations. The rapid spike in nicotine levels from a cigarette is known as a bolus effect.
- Among the NRT formulations, the nasal spray has the most rapid absorption, followed by the gum, lozenge, and inhaler; absorption is slowest with the transdermal formulations.
- Because NRT formulations deliver nicotine more slowly and at lower levels (e.g., 30–75% of those achieved by smoking), these agents are far less likely to be associated with dependence when compared to tobacco-based products.
- Nasal Spray is most rapid NRT – however, uncomfortable side effects of rhinitis and it is expensive. Not used often.
- You can see by this slide that NRT delivers nicotine more slowly and at lower levels – they are far less likely to be associated with dependence when compared to cigarettes.
- ALSO POINT OUT Nicotine Content Handout in their manual for comparison of nicotine delivered by the different products.

REFERENCES: Choi, 2003; Fant , 1999; Schneider, 2001



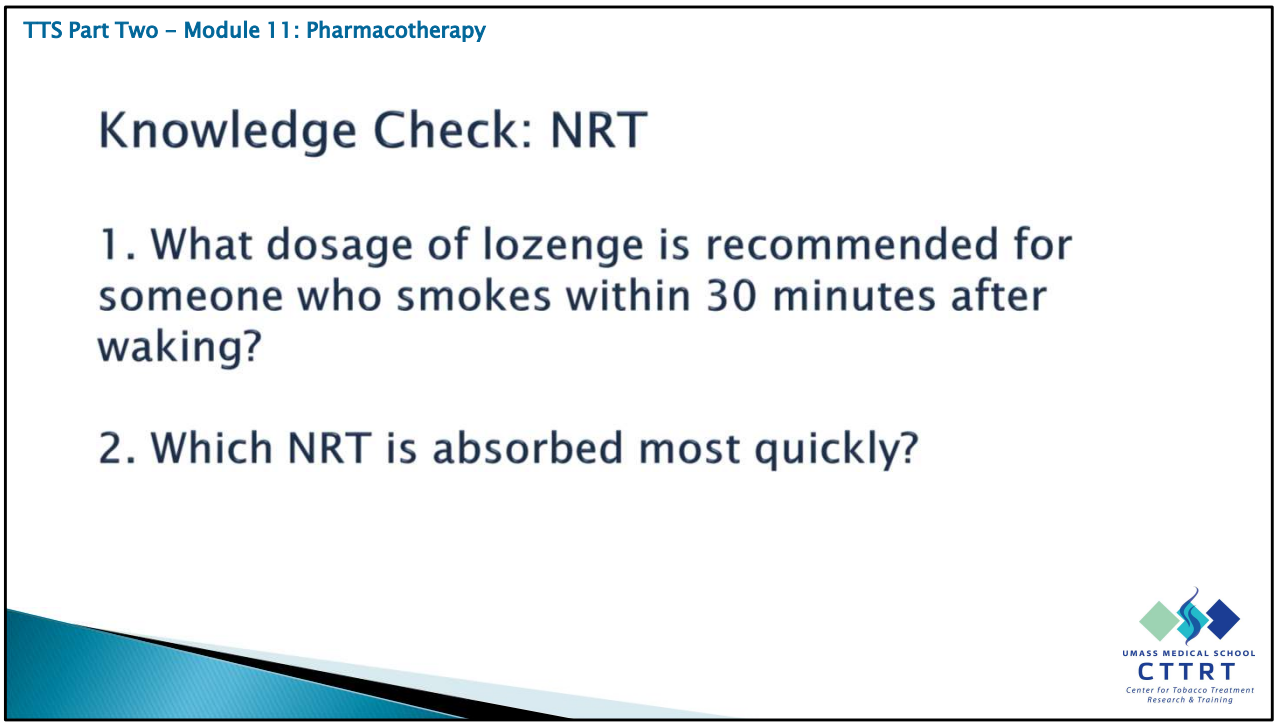
KEY POINTS;

- **Please note the word *precautions.* This does not read contraindication.**

- It is important to understand that these medical conditions require more caution and consideration. In many cases would need the collaboration of prescribing clinician.

- In the case of acute coronary events (i.e., recent heart attack and/or arrhythmia or unstable angina) the guidelines did not support pharmacotherapy due to lack of research in these groups. However: (refer to references below) We know from observational analyses of patients in these categories who received NRT while hospitalized that there were no associations with increased risk of another cardiac event or death and appeared to be safe. Of note: in most medical centers now, patients in CCU's are routinely given the patch. From a risk mitigation standpoint, if the patient is going to be exposed to nicotine either way (tobacco product use or NRT), it is probably safer to be from NRT.

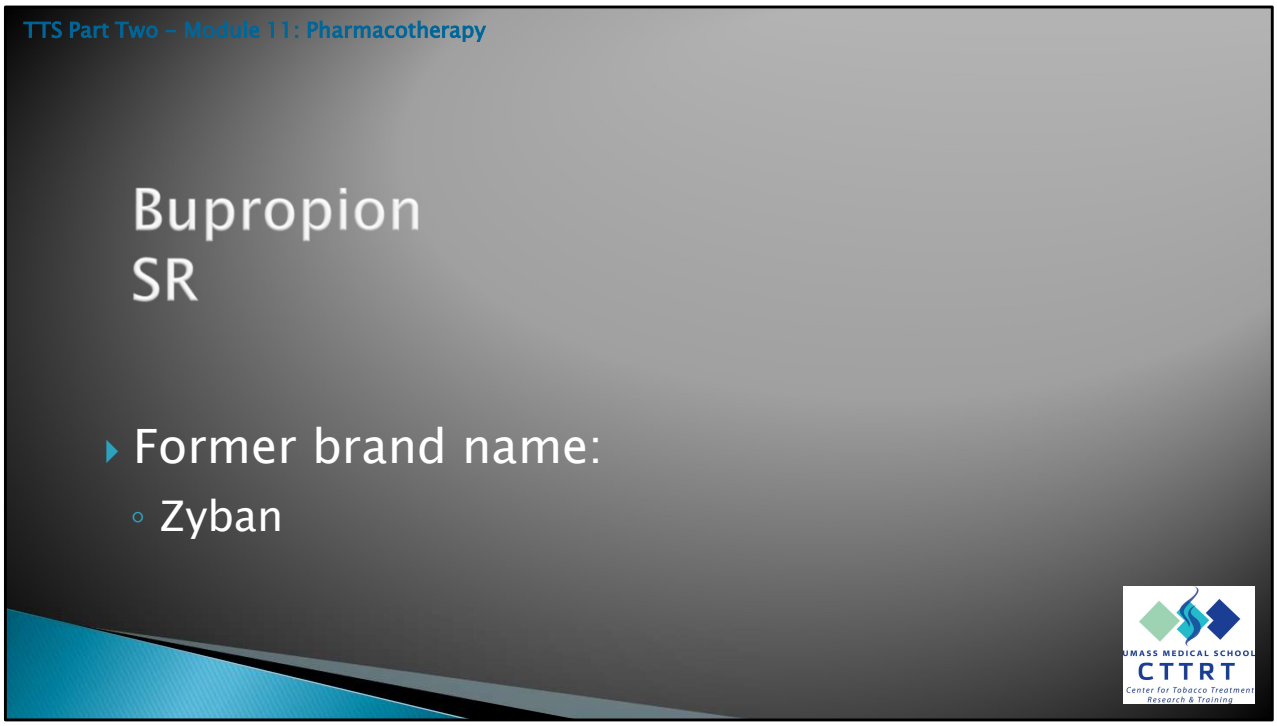
REFERENCES: Hubbard, 2005; Meine, 2005; Rigotti, 2013



Use poll or other method to engage participants to think about previous slides.
Sample questions:
1. What dosage of lozenge is recommended for someone who smokes within 30 minutes after waking?
(4 mg)
2. Which NRT is absorbed most quickly?
(Nasal spray)

Non-NRT First Line Treatment: Bupropion and Varenicline

- Let's turn now to a discussion of Bupropion and Varenicline



- Sustained release (SR) bupropion is a prescription medication approved for the use in the treatment of tobacco dependency. It is dosed twice daily (or BID) as it is a 12 hour formulation.
- The XL is dosed once daily as it is a 24 hour formulation.
- Sustained release forms (SR): Less variation in blood levels and less toxicity
- Under the trade name of Wellbutrin it has long been used to treat depression before found to be effective for tobacco treatment.
- Buproprion is no longer sold as brand name Zyban.

Bupropion SR: Mechanism of Action

- Mechanism of action for tobacco cessation: unknown
  - Weak inhibitor of uptake of dopamine (DA) and norepinephrine (NE)
  - Benefit likely related to the reduction in NE and DA during withdrawal
  - PET scans show that brain cells known to be involved in drug craving do NOT activate in response to cigarette-related cues when in the presence of bupropion*

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KEY POINTS:

- Bupropion was originally just approved and used in the treatment of depression. When used for depression its brand name was Wellbutrin.
- It began being studied as a smoking cessation tool when those on the Wellbutrin reported decreased desire to smoke.
- In 1997 it was approved for use in treating tobacco dependence and marketed under the brand name Zyban.
- It is now available in the generic form, Bupropion.
- Mechanism of action not completely understood but believed to be related to the smoker's level of dopamine. Interestingly, bupropion is now being used as part of a drug combination for binge eating disorder further supporting the theory that it has some effect on reward/addiction pathway.

REFERNCES: *Arthur Brody and colleagues; published online in the April 2004 issue of Psychiatry Research: Neuroimaging.
Zyban Package Insert . GSK. 2017
Roddy. BMJ. 2004 Feb 28; 328(7438): 509–511
Hurt, 1997; Lerman, 2004

Bupropion SR: Dosing Guideline

BUPROPION SR *May be combined with nicotine replacement*	
150 mg tablets	
Dose: (begin 1–2 weeks before quit date)	150 mg once per day (days 1–3) 150 mg twice per day (day 4+)
Max:	300 mg/day
Duration:	12 weeks*

* If quit at 12 wks, consider 12 more weeks of drug

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- Start taking bupropion 1- 2 weeks before the quit date:
- 1 tablet daily for 3 days then 1 tablet twice daily for 7 – 12 weeks
- Bupropion may be combined with nicotine replacement therapies.

Precautions and Contraindications: Bupropion SR

- History of seizure or condition that lowers seizure threshold
  - History of anorexia or bulimia
  - Excessive or binge drinking
  - Medications associated with increased seizure risk
- MAO inhibitor use within 14 days
- History of mania
- Concomitant use of Wellbutrin/bupropion for another indication
- Liver disease and/or renal insufficiency
  - Consider reduced dose

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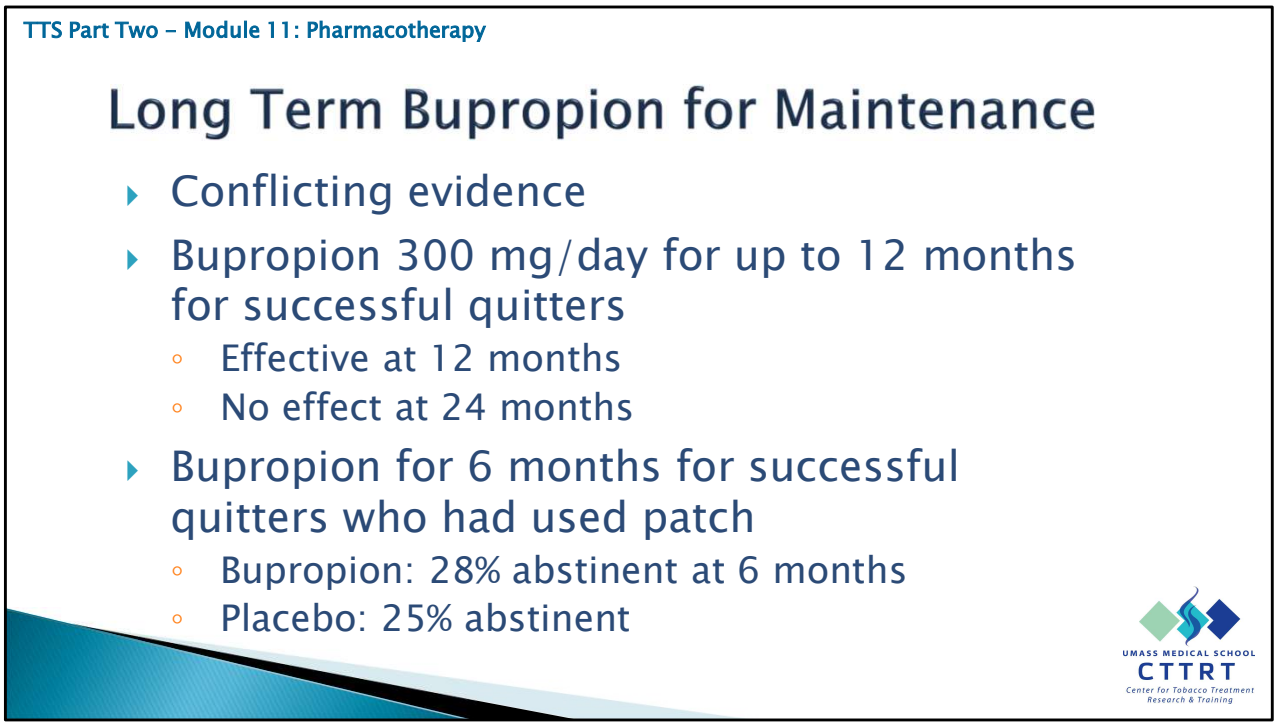
KEY POINTS:

- The risk of seizure is associated with the use of bupropion (approx. 1 in 1,000) therefore is not used in those with a definite history of seizures.
- Likewise with a history of anorexia/bulimia or heavy drinking, which are known to lower the seizure threshold, specifically alcohol withdrawal and electrolyte abnormalities associated with eating disorders are what increase seizure risk.
- As there is with many meds, precaution is taken with anyone with liver or renal disease but still used but at a reduced dose.
- There is a risk of increasing blood pressure. In the case of someone with significant uncontrolled hypertension, bupropion would be avoided.
- Any medication, including bupropion, varenicline and NRT should be avoided if patient has a history of allergy to that specific agent.



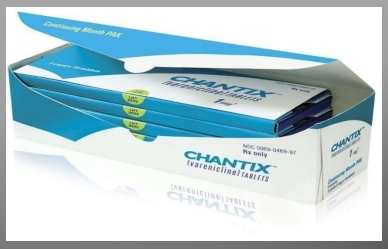
KEY POINTS:

- Anyone who has worked with smokers trying to quit, knows how preventing relapse is "the name of the game".
- As Mark Twain is to have said "Quitting smoking is easy….I've done it hundreds of times".
- Prevention of relapse is the next major challenge for pharmacotherapy.
- Bupropion has been looked at as a potential tool. But as you can see, evidence is not completely convincing. At 6mths – 12 mths an effect, not so at 24mths.

REFERENCES: Hays, 2001; Hurt, 2003

Varenicline

(Chantix)



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- Varenicline is a prescription medicine approved by FDA in 2006 to help adults in the treatment of tobacco dependency. The brand name in the US is Chantix, other countries, Champix.

Varenicline: Mechanism of Action

- Varenicline acts as a partial agonist/antagonist on the nicotinic acetylcholine receptors:
  - Providing some nicotine effects to ease the withdrawal symptoms and
  - Blocking the effects of nicotine from cigarettes if they resume smoking

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KEY POINTS:

- Designer drug (developed solely for the purpose of tobacco dependence treatment).
- Approved by FDA in 2006.
- Both a nicotine agonist and an antagonist.
- Decreases withdrawal symptoms.
- Decreases cravings.

REFERENCES: Aubin, 2008; Gonzales, 2006; Jorenby, 2006

Varenicline: Dosing Guideline

VARENICLINE (Chantix®)	
0.5 mg, 1 mg tablets	
Dose: (begin 8 – 35 days before quit date)	Starting Month Pak = 0.5 mg once per day (days 1–3) 0.5 mg twice per day (days 4–7) 1 mg twice per day (days 8+) Continuing Month Pak = 1 mg twice per day
Max:	2mg/day
Duration:	12 weeks*

* If quit at 12 weeks, then 12 more weeks of therapy may be considered

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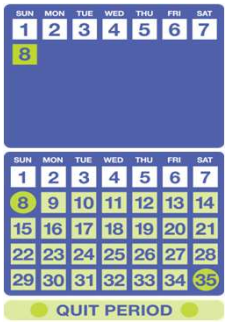
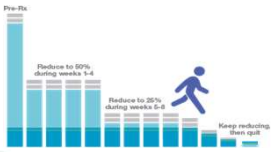
- Start taking varenicline at least 1 week before the quit date – it can be used for up to 35 days before complete abstinence.
- Take 1 white tablet daily (0.5mg) for 3 days
- Then one white tablet (0.5 mg) twice daily for 4 days
- Then one blue tablet (1mg) twice daily for up to 12 weeks.
- Individuals should tell their physicians or pharmacist all the medications they are taking, especially insulin, asthma medications or blood thinners because when someone stops smoking, there may be a change in how these and other medicines works for them.
- Safety and efficacy of varenicline has not been established in children under 18 years, in pregnant women, in women who are breastfeeding or those who are planning to become pregnant.
- Combining varenicline with nicotine patch (21mg) did not affect the efficacy of the drug but caused nausea, headaches, dizziness, fatigue and dyspepsia.

TTS Part Two – Module 11: Pharmacotherapy

VARENICLINE QUIT APPROACHES





FIXED QUIT approach

- Set quit date for 1 week after starting varenicline
- Continue treatment for 12 weeks

FLEXIBLE QUIT approach

- Start taking varenicline and pick a quit date between 8 to 35 days from treatment initiation
- Continue treatment for 12 weeks

GRADUAL QUIT approach

- Start taking varenicline and reduce smoking by 50% within the first 4 weeks, an additional 50% in the next 4 weeks, and continue until complete abstinence by 12 weeks

Images from: https://www.pfizerpro.com/product/chantix/hcp/quit-approaches

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While most patients use the standard dosing of varenicline for smoking cessation (e.g., "fixed quit" approach), there are three dosing regimens described in the product package insert:

Fixed Quit Approach
As described previously, for this approach patients must set a quit date for 1 week after initiating varenicline, and treatment is continued for 12 weeks.

Flexible Quit Approach
Begin therapy and then quit smoking between days 8–35 of treatment (Pfizer, 2019).

Gradual Quit Approach
For patients who are not able to or willing to quit abruptly, consider a gradual approach to quitting smoking. Initiate varenicline and reduce smoking by 50% from baseline within the first four weeks, by an additional 50% in the next four weeks, and continue reducing with the goal of reaching complete abstinence by 12 weeks. Continue treatment for an additional 12 weeks, for a total of 24 weeks (Pfizer, 2019).

In general, the flexible and gradual quit approaches should be reserved for individuals who might need more confidence prior to quitting completely completely or those who experienced some success with a prior attempt with varenicline and is a candidate for re-treatment. Regardless of the approach selected, it is advisable that the cessation counselor work with the patient to establish a firm quit date and, for the gradual quit approach, specify dates on which the patient will implement reductions in the number of cigarettes smoked per day.

Pfizer Inc. (2019, February). Chantix Package Insert. New York, NY.

Side Effects of Varenicline

- Most common side effect: nausea
- Other side effects include: headaches, abnormal dreams, constipation, insomnia, vomiting and flatulence
  - Some of the side effects like nausea and insomnia may improve with dose reduction
- Anyone experiencing worsening depression or suicidal thoughts should contact their doctor immediately

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- Nausea can often be managed by taking the medication in the middle of a full meal and with at least 8 oz of water.
- Reducing the dosage from 2 mg to 1 mg per day (.5mg 2x/day vs 1mg 2s/day) has been shown to be effective for cessation and reduces nausea.

Varenicline: Precautions

- Use lower dosage if kidney function is severely impaired
- An important study has shown NO increased risk for neuropsychiatric symptoms (Anthenelli, R et al, 2016)
- In 2016 FDA removed the black box warning
- As with any medication close medical supervision is recommended

For additional information go to this link
https://www.chantix.com/getting-started-with-chantix/what-to-expect

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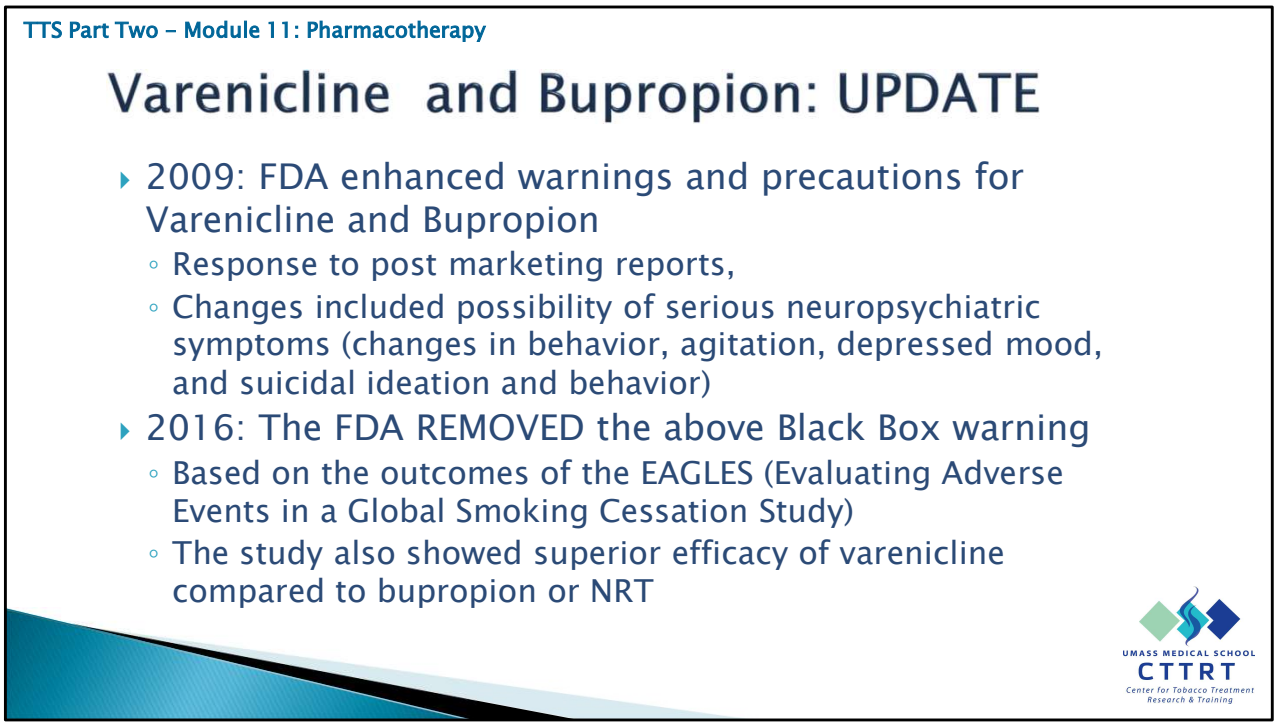
- One of the most significant precautions is related to use in patients with impaired kidney function. Reduced dosage may be required
- In 2009 the FDA had included information in the WARNINGS and PRECAUTIONS sections about the possibility of serious neuropsychiatric symptoms.
- HOWEVER, this was reversed in 2016 after the publication of the EAGLES study (Anthenelli, R et al, 2016) demonstrating no increased risk of symptoms with the use of varenicline by smokers with and without a history of psychiatric disorders.

TTS Part Two – Module 11: Pharmacotherapy

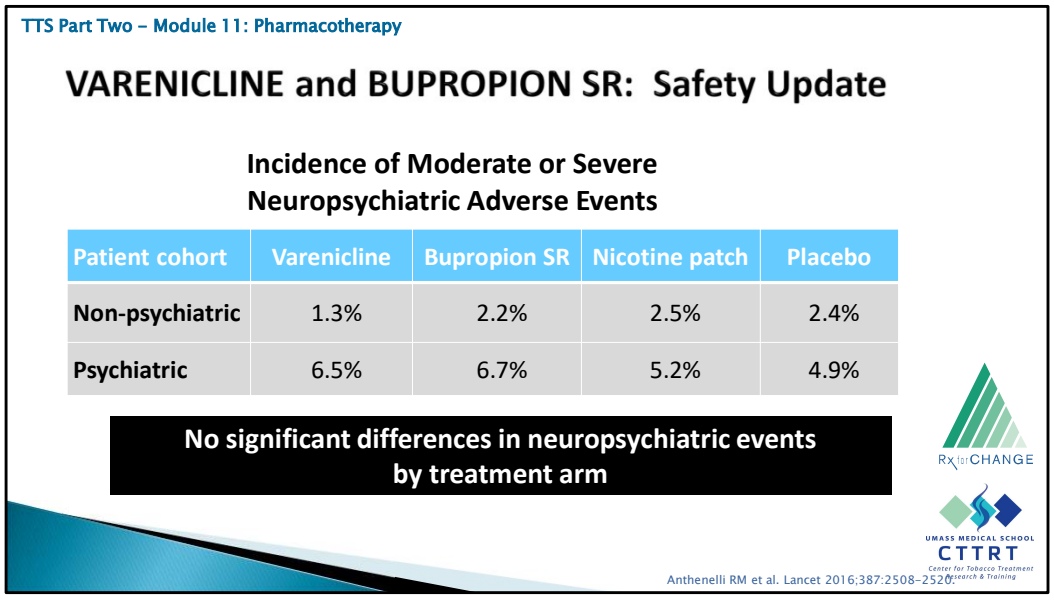


KEY POINTS:

- In 2009, at the request of FDA due to the post marketing reports, the Chantix full prescribing information included information in the WARNINGS and PRECAUTIONS sections about the possibility of serious neuropsychiatric symptoms (changes in behavior, agitation, depressed mood, and suicidal ideation and behavior) in patients taking Chantix. Recommendations and Considerations for Healthcare Professionals
- However, since that Black Box warning there has not been any research to back this up. In fact, in 5/2013 An article in the American Journal of Psychiatry by Gibbons and Mann concluded that their analysis revealed no evidence of increase in these events. The authors reanalyzed data from 17 placebo-controlled randomized (considered the gold standard in research) trials to look at this as well as data from a large Dept. of Defense observational study. These trials included both those with mental illness and those without it. There was no evidence (n=8000+) of adverse neuropsychiatric events.

- In 2016 the FDA removed the black box warning based on the outcome of the EAGLES study. The EAGLES study showed that there were no significantly increased neuropsychiatric safety risk vs. placebo, in smokers with or without a history of psychiatric disorders. It also found significantly higher continuous abstinence rates vs. bupropion, NRT patch and placebo at weeks 9-12 and 9-24 in both cohorts.

REFERENCES: Anthenelli, R et al, 2016; Gibbons, 2013



In this slide we show the proportion of individuals who experienced a moderate or severe neuropsychiatric event while on study. As you can see from the data, the proportion does not differ by treatment arm for either the non-psychiatric participants or the psychiatric participants. Overall, the psychiatric cohort exhibited more events than did the non-psychiatric (but this did not differ significantly by treatment arm).

EAGLES STUDY: Efficacy Data

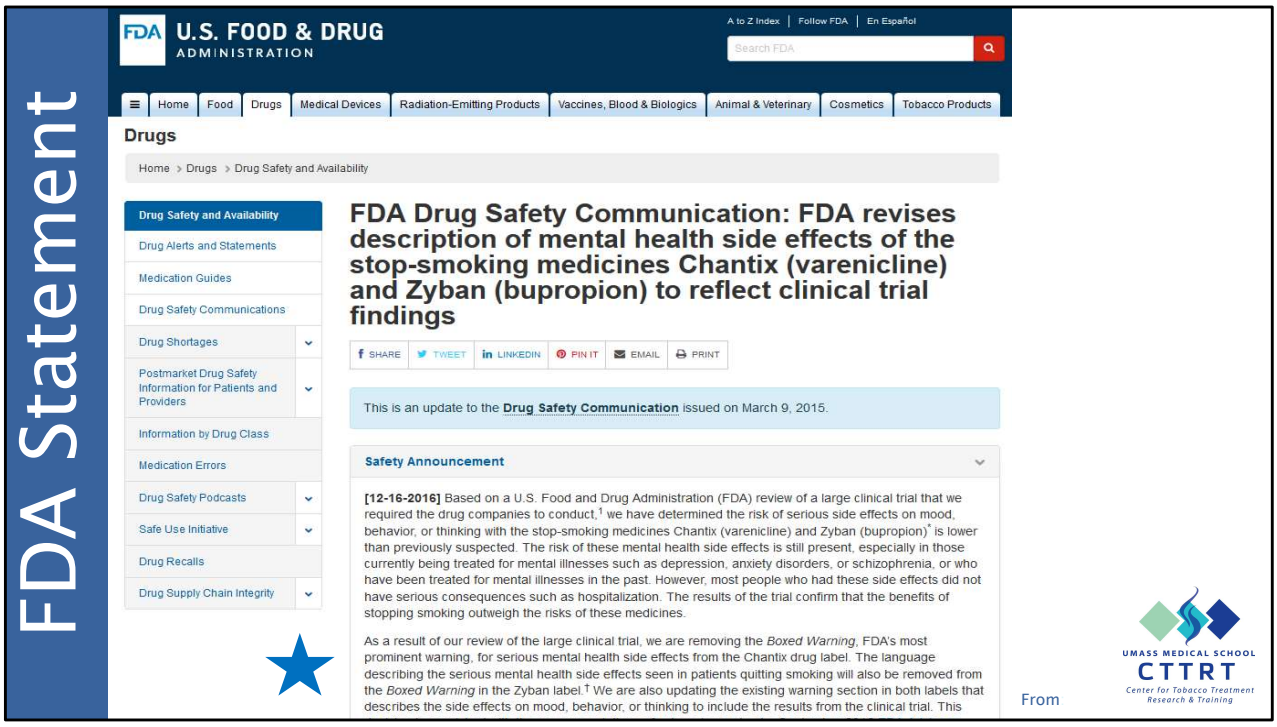
% Achieving Continuous Abstinence, Weeks 9-24

Patient cohort	Varenicline	Bupropion SR	Nicotine patch	Placebo
Non-psychiatric	25.5%	18.8%	18.5%	10.5%
Psychiatric	18.3%	13.7%	13.0%	8.3%

Highest efficacy with varenicline

Anthenelli RM et al. Lancet 2016;387:2508–2520.

FDA Statement



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FDA Drug Safety Communication: FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings

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This is an update to the **Drug Safety Communication** issued on March 9, 2015.

Safety Announcement

[12-16-2016] Based on a U.S. Food and Drug Administration (FDA) review of a large clinical trial that we required the drug companies to conduct,[1] we have determined the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion)* is lower than previously suspected. The risk of these mental health side effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past. However, most people who had these side effects did not have serious consequences such as hospitalization. The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines.

As a result of our review of the large clinical trial, we are removing the *Boxed Warning*, FDA's most prominent warning, for serious mental health side effects from the Chantix drug label. The language describing the serious mental health side effects seen in patients quitting smoking will also be removed from the *Boxed Warning* in the Zyban label.† We are also updating the existing warning section in both labels that describes the side effects on mood, behavior, or thinking to include the results from the clinical trial. This

From

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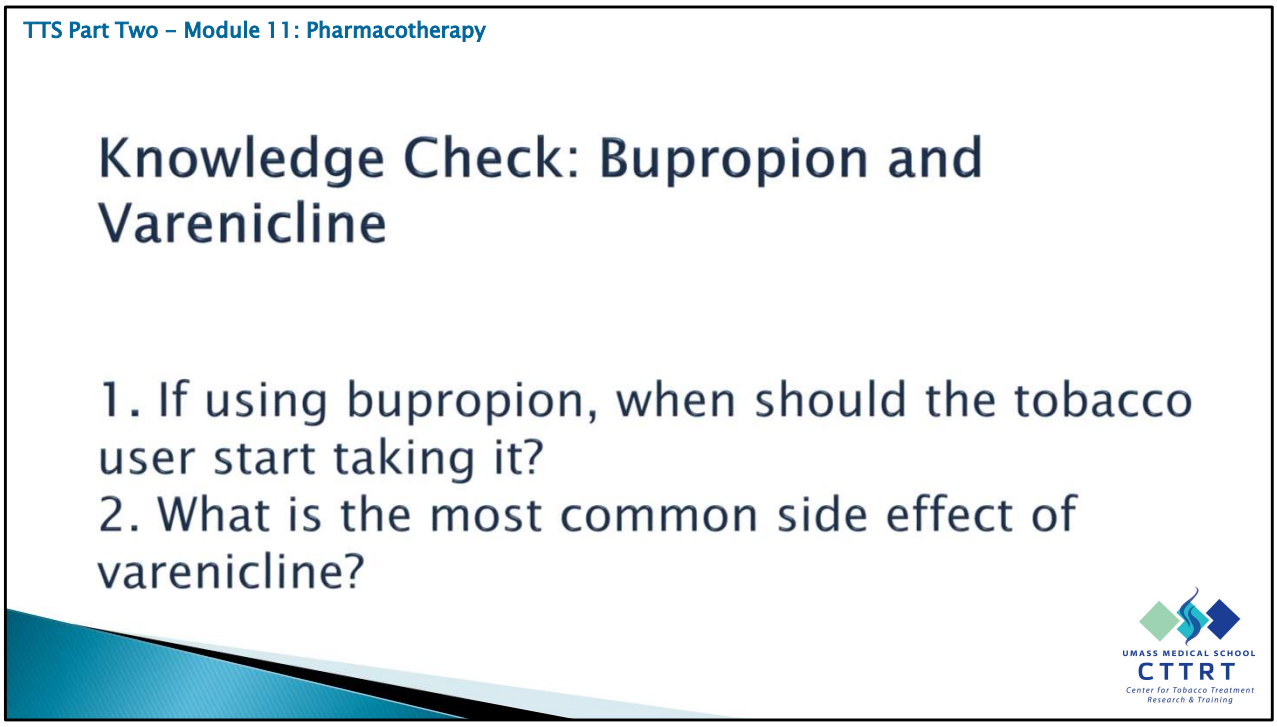


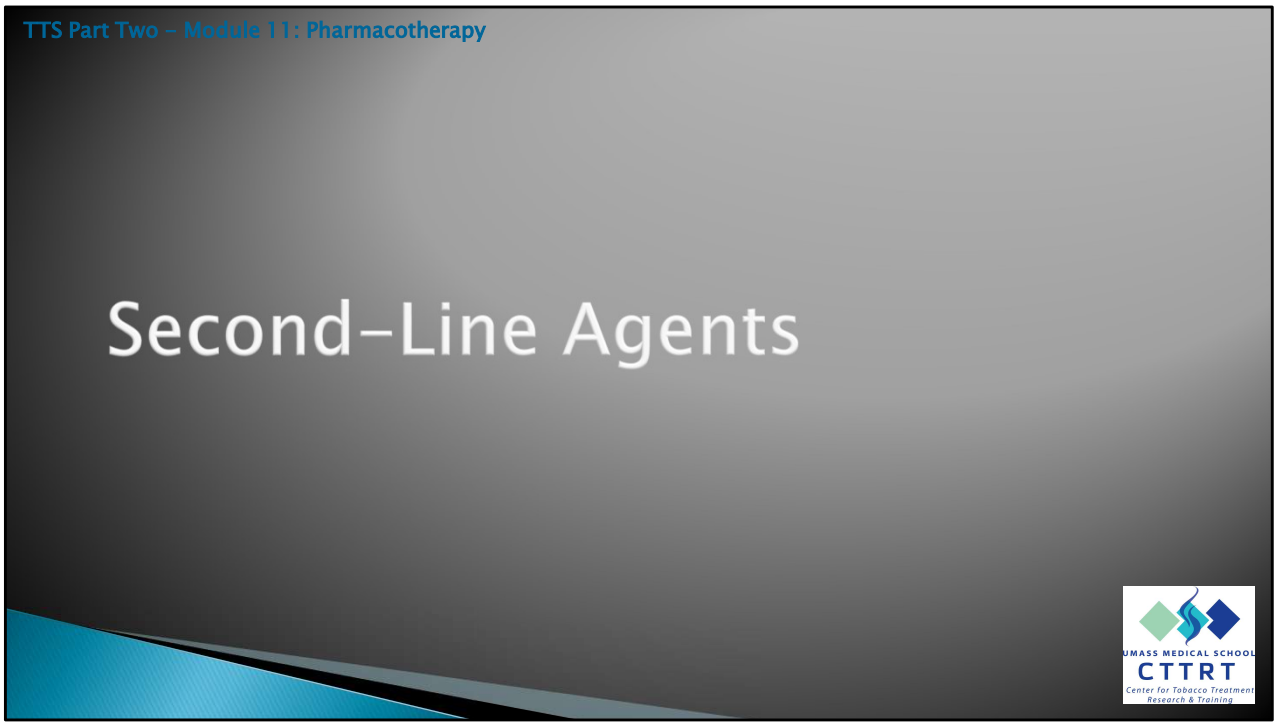
Use poll or other method to engage participants to think about previous slides.
Sample questions:

1. If using bupropion, when should the tobacco user start taking it?

(Start taking bupropion 1- 2 weeks before the quit date)

2. What is the most common side effect of varenicline?

(nausea)



- These are mentioned in the guidelines as second line agents. They are not FDA approved for smoking cessation so use I off label.

Second-Line Agents

Clonidine (Catapres)

- May be useful in patients recovering from opioid addiction
- Monitoring: blood pressure
  - Can cause low blood pressure, especially upon standing (orthostatic hypotension)
- Do not abruptly stop this medication due to rebound effects
- Dosing:
  - Oral: Initial: 0.1 mg twice daily by mouth
  - Transdermal: Initial: 0.1 mg/24 hour patch applied once every 7 days

Nortriptyline (Pamelor, Aventyl)

- Tricyclic antidepressant
- Side effects: blurred vision, sedation dry mouth, urinary retention, lightheadedness, tremor
- Dosing:
  - 25 mg once daily starting prior to quit date
  - May increase to 75–100 mg/day

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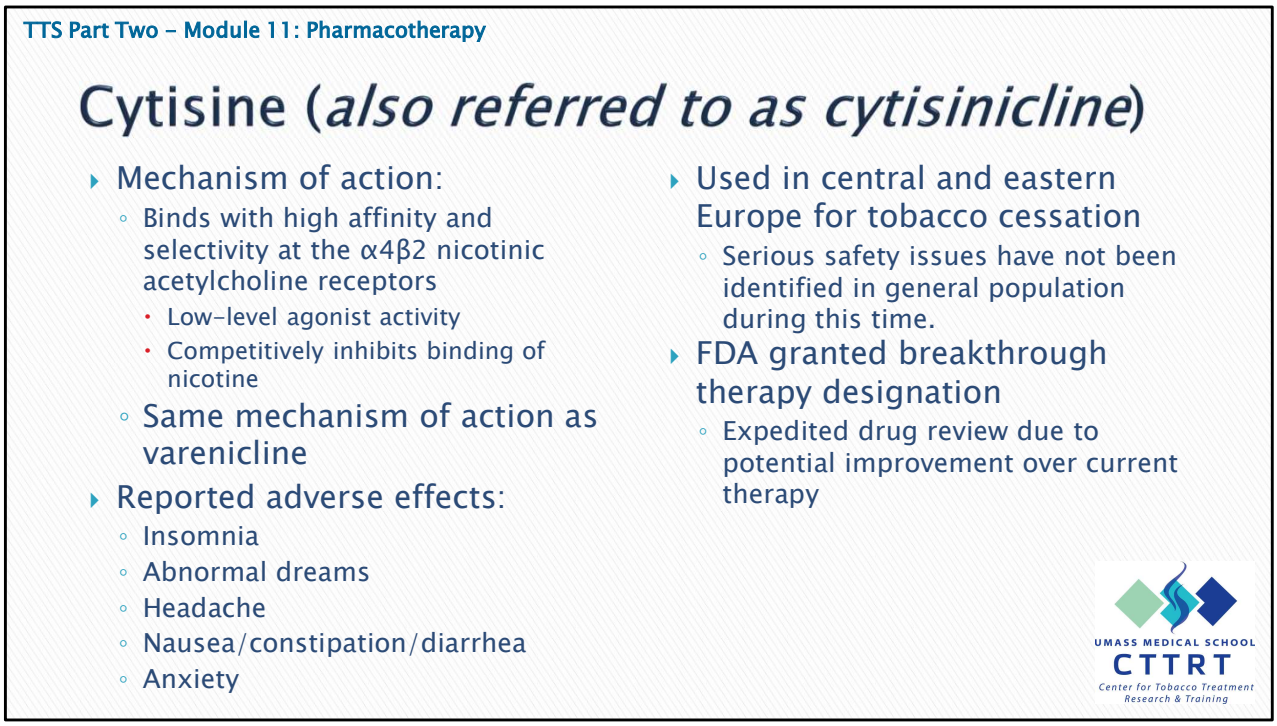
These second line agents should only be used when primary has failed or is not tolerated
Nortriptyline is a tricyclic antidepressant. It is hypothesized to decrease the activation of the pleasure center of the brain during smoking. It's side effects are mostly due to it's anticholinergic properties.
Duration of therapy is 6-12 months

Non FDA-Approved: Cytisine

- This is not FDA approved, but has studies in the pipeline and may be in the future.

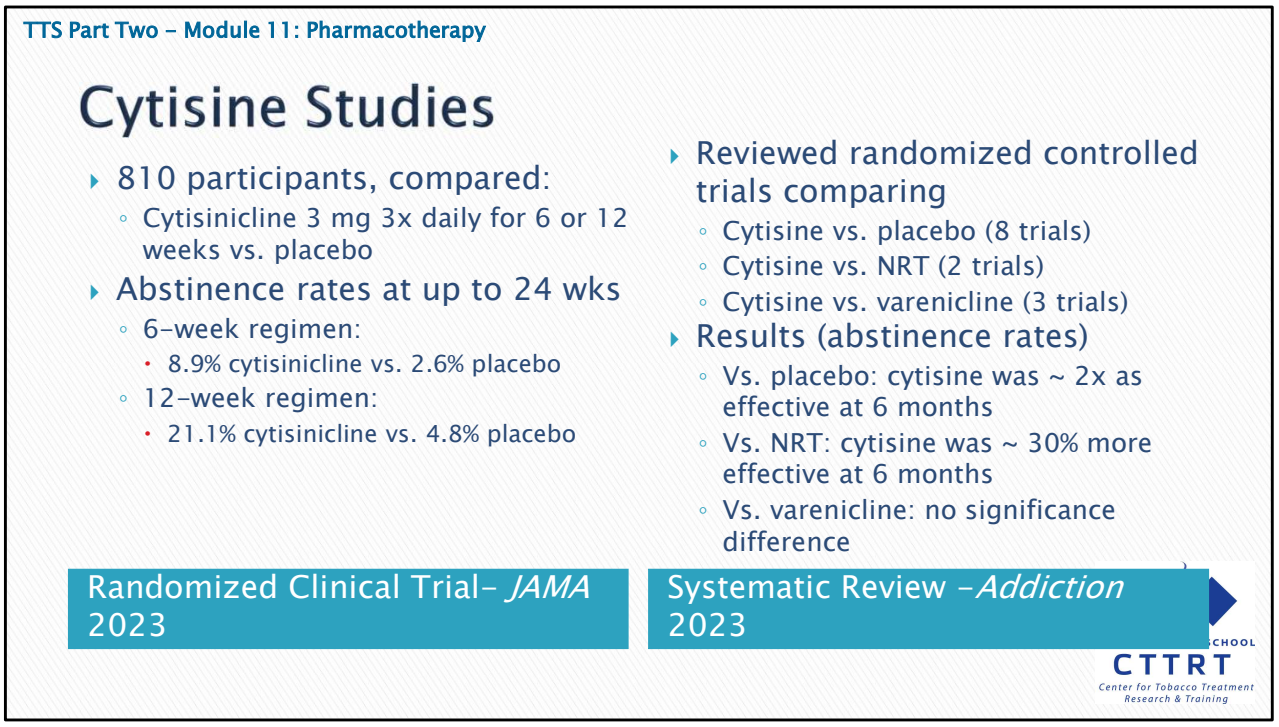


Rigotti et al JAMA 2023
No serious ADRs in previous students in Poland, New Zealand or Australian. Commercially available in Poland.

It is a plant based alkaloid. Not approved outside these countries.

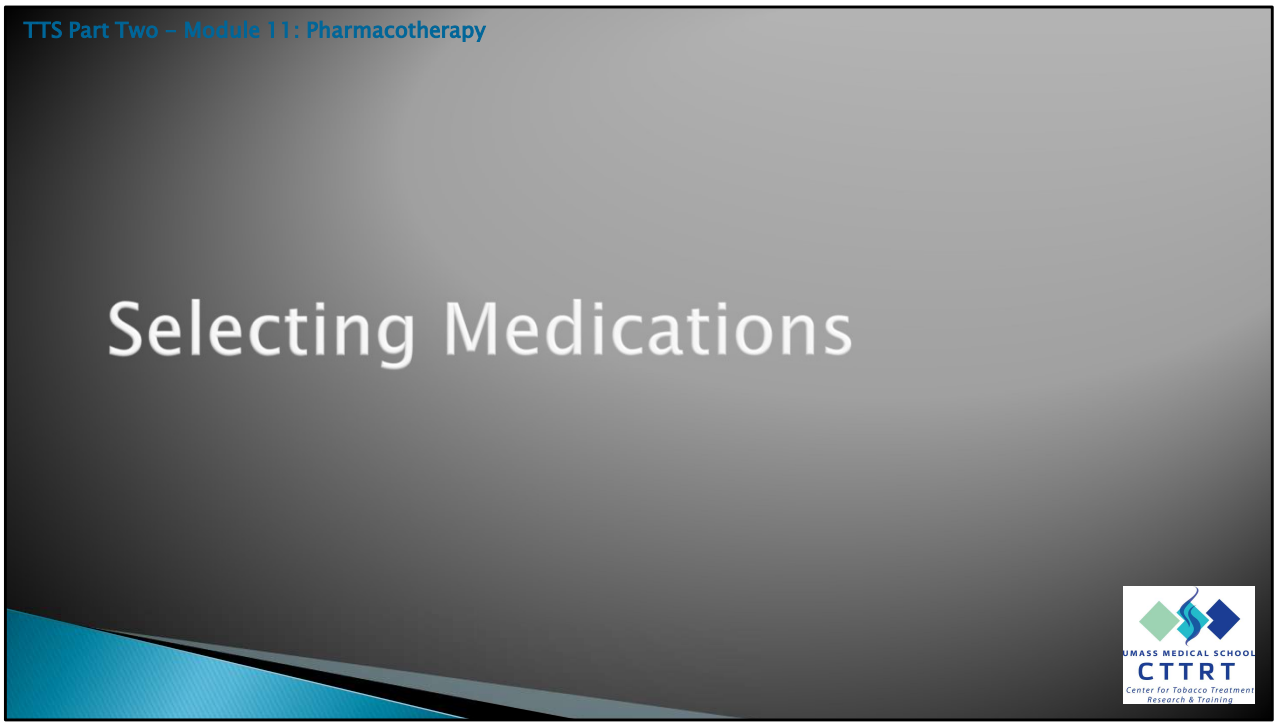
FDA designation approved in July 2024. This designation means that the drug is being expedited in its development and review process because the drug may represent a substantial improvement over current therapy. The breakthrough therapy designation of cytisinicline represents an exciting development in e-cigarette cessation treatment, as, if ultimately approved by FDA, it will be a first-in-class drug for this indication. Additionally, cytisinicline, if approved, will be the first

new drug approved for tobacco cessation since 2006, when varenicline was approved.[15].

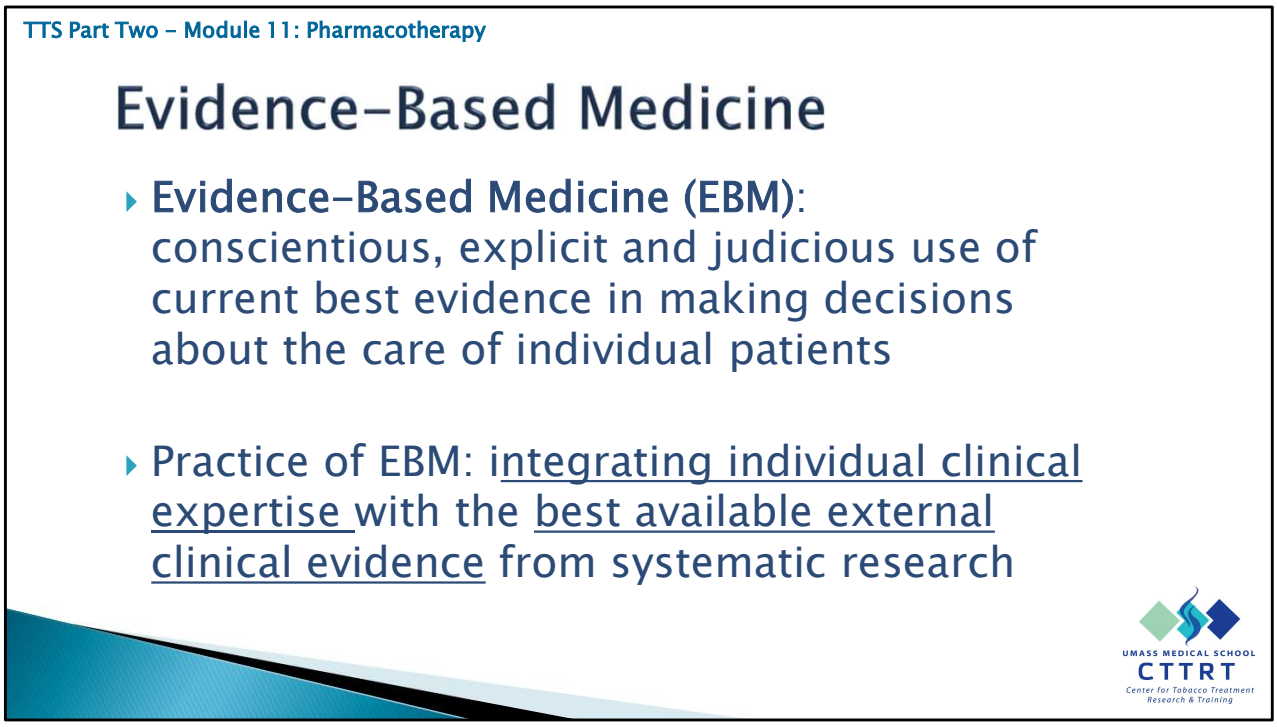


Rigotti et al JAMA 2023- 810 adults in 17 US sites. All participants received behavioral supports. Statistically significant results reported unless otherwise noted. Sixteen people stopped due to adverse events, though none serious.

Santi et al Addiction 2023- outcomes were cessation rates at 6 and 12 months. Subgroup analyses were completed for low/middle income countries. Most frequent side effect with GI upset in treatment v. comparator groups for placebo and NRT. When compared to varenicline, none serious side effects were more common in the varenicline group and were vivid dreams, headaches and stomach upset. There was no serious difference in serious adverse effects across all studies and treatment groups. Found that behavioral interventions improved outcomes.



- Let's turn now to a discussion of Bupropion and Varenicline

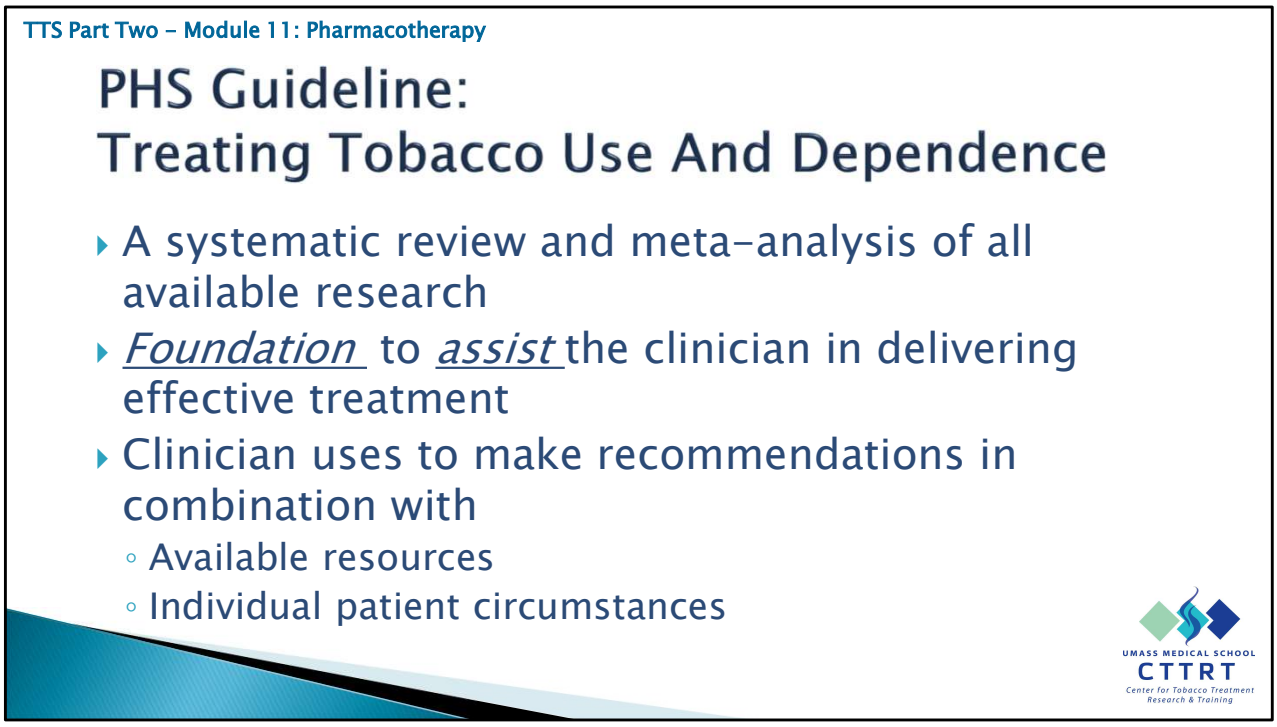


KEY POINTS:

- Evidence based medicine means to:
  1. Understand the up to date evidence/research on a subject.
  2. Also understand what the research does not or has not yet determined.

- Practice involves the following:
  1. Your patient: preferences, health history, past attempts, finances.
  2. Your experience.
  3. The evidence.

  THERE IS NO HARD AND FAST ALGORITHM!

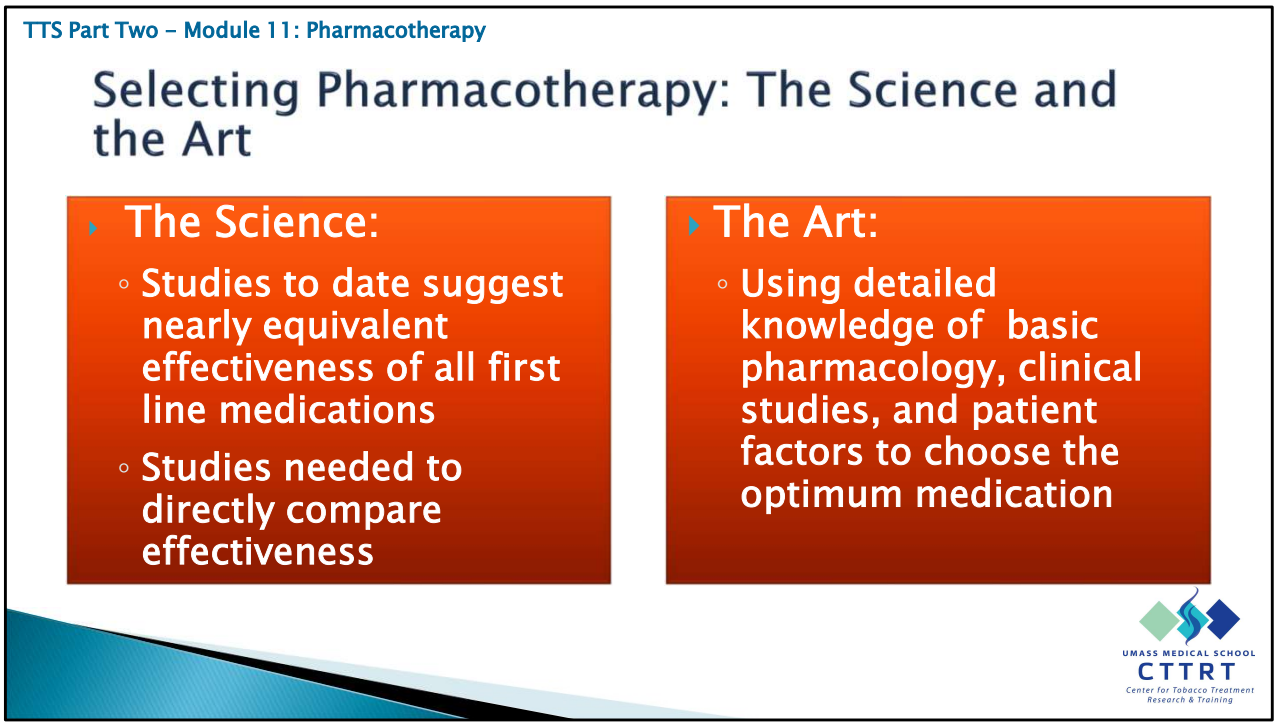


KEY POINTS:

- Again as in the discussion re evidence-based medicine, there is a foundation on which to begin when developing a particular treatment strategy for clients.
- Latest guidelines where published in 2008.
- Keep in mind, research continues and there are many good studies to consider that have been published since this.

KEY POINTS:

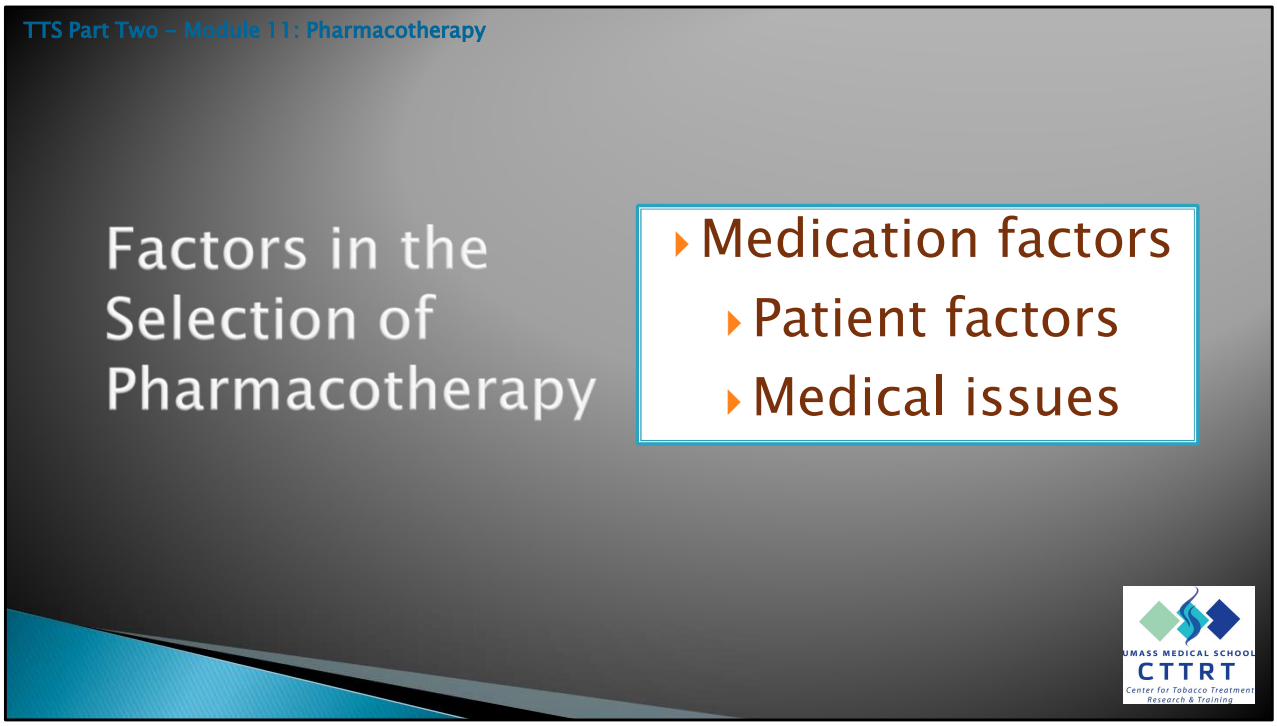
- RCTs or randomized controlled trials are considered the gold standard of a research study.
- An RCT includes strict and defined criteria re: patient population.
- For example, many studies exclude those with mental health diagnosis.
- Another example was deciding on a minimum # of cigs/day that the participant needed to smoke to be included in the study. This may be more or less than your patient. Intensive counseling is often provided.
- Finally, patients are often self-selected and may be compensated, meaning they could have more motivation.
- Therefore, conclusions of a particular study can only be drawn on the population included.
- Role of TTS (if not a prescriber)
    - Educate client about all medications
    - Make recommendations regarding use of OTC meds
    - Coordinate with prescribing clinician for Rx meds



KEY POINTS;

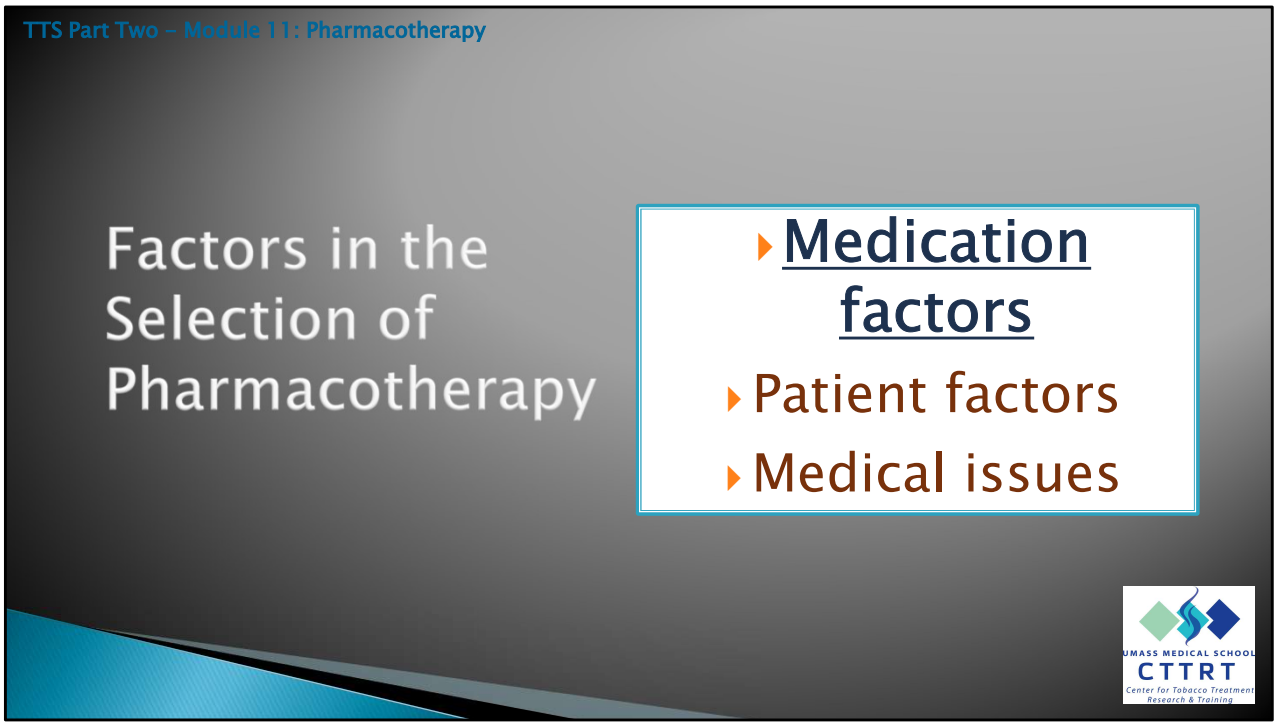
- Remember, different studies often have different study populations.
- Therefore, some of the apparent differences in effectiveness can be due to the different populations.
- Unless a study directly compares one agent against another can you really define the differences in effectiveness of various agents.
- Examine recent studies comparing agents.

REFERENCES: Mills, 2012; Aubin, 2008



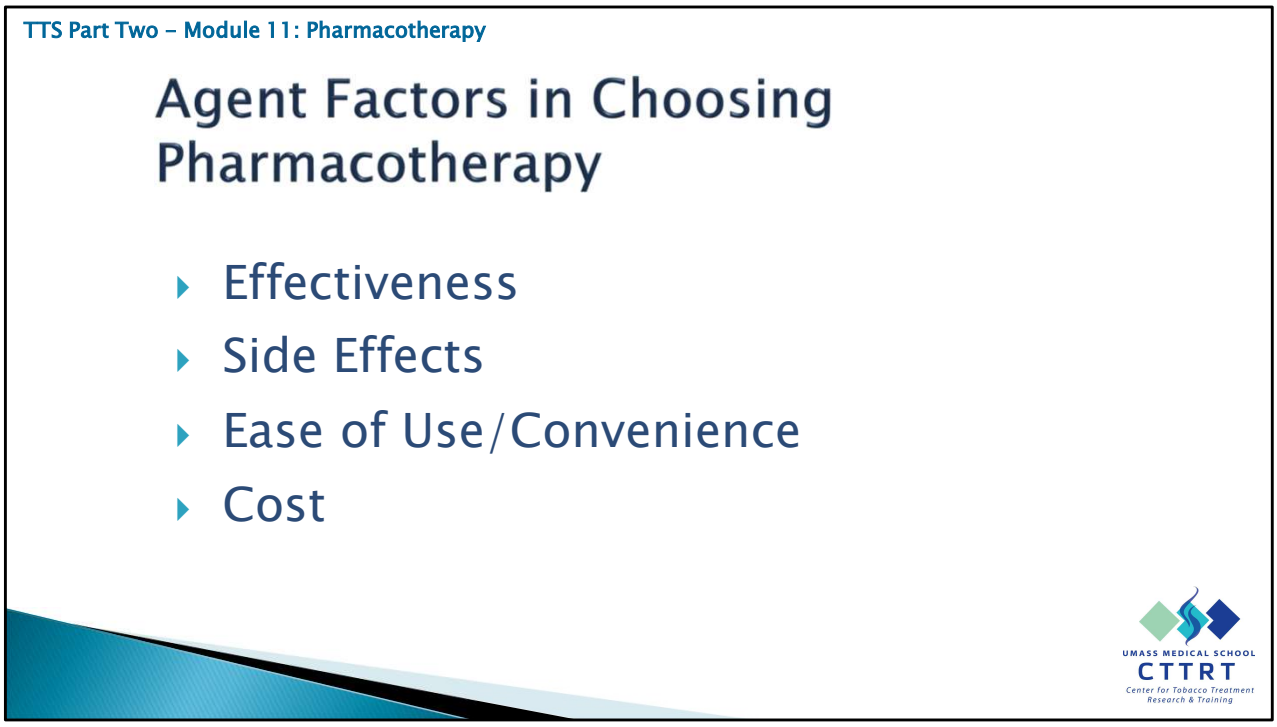
KEY POINTS:

- Considering each of these factors will help you make a recommendation of pharmacotherapy.
- We will review each of these factor and how they contribute to decision making with respect to pharmacotherapy.



AGENT FACTORS

Factors related directly to the medication itself



KEY POINTS:

Each of these factors will be reviewed separately

Effectiveness of First Line Medications: NRT

Results from meta-analyses

Medication(s)	OR	95% CI
Patch vs. placebo	1.91	1.71–2.14
Gum vs. placebo	1.68	1.51–1.88
Combo NRT vs. placebo	**2.73**	**2.07–3.65**
Bupropion vs. placebo	1.85	1.6–2.1
Varenicline vs. placebo	**2.89**	**2.4–3.48**
Bupropion vs. NRT patch	0.97	0.83–1.13
Varenicline vs. NRT patch	1.51	1.22–1.87
Varenicline vs. combo NRT	1.06	0.75–1.48

Cahill K, et al. 2013

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KEY POINTS :

This table summarizes the results of the meta-analyses published Cochrane Review by Cahill in 2013

- A meta-analysis combines the results of similar studies, using very specific criteria.
- OR refers to Odd Ratio – a statistical term that describes the effect size. So OR of 1.84 for NRT indicates that it is almost twice as effective as placebo.
- CI refers to the Confidence Interval – the range of effect size that can be expected. The smaller the range the stronger the result. We can see that the analyses with the smallest number of studies have the widest CI – which indicates a need for additional studies.
- Generally the larger the number of studies the more confidence we have in the results. Given that there are different number of studies for each one, it is hard to compare head to head, but this gives us a good idea.

REFERENCE : Cahill et al., 2013

Comparison of Nicotine Gum, Patch, Spray, and Inhaler

NRT	12 Week Abstinence	Compliance
Gum	20%	Low
Patch	21%	High
Spray	24%	Very Low
Inhaler	24%	Very Low

Hajeck et al. 1999; Stead et al. 2012

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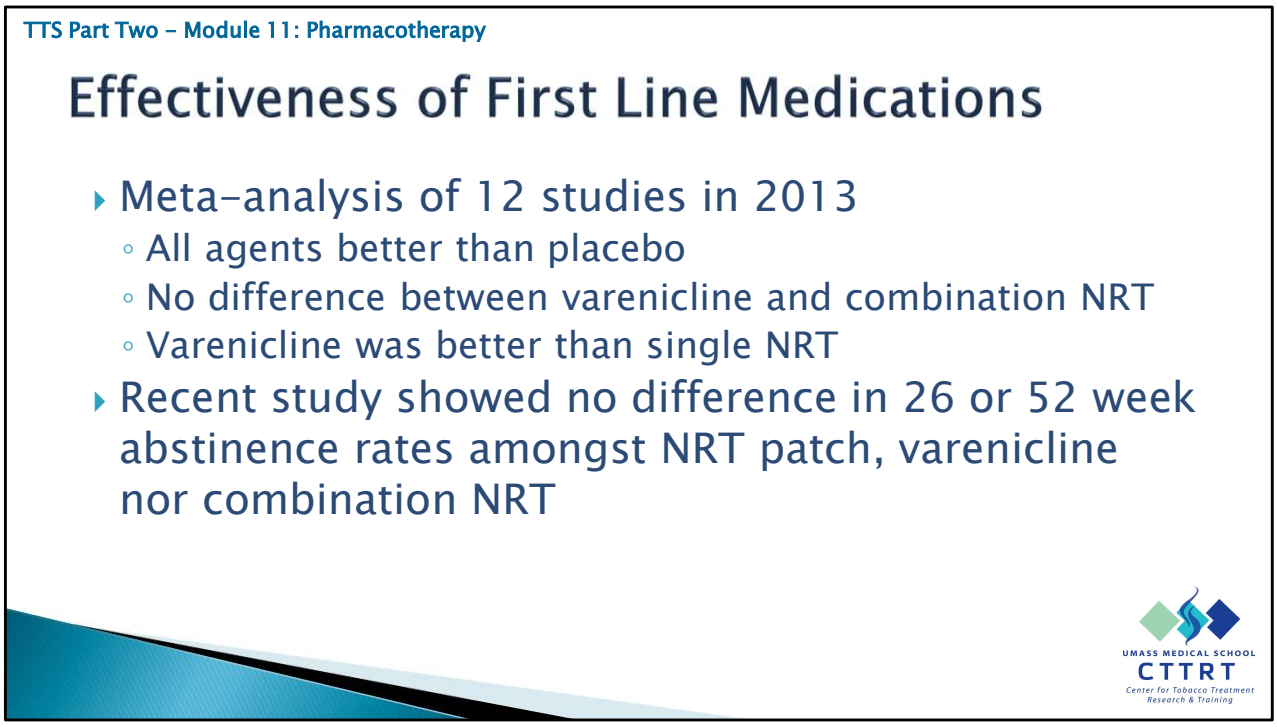
- This slide presents some results from a study that compared the effectiveness of the patch, gum, spray and inhaler at 1, 4 and 12 weeks post quit day.
- All subjects received brief advice about quitting prior to purchasing their NRT.
- Compliance with NRT was high for the patch, low for the gum and very low for the spray and inhaler.
- The spray was underused because of more adverse effects than the other NRT.
- The inhaler was rated as more embarrassing than the other products but provided as much nicotine as the gum.
- Overall the investigators reported that “the products did not differ in their effects on withdrawal discomfort, urges to smoke or rates of abstinence”.
- **A more recent review by Stead and colleagues (2012) looked at studies directly comparing types of NRT and found no statistical differences in effectiveness between different forms of NRT.**
- **Newer studies indicate that the difference In efficacy may not be as much as previously thought.**
- The take away is that it is not necessarily important what is the best in studies,

but more so what is the best for your patient. In practice, I usually say most are about equal, so let's focus on what fits your situation.

- Interestingly, NRT gum performed slightly better than other NRTs

REFERENCES: Baker JAMA 2016; Cahill Cochrane Review 2014



KEY POINTS:

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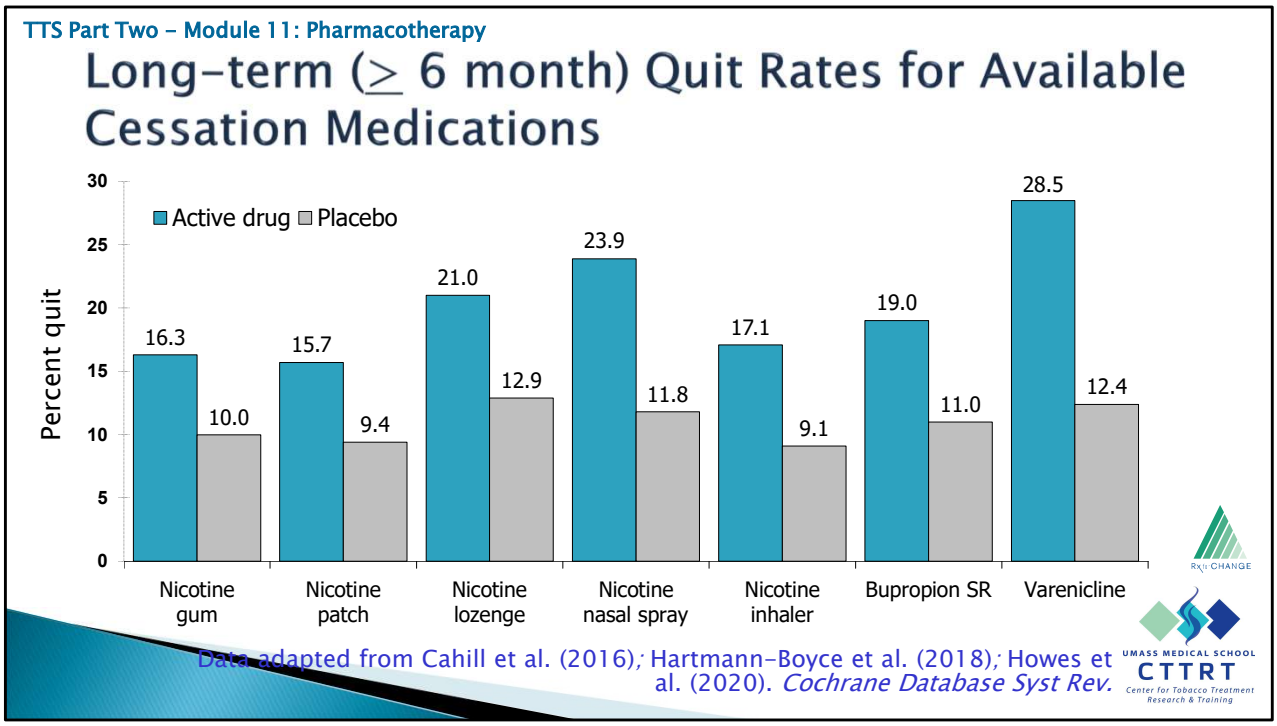
- The take away is that it is not necessarily important what is the best in studies, but more so what is the best for your patient. In practice, I usually say most are about equal, so let's focus on what fits your situation.
- Interestingly, NRT gum performed slightly better than other NRTs

REFERENCES: Baker JAMA 2016; Cahill Cochrane Review 2013



This study shows that actual results from the study, not the OR. It is important to take these quit rates with a grain of salt as the populations included may be self-selected and have increased likelihood on quitting since they are in a study. It is important to look at this as well as the OR, and pay attention to the difference between the active ingredient and the placebo.

REFERENCE: Silagy, 2004; Hughes, 2005; Gonzales, 2006; Jorenby, 2006

Effectiveness of Mono-therapy Compared to Nicotine Patch

Medication	No. Studies	OR	95% CI
Nic. Patch (6-14 wks)	32	1.0	Reference Group
Nic. Gum (6-14 wks)	15	0.8	0.6-1.0
Nic. Inhaler	6	1.1	0.8-1.5
Nic. Spray	4	1.2	0.9-1.6
Bupropion	26	1.0	0.9-1.2
Varenicline (2mg/day)	5	1.6	1.3-2.0

PHS Clinical Practice Guideline 2008 Update

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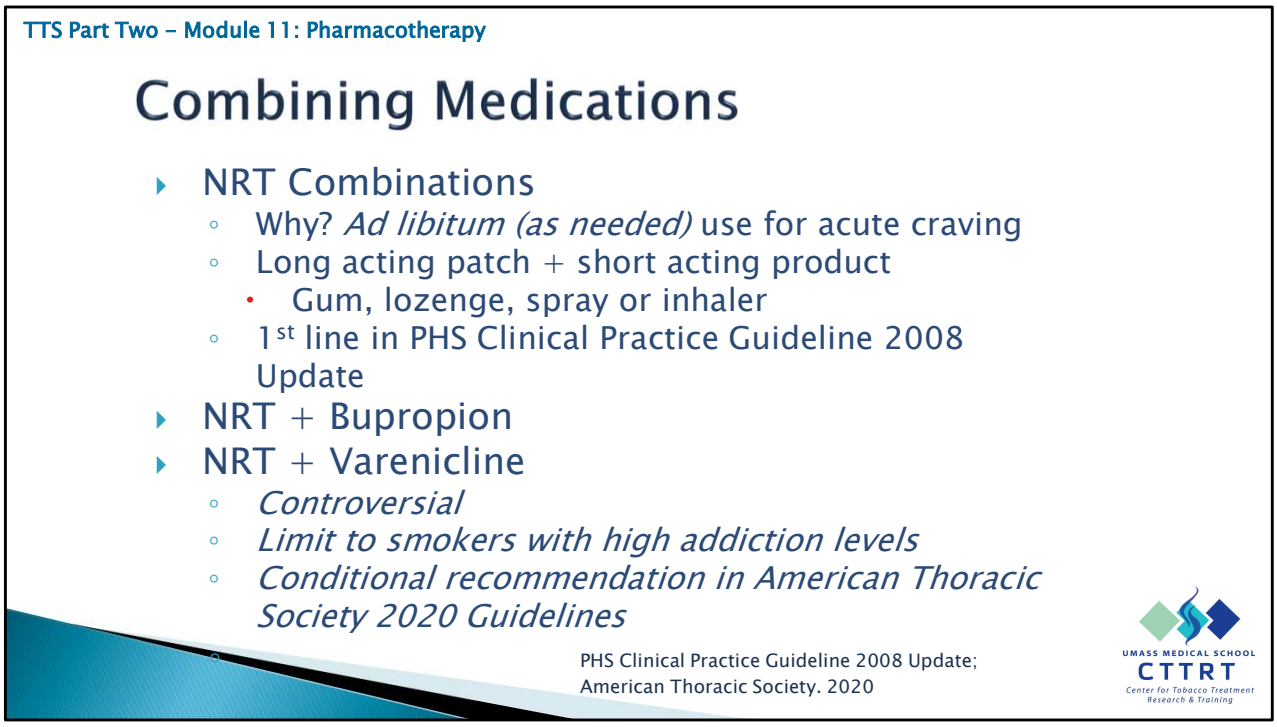
KEY POINTS:

- These analyses use the nicotine patch as the comparison or reference group.
- Except for varenicline we see very little difference when comparing to the nicotine patch.
- Note however that there are far fewer studies of Varenicline than the patch – this likely contributes to the wider confidence interval.
- This is also from a meta-analysis in in 2008, and there have been studies done since then, so newer meta-analyses may have slightly different results.

REFERENCE: USPHS, 2008



KEY POINTS:

- Published studies suggest that all 7 first line meds are effective, with varenicline being most effective and combination therapy being more effective than solo NRT
- Combination therapy is rapidly becoming a standard of treatment and is recommended in the PHS Guidelines
- Provides long-acting medication with ability to use short acting as needed
- Consider for all smokers
- The patch: administered transdermally. Slow, steady distribution of nicotine, i.e., The Foundation, to mitigate craving and withdrawal symptoms.
- Short-acting NRT can be used for breakthrough cravings that occur with various triggers, i.e., upon waking, break time at work, leaving work, stress.
- The combination gives a more complete coverage for the smoker.
- Allows treatment “in the moment”.
- Very low potential for nicotine toxicity, very rare. Similar, to fingertip control, smokers can control their nicotine levels through the as needed use of the gum/lozenge.
- Bupropion combines nicely with NRT, see references below to allow a 2 pronged approach as well. Bupropion has also been shown to increase quit rates combined with NRT (reference “Triple Therapy”

Bupropion, Patch, Lozenges)

- Single study shows some benefit of combining bupropion and varenicline, particularly in smokers who are considered more highly addicted. This was associated with increased anxiety and depression though. Will need more research before it is generally recommended.
- Varenicline use with NRT is controversial due to the mechanism of each. NRT works by providing nicotine for the NAC receptors to decrease craving and withdrawal symptoms. Similarly, varenicline acts as a partial agonist/antagonist on the NAC receptors. So if used together, they would be trying to occupy the same receptors. It may work with smokers who have high addiction levels (some studies showed benefit in smokers who use > 3ppd) due to the up-regulation of nicotine receptors. Note: The studies using combination therapy were with a 15 mg patch.

REFERENCES: Killen, 2004; Mills, 2014; Schneider, 2008; Shiffman, 2005; USPHS, 2008, Steinberg, 2009; Ebbert, 2014; Kozlowski, 2007; Schnieder, 2001; Shiffman, 2005; Sweeney, 2005; Koegelenberg, 2014; American Thoracic Society, 2020

Effectiveness of Combination Therapy Compared to Nicotine Patch

Medication	No. of arms	Est. Odds Ratio	95% Confidence Level
Nicotine Patch (reference group)	32	1.0	
COMBINATION THERAPIES			
Patch (long-term >14 wks) + NRT (gum or spray)	3	1.9	1.3–2.7
Patch + Bupropion	3	1.3	1.0–1.8

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KEY POINTS:

- This table from USPHS Guidelines compares 2 combinations against the patch alone.
- These are the 2 types of combination therapy approved by FDA at this time.
- Combining different forms of NRT provides a stable baseline nicotine level (i.e. the patch) with the opportunity for intermittent increases in the nicotine level from immediate-release NRT (gum, lozenges, inhaler, spray) in response to withdrawal symptoms.
- Combining 2 different drugs (i.e. bupropion plus patch) provides the opportunity to gain therapeutic synergism by using medications with distinct mechanisms of action.
- Since these Guidelines have been published research continues on various combinations. Steinberg and colleagues (below reference) added short acting NRT to patch and bupropion in medically ill patients with good results.
- Research is ongoing on combining varenicline and bupropion.

REFERENCES: Steinberg, 2009; Ebbert, 2014; Ebbert, 2009; Hajek, 2013; USPHS, 2008

High Dose Patch (28-42mg)

- High dose NRT for heavy smokers >1ppd has been clearly shown to induce initial abstinence
- More complete nicotine replacement
- Consider lengthening treatment duration for heavily dependent smokers
- Cochrane reviewers suggest possible small benefit from high dose; PHS update reports no added benefit beyond standard dose & duration

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KEY POINTS:

- For long term efficacy, we know that the 21mg patch delivers approx. 50-60% of what a 1ppd smoker takes in. Some facilities recommend 2 patches (42 mg) for smokers using >1 ppd, but this is not recommended by the guidelines. It also states on the patch box to not use more than 1, so this would be a opportunity for education.
- For those smoking >1ppd, it might make sense to "increase the foundation level" of their nicotine replacement and then add your short acting to that.
- The goal is not to full replace nicotine levels, but to mitigate withdrawal symptoms.
- Those with hx of mental illness have been shown to be heavily dependent and often need more aggressive treatment
- Study in 2014 summarizing 11 articles using high dose nicotine patch shows that there is a dose response relationship with adverse effects, but no safety concerns. The same study showed no benefit

REFERENCES: Mills et all, 2012; Stead, Perera et al 2012; USPHS 2008; Brokowski 2014

PHS Guideline: Treating Tobacco Use And Dependence

- Recommends 7 first line medications
  - Use for all patients without contraindications
  - Use of combination NRT over monotherapy NRT
- Use medications with counseling rather than either alone

PHS Clinical Practice Guideline 2008 Update

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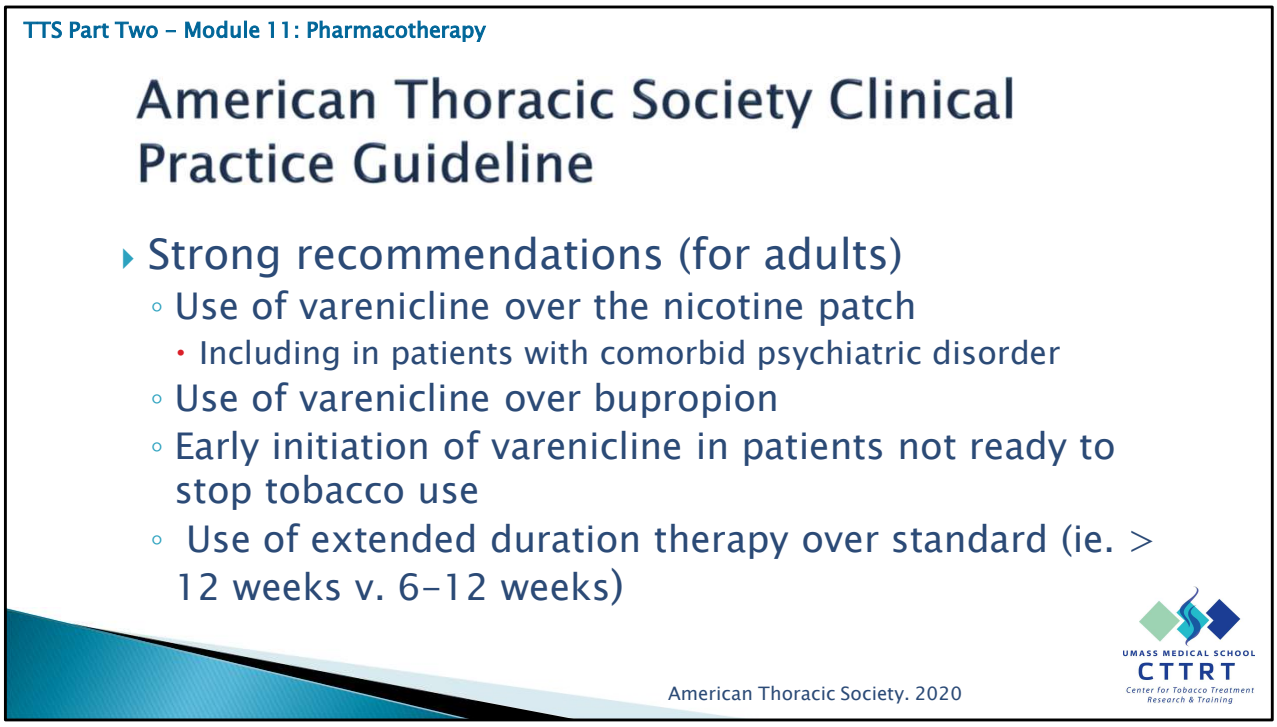
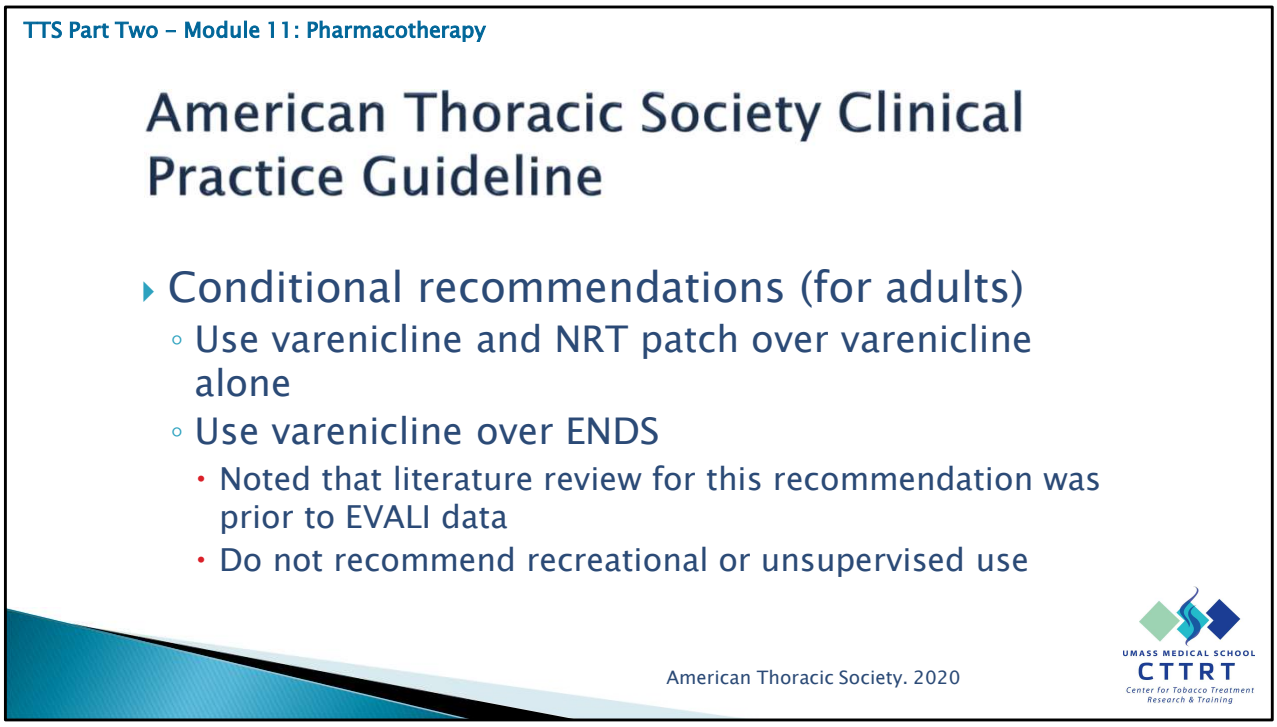
- Reiterate- from 2008. Currently being updated. This is backbone of many recommendations.
- This slide has the main highlights of an extensive guideline. Many of the comparisons of medication effectiveness used in these guidelines have already been discussed.
- These guidelines recommend the 7 first line medications we have already discussed (5 NRT and 2 non NRT)
- Interestingly, they removed the 2000 recommendation for long term cessation medication for patients at high risk of relapse from the 2008 update.
- Does not address varenicline and NRT combination.
- They stated that there was not enough data at the time to recommend using NRT patch precessation in patients not ready to quit.



- Recent Updates that includes the PHS recommendations with new literature. It is important to take this information and use the patient specific information and recent literature to make a recommendation. TAKE-AWAY- all medications still work, but if the patient doesn't have contraindications or a preference, then this can be used to break a tie for a recommendation.
- Released in May 2020
- Presented as a series of clinical questions and recommendations for answers that were graded based on strength of evidence from a systematic review.
- Strong recommendations:
- using varenicline rather than a nicotine patch (rationale: adherence, also recommend by the American College of Cardiology. Note limited long term and WOL data available)
- using varenicline rather than bupropion (rationale: both are effective, but varenicline has higher evidence of efficacy and less adverse effects)
- Using varenicline rather than a nicotine patch in adults with a comorbid psychiatric condition (e.g. bipolar, SUD, anxiety, depression, schizophrenia)
- initiating varenicline in adults even if they are unready to quit
- using controller therapy for an extended treatment duration greater than 12 weeks.



- Conditional recommendations have low evidence to support
- Authors will review data in regards to ENDS and state that if adverse effects continue to be reported, this may change.
- Conditional recommendations :
    - combining a nicotine patch with varenicline rather than using varenicline alone (rationale: 3 studies available, showed increased abstinence at 7 days, given a conditional recommendation because of the possible increase in ADRs.)
    - using varenicline rather than electronic cigarettes.

KEY POINTS:

PRETREATMENT-

- Various studies have demonstrated that pre treatment (using patch prior to quit date and then adding more on quit date) doubled the odds of quitting successfully over and above the more standard regimen for nicotine patches (beginning patch on quit date)

WHY? POSSIBLE MECHANISMS:

- Often there is a spontaneous reduction in # of cigs smoked and/or the intake of nicotine from each cig.(even though in most studies not instructed to do so)
- Smoking on top of ongoing, steady nicotine infusion from the patch may help break some of the learned associations that help maintain smoking
- This may give the smoker the confidence or self-efficacy to believe that becoming smoke free is possible
- Having substantial blood levels of nicotine may blunt the effect (or reinforcement) of additional smoking- less satisfaction

(REMEMBER BOTH BUPROPION AND VARENICLINE USE PRE-CESSATION TREATMENT- RAISING THE POSSIBILITY THAT DIMINISHING SMOKING REINFORCEMENT THROUGH PRE-CESSATION TREATMENT MAY BE A COMMON MECHANISM DESPITE THE DIFFERENCES OF PHARMACOLOGY OF THESE DRUGS)

REDUCE TO QUIT-

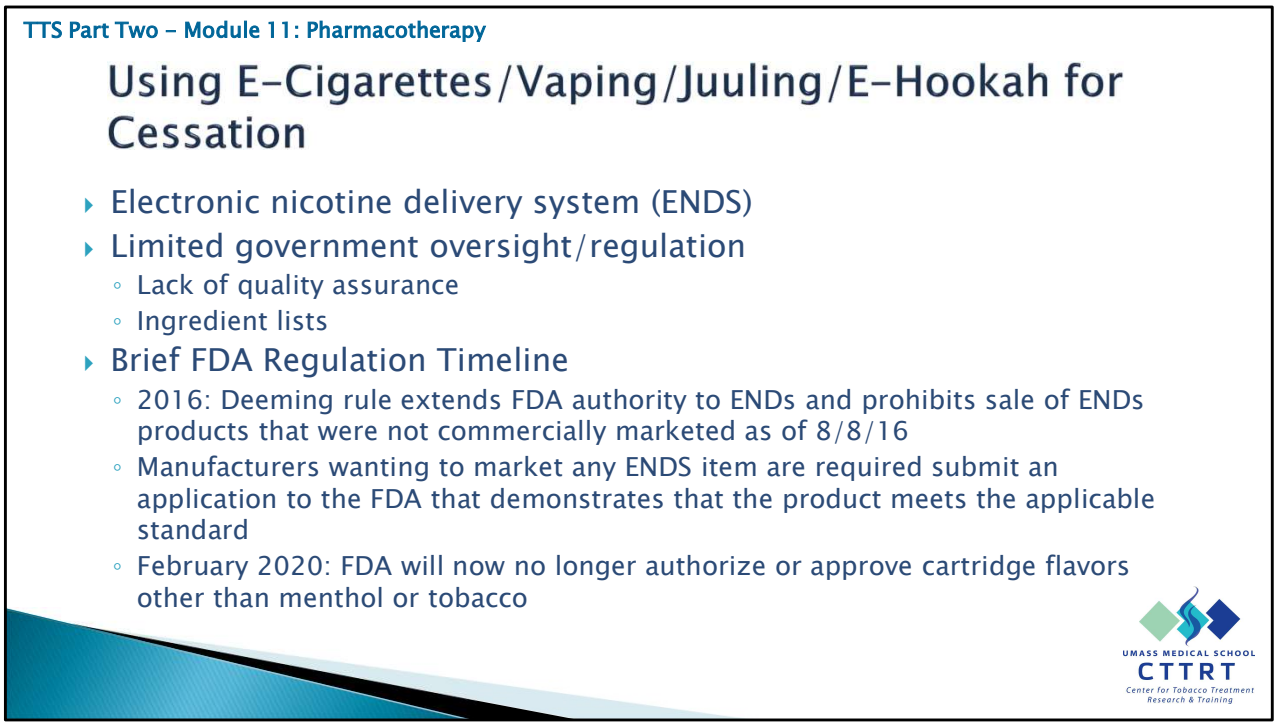
- We know from 7 studies on those not willing to make a quit attempt, that using NRT (patch, gum inhaler) for 6 months or more increased quit rates. New study just published using varenicline on those not ready to quit which showed increased abstinence.
- We find we are using this concept more and more. This is less daunting to those with little confidence, less pressure, more doable.

SLIPS DURING NRT-

- Smokers should be encouraged to continue wearing patch even if they have a slip- recent study (below) indicates greater likelihood they will go on to successfully quit. *NRT LABELS CHANGED 12/2013 TO REFLECT THIS

REFERENCES: Ferguson, 2012; Shiffman, 2008

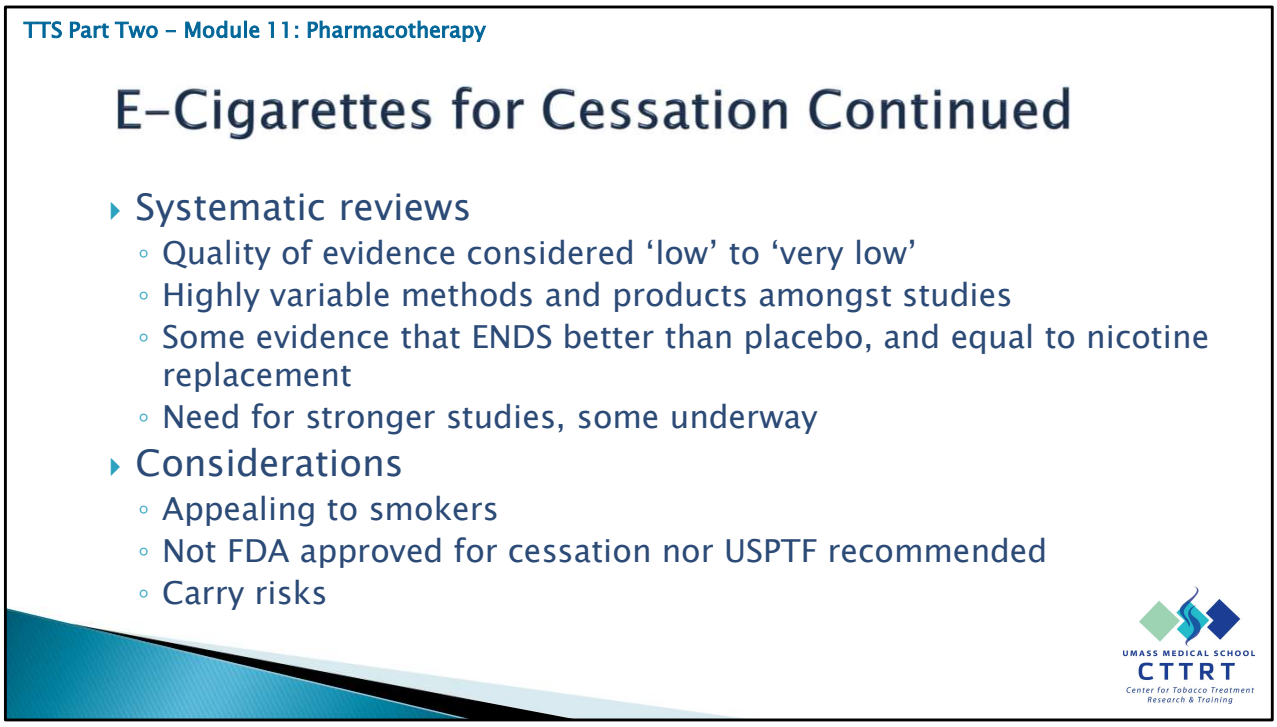
Ebbert 2/17/2015



KEY POINTS:

- E-cigarettes are officially known by the FDA as electronic nicotine delivery systems
- Unlike, NRT and tobacco products (cigarettes, cigars, dip, etc.), electronic cigarettes are not regulated by the FDA, and investigations have shown that there is a lack of standard of manufacturing practices and labelling reflecting ingredients
- February 2020: FDA will now no longer authorize or approve cartridge flavors other than menthol or tobacco. This is only for cartridge models (like JUUL) and does not impact tank models and disposables.

REFERENCES: FDA Website: https://www.fda.gov/tobaccoproducts/labeling/rulesregulationsguidance/ucm394909.htm



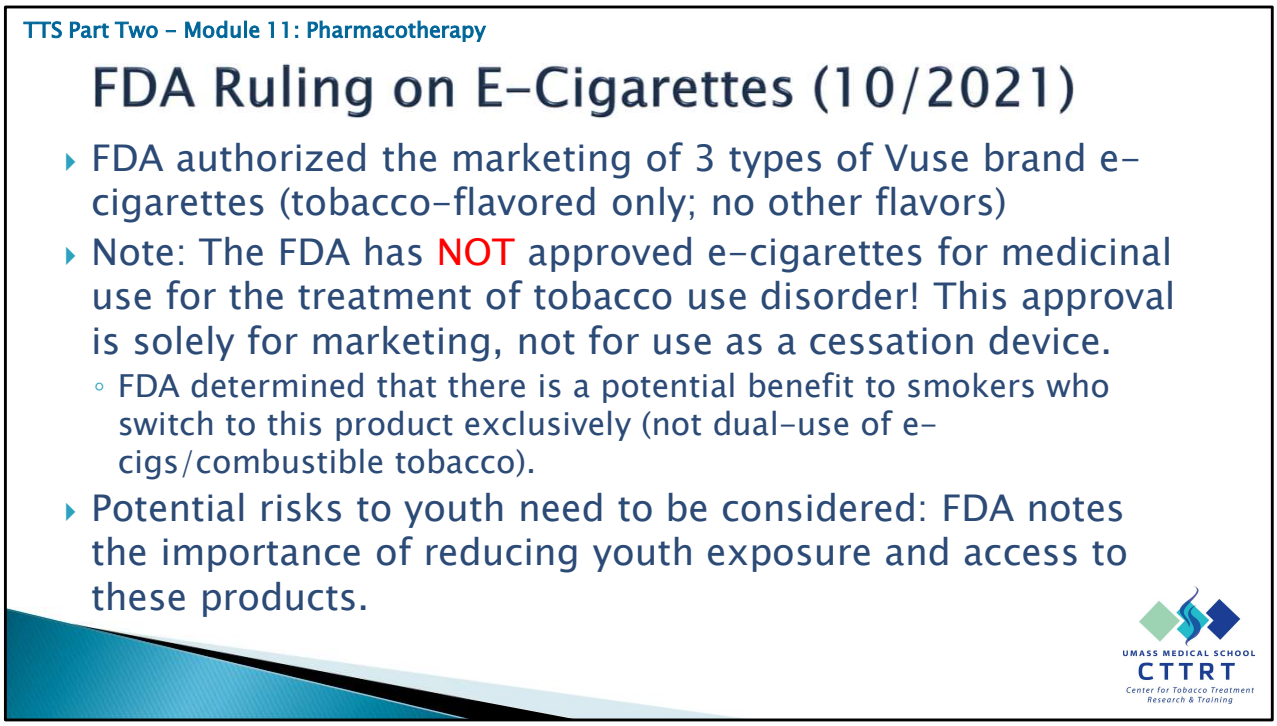
KEY POINTS:

- Use of e-cigarettes as a cessation tool is not evidence-based. Evidence regarding using e-cigarettes for cessation is very limited. There is evidence from two trials that e-cigarettes with nicotine helped smokers to quit or reduce smoking compared to placebo e-cigarettes, but the authors of the meta-analysis noted the need for further randomized controlled trails with adequate power and applicability to real-life settings.
- Additionally, the safety has not been established and there is high variability between the inert ingredients and nicotine contents of ENDS devices.
- Possible discussion: how to help the smoker already using ENDS with the goal of quitting
- It can be seen as transferring the addiction from one nicotine delivery system to another without addressing the behavioral portion.

Background

- McRobbie et all reported:
- 2 RCTs compared EC to placebo: % quit at 6 mos: 9% EC vs 4% placebo (RR 2.29, 95% CI 1.05 to 4.96)
- 1 RCT compared EC to nicotine patch: No difference in quit rates (RR 1.26, 95% CI: 0.68 to 2.34)
- Note the wide confidence intervals indicating potential low confidence in the stability of the results

- FDA regulation will not necessarily indicate safety as the ENDs would be regulated in the same way as tobacco. It would, however, provide more clarity about the ingredients and manufacturing processes. Source: McRobbie et al, 2014; Malas et al, 2016



KEY POINTS:

- These specific e-cigarettes have been approved for marketing through the Tobacco Product Application (PMTA) pathway. "Under the PMTA pathway, manufacturers must demonstrate to the agency that, among other things, marketing of the new tobacco product would be appropriate for the protection of the public health. These products were found to meet this standard because, among several key considerations, the agency determined that study participants who used only the authorized products were exposed to fewer harmful and potentially harmful constituents (HPHCs) from aerosols compared to users of combusted cigarettes. The toxicological assessment also found the authorized products' aerosols are significantly less toxic than combusted cigarettes based on available data comparisons and results of nonclinical studies. Additionally, the FDA considered the risks and benefits to the population as a whole, including users and non-users of tobacco products, and importantly, youth. This included review of available data on the likelihood of use of the product by young people. For these products, the FDA determined that the potential benefit to smokers who switch completely or significantly reduce their cigarette use, would outweigh the risk to youth, provided the applicant follows post-marketing requirements aimed at reducing youth exposure and access to the products."

- Source: FDA press release: https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-e-cigarette-products-marking-

first-authorization-its-kind-agency

Cessation Approaches for Vaping: Little Evidence to Guide Treatment

- Behavioral counseling throughout quit attempt
- Pharmacotherapy
  - Nicotine replacement therapy
    - If patient has switched from smoking to vaping: start with pre-vaping # cigarettes/day and TTFC to guide initial dosing
    - If user has only vaped nicotine: Estimate nicotine intake
      - ≥20 mg/day, start with 21 mg patch
      - <20 mg/day, start with 14 mg patch
      - Add short-acting NRT for break-through
    - Early follow-up to assess response and adjust dosing as needed
  - Varenicline or Bupropion SR, standard dosing

Therapeutic Research Center. (2019). Help patients break the e-cigarette habit. *Pharmacists Letter* (December).

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Potential Side Effects of NRT

Patch	Skin redness is common (50%), abnormal dreams
Gum	Mouth or jaw soreness, stomach upset. Dependence: 15–20% will use for > 1 year
Lozenge	Irritation of mouth, nausea, heartburn
Inhaler	Irritation of mouth and throat, cough, rhinitis
Nasal Spray	Irritation of nose and throat, cough, rhinitis, sneezing
Bupropion	Dry mouth, difficulty sleeping, shakiness, agitation, sedation, increased blood pressure
Varenicline	Nausea, insomnia, headaches, abnormal dreams, irritability, depression

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KEY POINTS:

- Side effects can impact compliance.
- Education and proper instruction is critical to minimize and/or manage any side effects.
- PATCH: Most common – localized skin irritation. Rotate sites – hips up, non hairy area. Use OTC hydrocortisone cream on area.
- Many report vivid dreams. May take off last thing before bed. Apply new one next AM.
- GUM: Proper technique – chew, park. Emphasize that nicotine is absorbed in mouth, not in stomach.
- LOZENGE: Make sure to park, do not bite, chew, swallow.
- INHALER: A "Puffer" not actually inhaled – can cause coughing fit.
- BUPROPION: If sleep disturbance, try taking 2nd dose in afternoon, early evening – not close to bedtime.
- VARENICLINE: Take with 10oz of H2O and food. Particularly in AM. [Note: Adverse effects occur at the following frequencies: Headache (12% to 19%), insomnia (9% to 19%), abnormal dreams (8% to 13%), irritability (11%), suicidal ideation (11%), depression (4% to 11%)]

{maybe expand the table to include recommendations to address the side effects}

Cost of Pharmacotherapy

Medication	Cost (package size)	Cost (per unit)	Cost (per month)
NRT Patch	$25.98 (box of 14)	$1.86/patch	$55.80
NRT Gum	$25.98 (100ct)	$0.26/piece	$124.80- 187.20
NRT Lozenge	$32.98 (108 ct)	$0.30/piece	$144- $180
NRT Inhaler	$443.39/device	$2.64/cartridge	*$475- 1267 (6-16 cartridges per day)*
NRT Nasal Spray	$465.14 (40mL)	$1.16/ 1 dose (2 sprays)	$279-1395 *(8-40 doses per day)*
Zyban (bupropion)	$267 (60 ct) ~$25-110 (60 ct)	$4.45/tab ($.41-1.83/tab)	$267 ~$25-110
Chantix	~$117-150 (30 ct)	~ $3.9- 5/tab	~$234-300/month

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KEY POINTS:
1 month = 30days

Patch is reflective of 21 mg patch/1 patch per day
Gum and lozenge is reflective of 4 mg gum/lozenge x 20 or 24 per day (max dose- 8 hours to sleep) – use less lozenges per day
Zyban- brand and top line and bupropion (generic) bottom line
Chantix is listed, but not generic because it is only available brand at this time.
Nasal spray monthly cost based on minimum and maximum daily recommended doses

- Generics will be cheaper.
- Coverage by insurance plans vary considerably. Have clients look into their coverage.
- Some insurers (such as MassHealth, MA's Medicaid program) will cover with script including those that are OTC.
- Practical suggestion is to have each individual do the math on their weekly, monthly, and yearly costs to smoking.

REFERENCES: Generic Walmart brand /drugs.com

Insurance Coverage of Pharmacotherapy

- The Affordable Care Act (ACA) and other federal rules require certain coverage of pharmacotherapy treatment:
  - Medicare: Covers prescribed medications (nicotine nasal spray, nicotine inhaler, bupropion and varenicline); Part D may cover others
  - Traditional Medicaid:
    - For pregnant women: all FDA-approved cessation medications*
    - For others: Required to cover FDA-approved cessation medications; may have cost-sharing or other barriers
  - Exchanges & Employer-sponsored:Required to cover FDA-approved cessation medications, but extent of coverage varies

*Note – PHS Guidelines recommend Behavioral counseling

Source: American Lung Association, 2016

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- While recent federal government rules and regulations require coverage of tobacco dependency treatment, not all insurance plans cover all 7 FDA approved medications. Some plans may cover some, or may create barriers by limiting the length of treatment or requiring co-payments.
- For more information, see the American Lung Association's State of Tobacco Control report at http://www.lung.org/our-initiatives/tobacco/reports-resources/sotc/

Adherence and Convenience

- Factors:
  - Frequency of dosing
  - Mode of administration
  - Side effects
  - Cost
- Among NRT products patch has highest adherence

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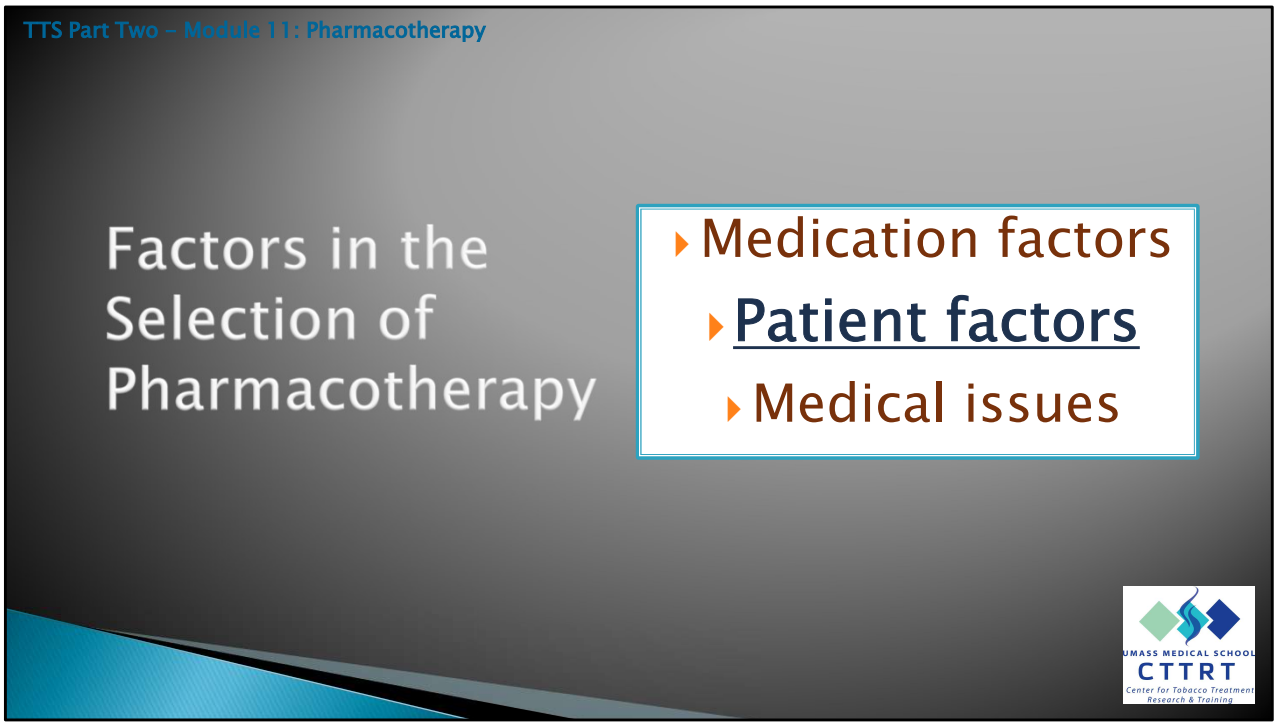
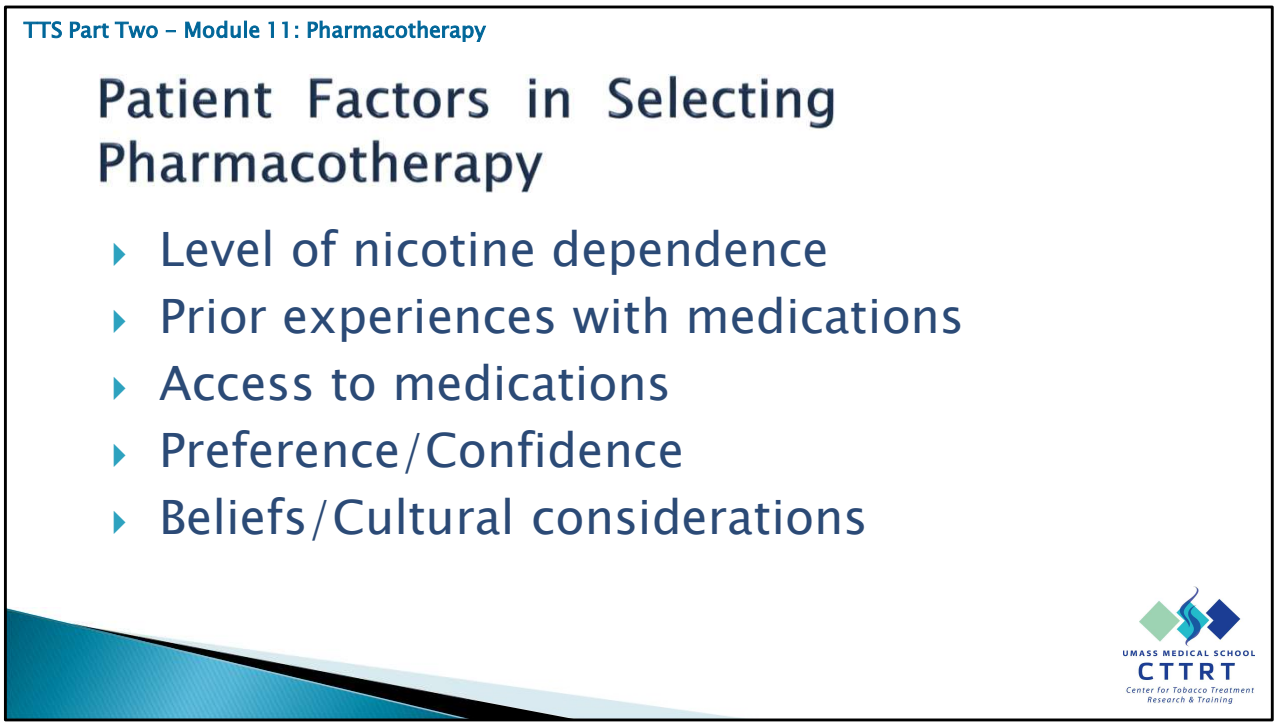
KEY POINTS:

- Compliance and convenience can often trump all other considerations when deciding on pharmacotherapy.
- The Patch often becomes a “go-to” or a starting point because it is relatively easy to use, once a day, few side effects.
- Using monotherapy with any of the short-acting NRTs requires a real vigilance and discipline by an individual to keep ahead of cravings.
- (Of course the combo of these can work well for many).
- If the smoker does not have coverage of varenicline, it is very expensive, as is the nasal spray
- The inhaler is also expensive if not covered.
- YOU NEED TO GET TO KNOW YOUR SMOKER, THEIR FINANCIAL RESOURCES, THEIR ABILITY AND DESIRE TO PROACTIVLY USE MEDS OR MORE “PASSIVELY” WITH THE PATCH FOR INSTANCE.

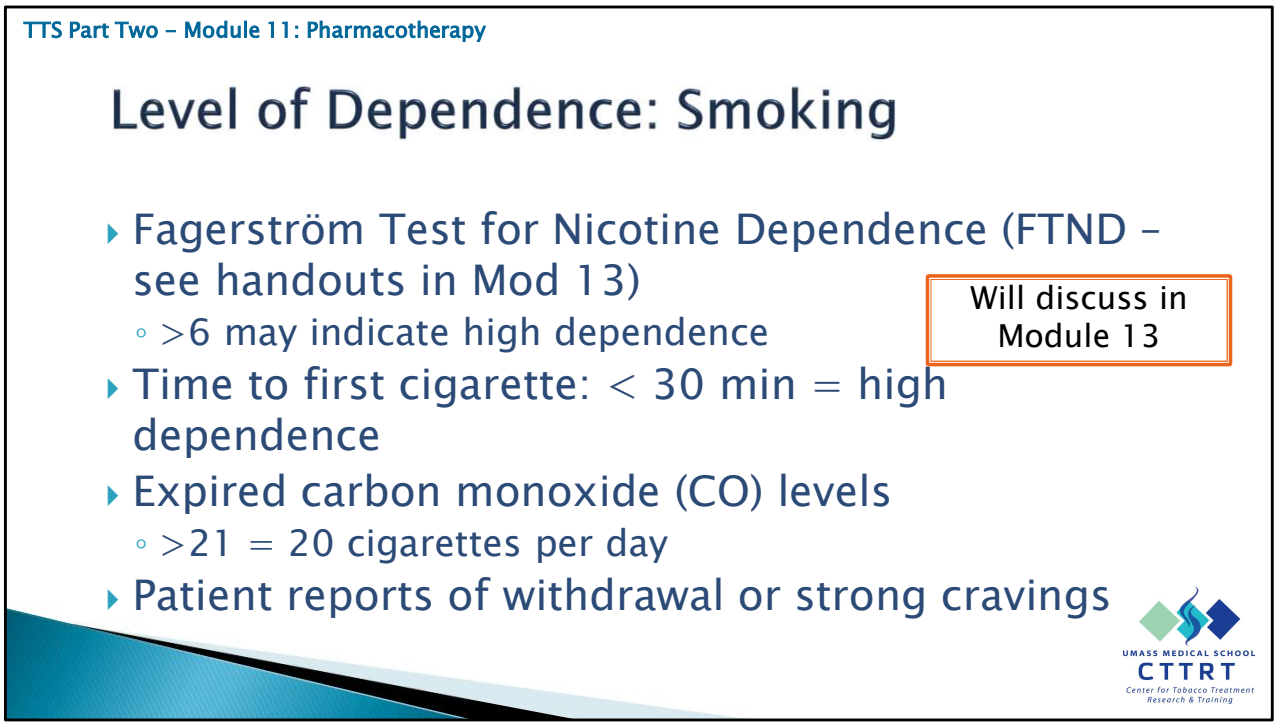


Now we will consider patient factors.



KEY POINTS:

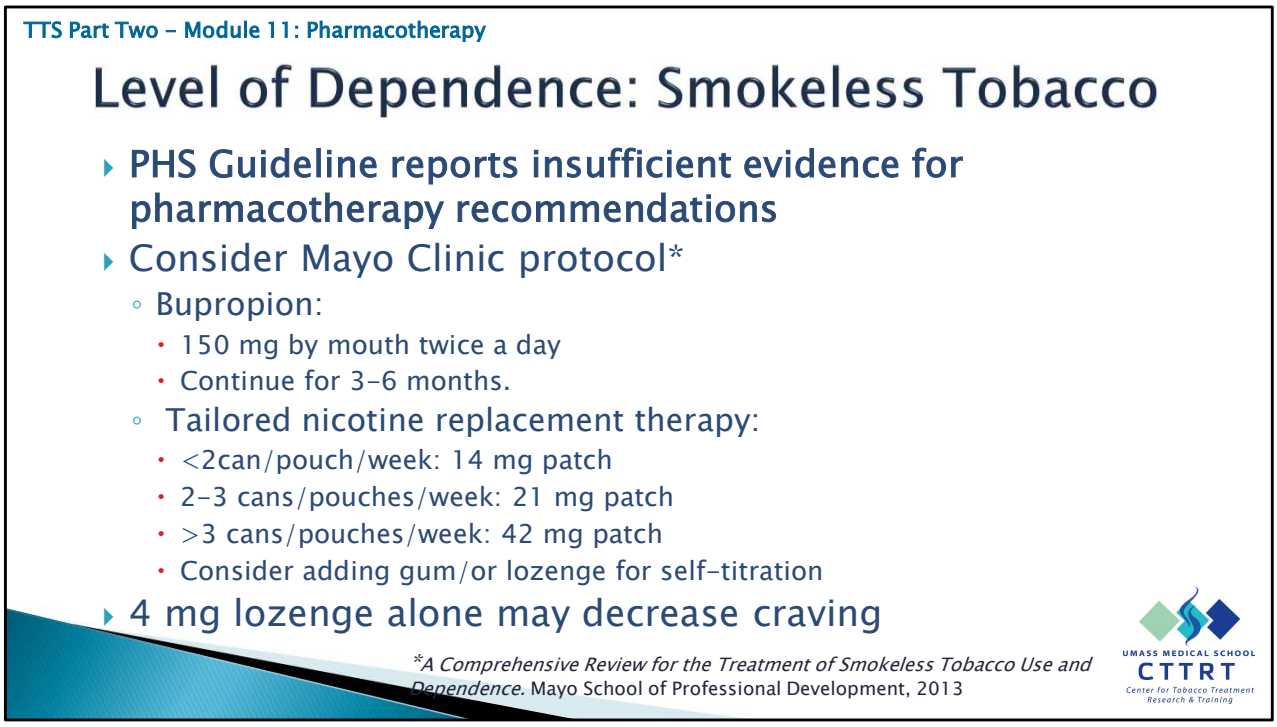
- GET TO KNOW YOUR CLIENT!!
- The more you understand about them, their life, their resources, their environment the more you will be able to guide them to a plan of pharmacotherapy that makes sense to them.
- What have they used before? What was that experience like? How long were they abstinent? What happened when they relapsed? "*The patch didn't work for me*"… Why not? Maybe it simply wasn't enough… they needed a higher dose or patch and/or short acting. EXPLORE!!
- Do they have a preference? E.g., Uncle Joe quit with varenicline and that's what they want to use.
- Honor their beliefs/cultural considerations…"*I don't want any meds I can stay addicted to*"…"*I don't want any more meds*"…Express your understanding while asking if they would like to have more information on what helps many other smoker quit successfully.



KEY POINTS:

- All 4 of the above are good tools in helping to determine an individual's dependence.
- Due to the changing landscape of tobacco use in recent years, such as increased taxes, increased costs and restrictions in smoking public places, many smokers smoke differently. Many restrict their smoking to certain places, certain times of day, and many re-light. This is important when getting a sense of the level of dependence. If we only take into consideration how MANY cigarettes per day they smoke we may miss how heavily dependent they are.
- Remember relighting each cigarette twice and smoking of a total of 5 CPD *IS NOT EQUAL* to smoking 5CPD without the relights. The first inhalations on a cigarette are deeper and more complete than those towards the end of the cigarette.
- Time to first use is being used more often to determine dependence.
- Also, night smoking is a marker for a heavily addicted smoker.
- When using bupropion or varenicline the doses are consistent no matter the dependence level.

REFERENCES: Baker, 2007



KEY POINTS:

- We don't have specific evidence regarding what might be most successful with smokeless tobacco users. MAYO has developed this protocol, which Mass General Hospital also uses.
- Because smokeless tobacco can be used more discreetly (say in the work environment) as well as concurrently with smoking cigarettes, the users are often heavily addicted.
- Both MAYO and MGH among others have found aggressive NRT (Patch, often more than one plus short acting) to be the first approach. Again, there is little evidence from trials to go off of when making recommendations.
- The gum and lozenge can be dose by time to first use (> or < 30 min after waking) or by >/= or < 2 cans per week.
- Due to the similar mode of administration, many patients like the lozenge, particularly those who "pack a lip"

REFERENCES: Ebbert, 2009; Ebbert, 2011;Mayo Clinic, 2013

Prior Experience with Medications

- What products were used?
- How were they used?
  - Check for proper administration and duration of use
- What side effects, withdrawal symptoms were experienced during use?

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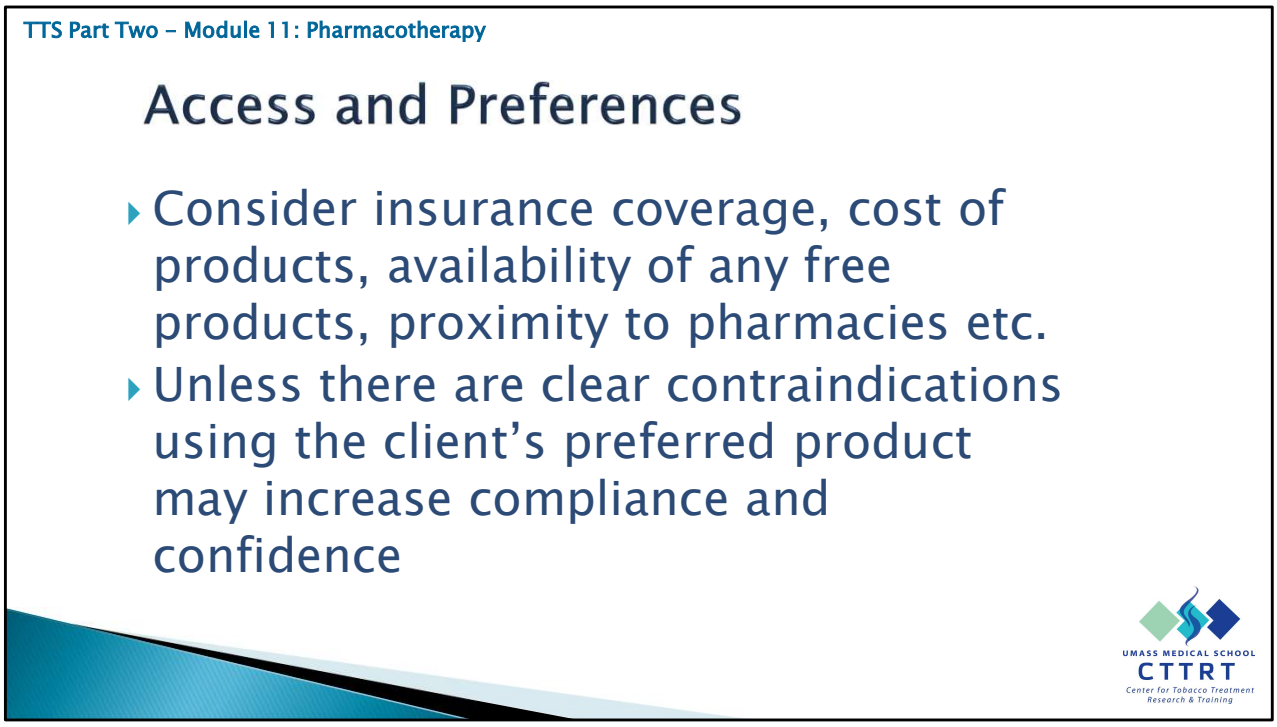
KEY POINTS:

ASK A LOT OF QUESTIONS!

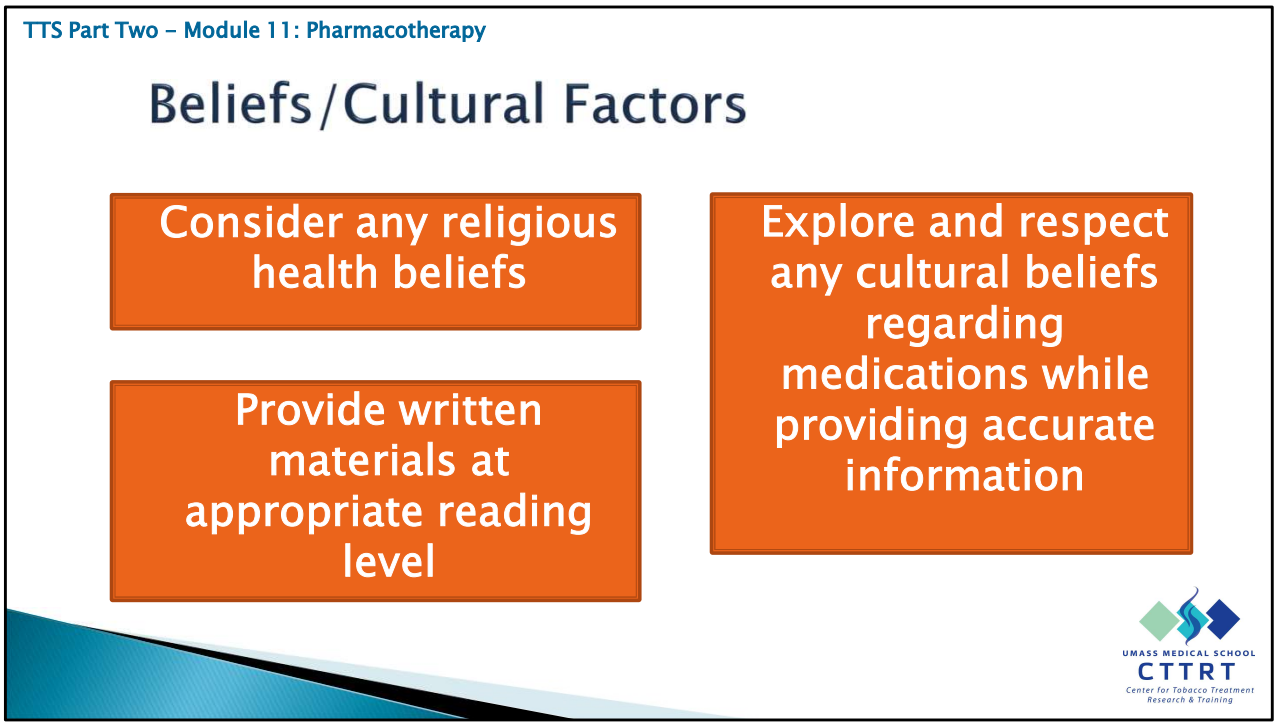
- What was their experience? Tell me how you used it? How often? How long? Many, many times people have *not used enough* and/or for *not long enough.*
- And not used properly…particularly with lozenges and gum.
- What have you heard about this med? Do you know anyone else who has used it? Why do you think that "cold turkey is the only real way to quit?"
- Also ask about the patient mindset during that quit attempt and any other life stressors?

GET TO KNOW THIS PERSON!



KEY POINTS:

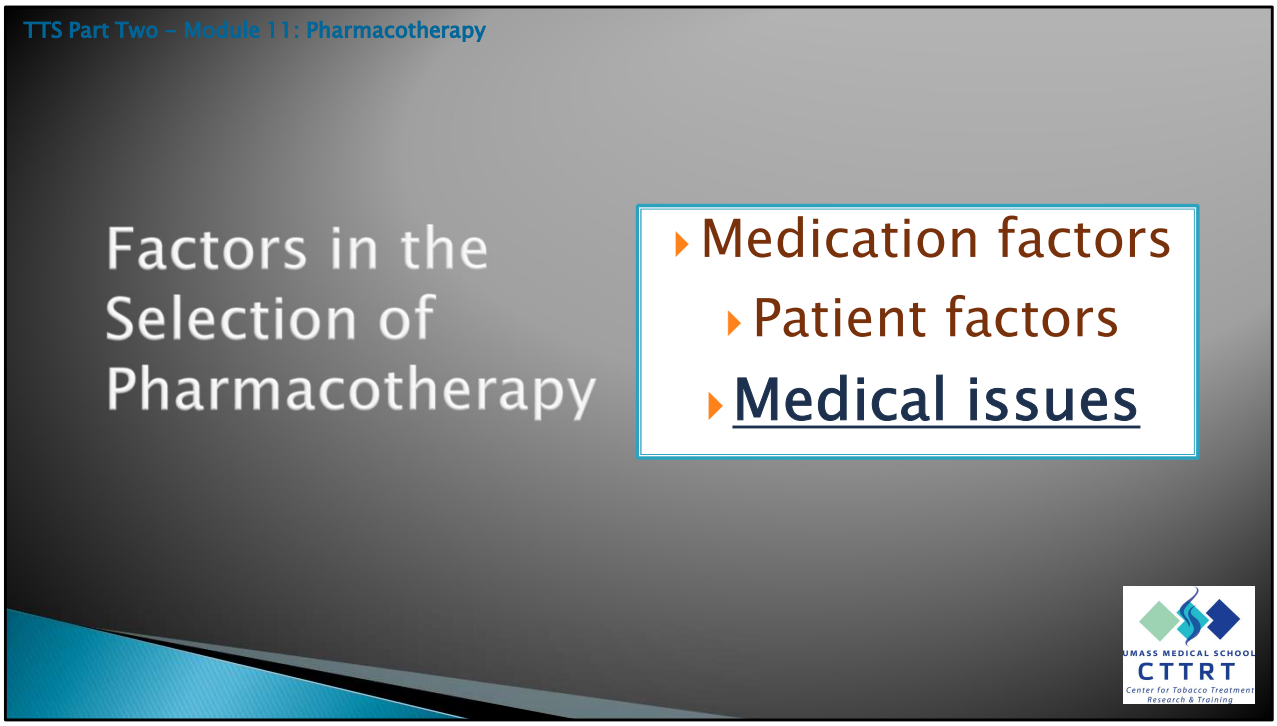
- Remember: all meds have approx. the same efficacy.
- The most important factor in deciding on a plan of pharmacotherapy for an individual is:
- Their preference!!
- However …..you want to make sure they have basic info about pros and cons of all meds and ways to use them, so that they can make an informed decision.



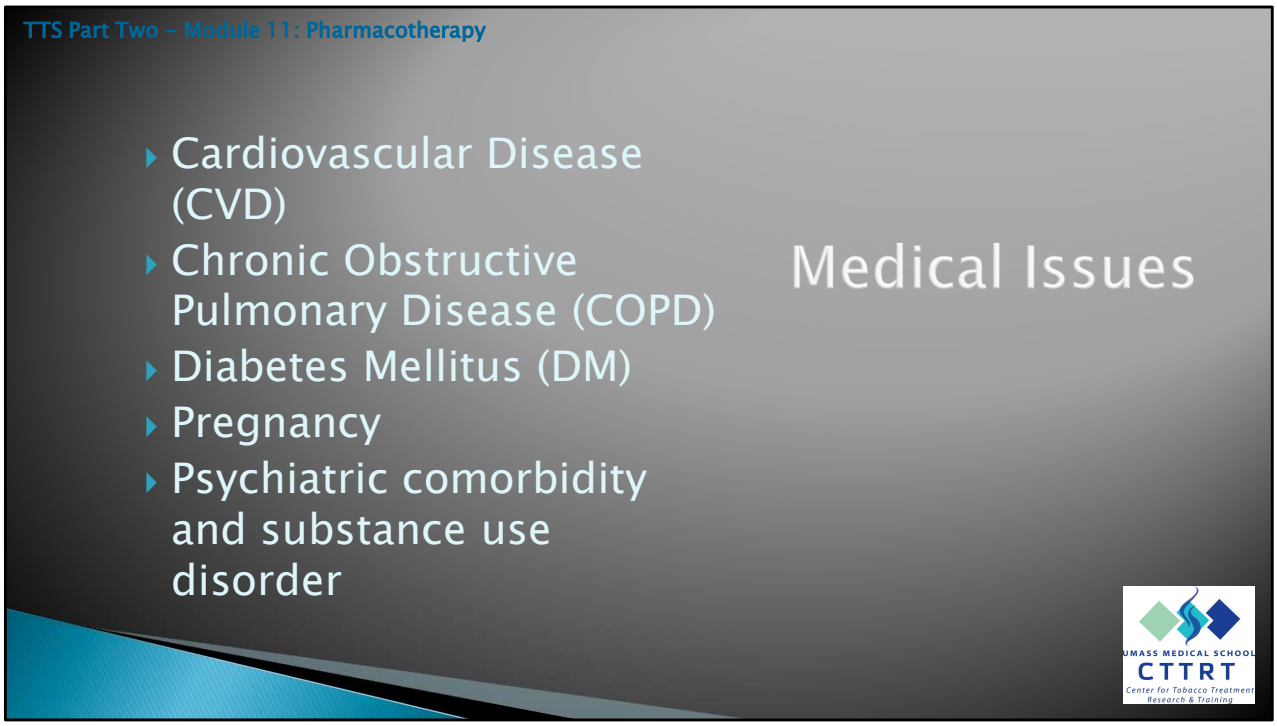
KEY POINTS:

- Research over decades has demonstrated that specific populations experience health disparities and are at greater risk for chronic disease and premature mortality simply due to racial/ethnic/economic group.
- Individuals with an income <$15,000 smoke at nearly 3x the rate of those with incomes >$50,000 .
- Ask questions and empower people to make a choice to quit. Avoid making assumptions about someone's culture and barriers to quitting.
- Avoid making assumptions about those with psych disorders and/or substance abuse.

REFERENCES: Centers for Disease Control and Prevention, 2012

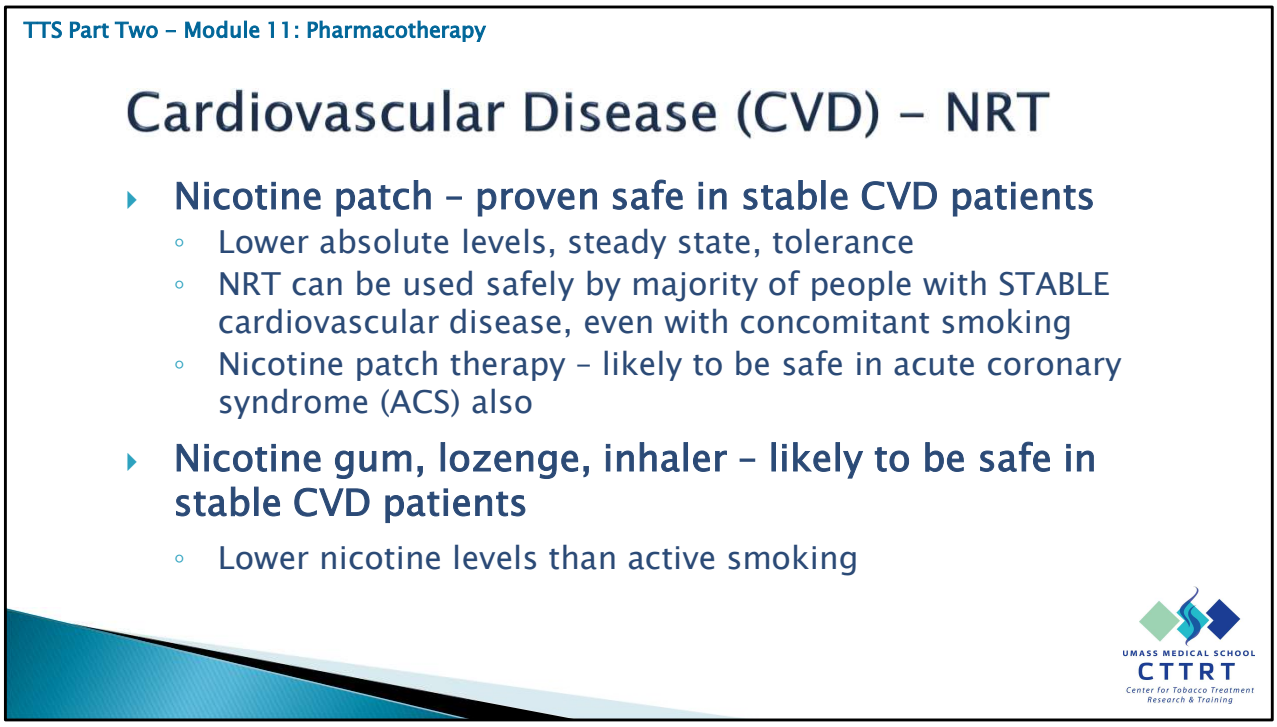


There are in fact very few medical issues that will impact the choice of pharmacotherapy. We will review the precautions for each product and briefly discuss some medical issues where there might be concerns.



KEY POINTS:

- Encourage participants to review the module on health effects of smoking in the basic skills course to gain a better understanding of these conditions.
- The first 3 conditions here are extremely common in smokers. Smoking is a critical risk factor in all of them. In fact, you often see a combination of all three of these conditions.
- Pregnancy is not a medical condition or disease but does require some special considerations regarding the use of pharmacotherapy.
- Smokers are over-represented in psychiatric populations.
- Psychiatric patients are 2-3 times more likely to smoke:
  - 40-50% of pts. with depression and anxiety disorders smoke.
  - 70-90% of pts. with schizophrenia smoke.
  - 75-100% of substance abusers smoke.
- 44% of all cigarettes smoked in U.S. are by individuals with psychiatric or substance abuse disorders



KEY POINTS:

Cardiovascular disease includes: Coronary artery disease, cerebrovascular accidents (stroke) and peripheral artery disease (plaque build up in legs)

- SMOKING IS THE #1 RISK FACTOR IN CVD:
- Emphasize that the patch provides a slow, steady, and lower level of nicotine than that of a cigarette which uses your best drug delivery system, i.e., your lungs.
- Key educational point to patients with CVD is that nicotine is not the problem….It is the carbon monoxide (robbing them of O2) and the 4000+ chemicals that act as an irritant to the lining of the vessels. This irritation is the cornerstone of the development of plaque in the vessels.

▪Nicotine nasal spray

  – More rapid rise in serum nicotine level
  – Possibly higher nicotine levels than with active smoking
  – Avoid unless other therapies have failed

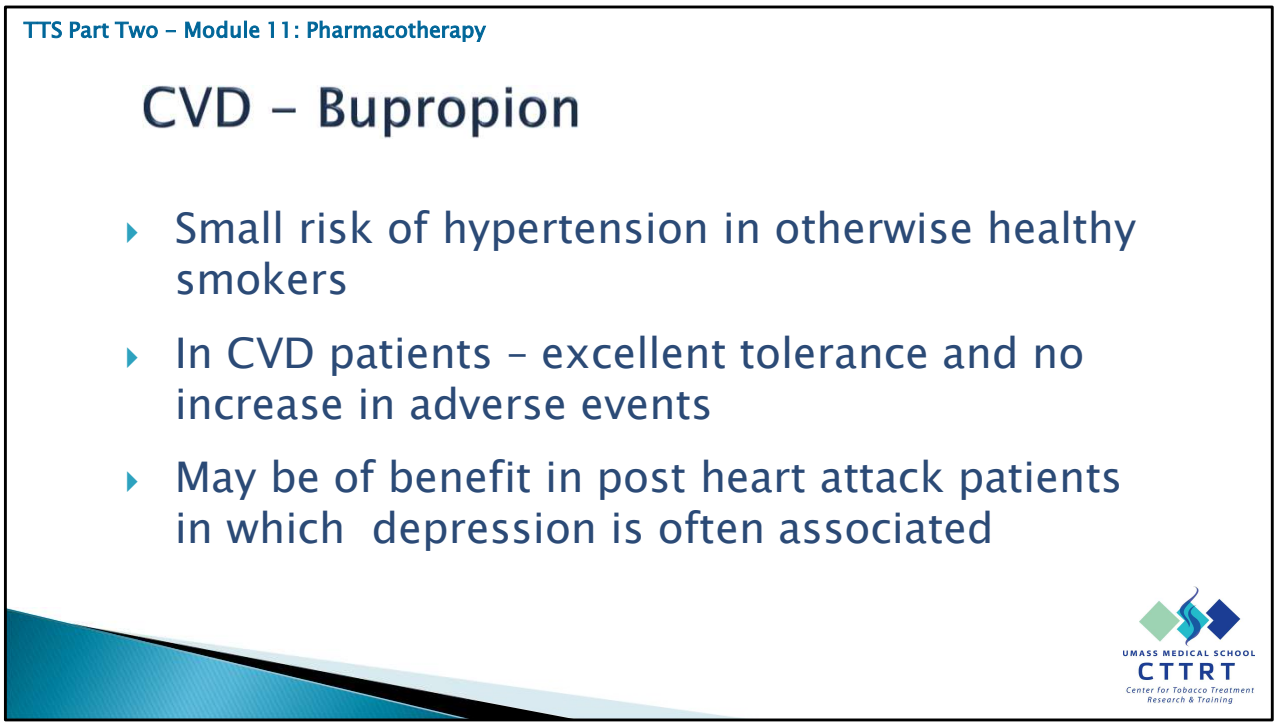
- Recommend to them to read the references below:
  - Hubbard, 2005
  - Meine, 2005

- Rigotti, 2013

Cardiovascular Disease (CVD) – NRT

All data have supported use of NRT in CVD patients

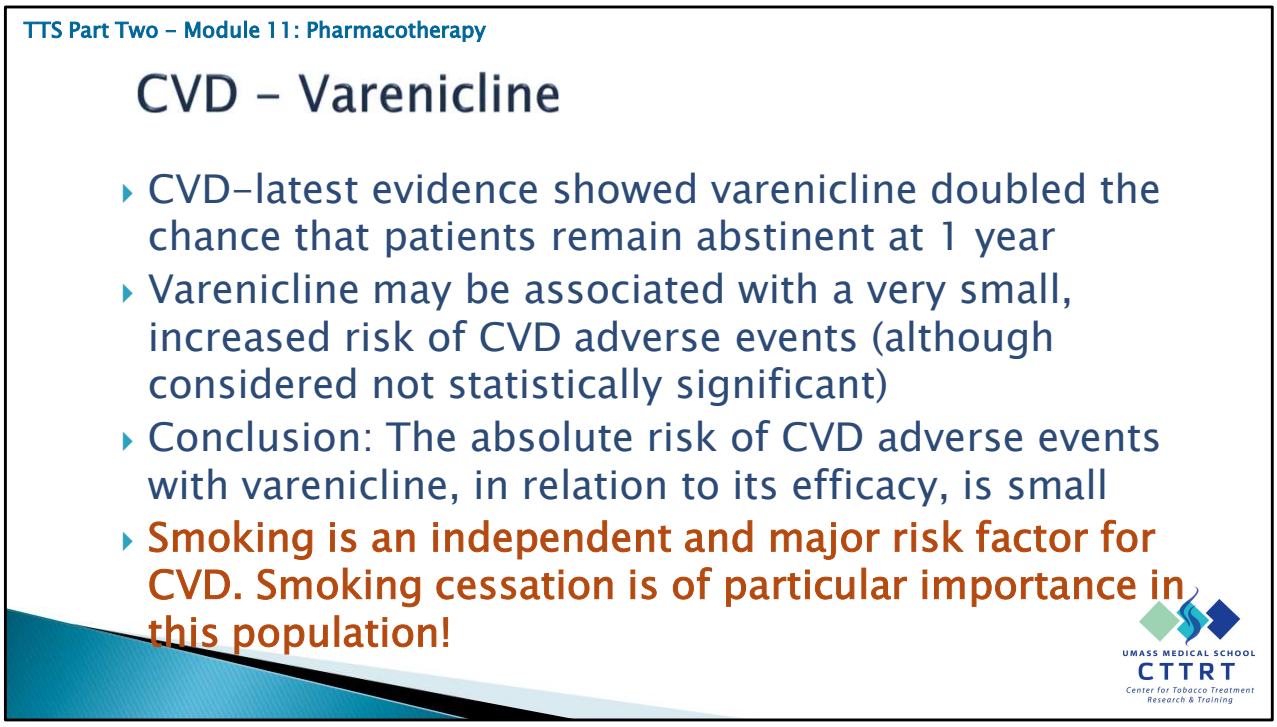
Carbon monoxide and 4000+ chemicals/toxins are the real threat to cardiovascular health!



KEY POINTS:

- In the studies done in this area, bupropion has been shown to be safe in CVD. No increase in cardiovascular events.
- An small increase in BP has been shown in some studies but not in others.
- It may be particularly good in this population as depression is associated with the development of CAD.

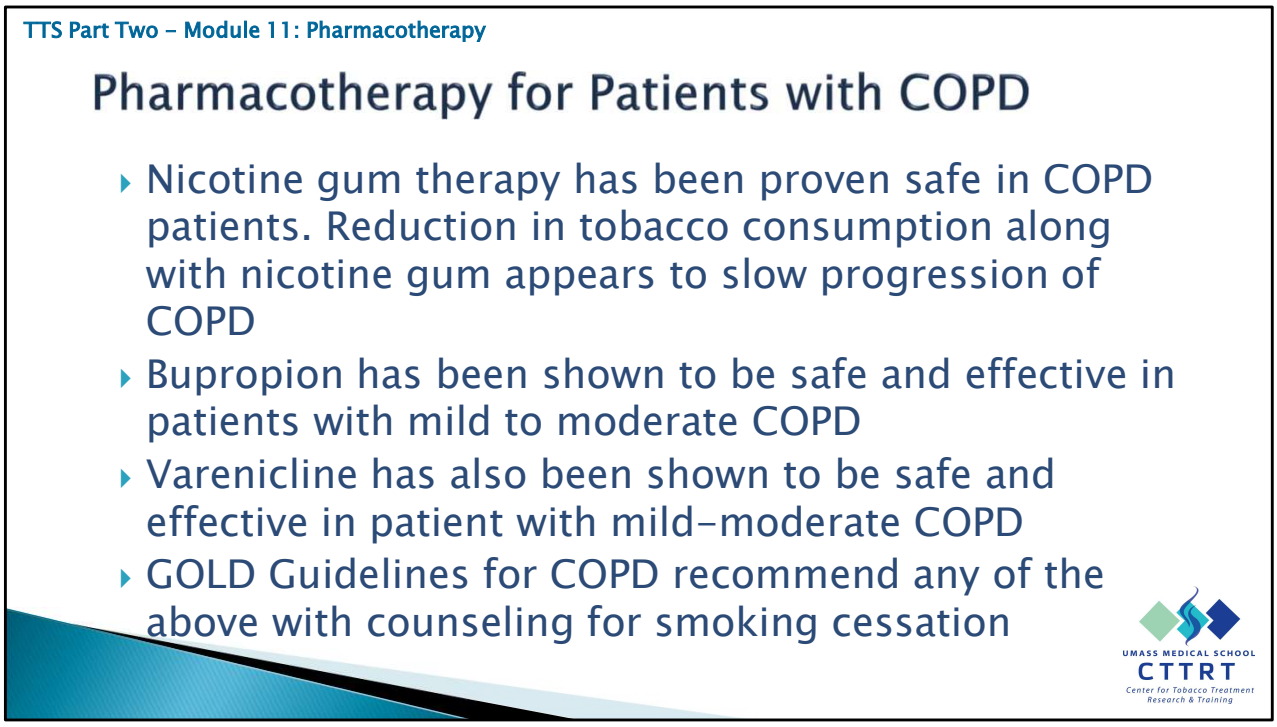
REFERENCES: Settle,1998; Kiev, 1994; Mills, 2014



KEY POINTS:

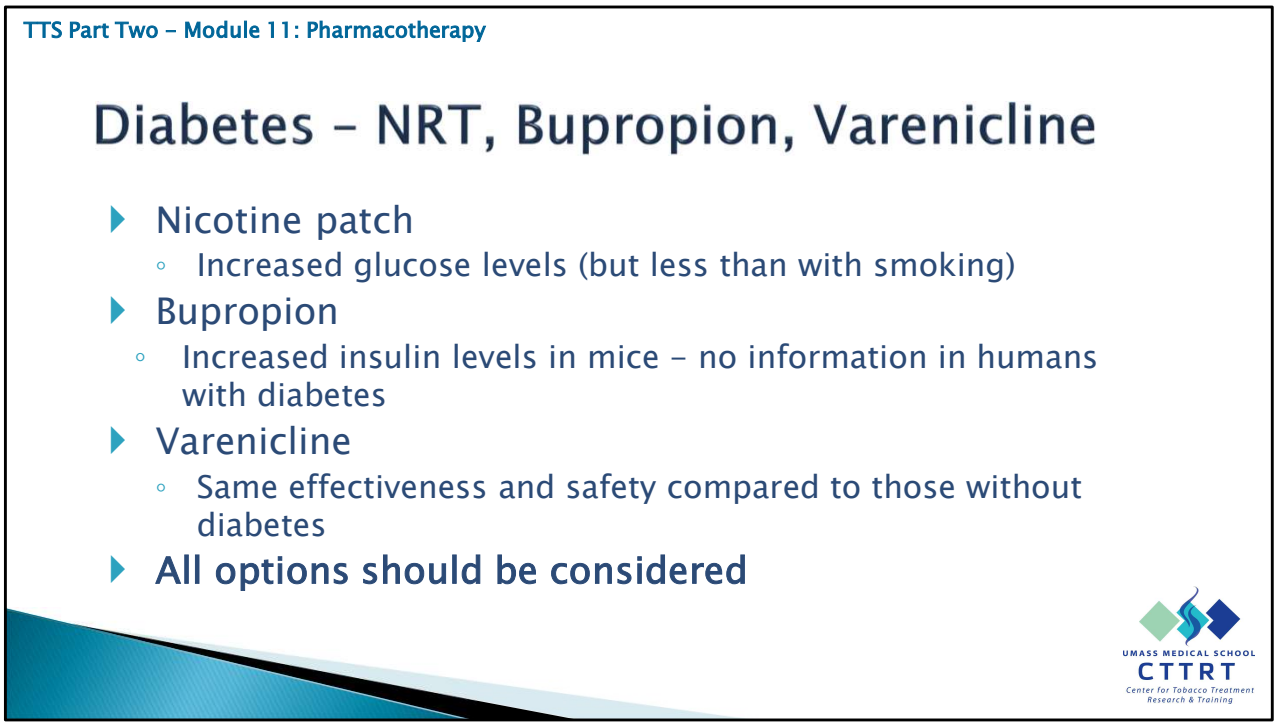
- There was a meta analysis published by Canadian Medical Association Journal re: varenicline and CAD. This is the study that prompted the label change. This raised a lot of controversy. Concerns were raised about the methodology of the analysis (types of events included, self-report of events, higher drop out rate in placebo group) and how the risk was reported.
- This was addressed in another article you have in your bibliography by Hays in the same journal.
- The major conclusion was that there appears to be a slight increase in the risk of major cardio events with the use of varenicline – although this is not statistically significant!
- The FDA then again released other updates the most recent being in 2012. Again emphasizing that the risk of continued smoking must be weighed against the risk of an event. " The agency continues to believe that the drug's benefits outweigh the risks"

REFERENCES: Singh, 2011; Hays, 2011; Rigotti, 2010



KEY POINTS:

- COPD refers to 2 diseases, chronic bronchitis and emphysema.
    - 3rd leading cause of death in US.
    - Smoking is the primary risk factor
    - 90% of all COPD patients were or are smokers
- It is firmly established that quitting smoking will slow the progression of this disease.
- In many cases, a patient who has smoked long enough to have developed and diagnosed with COPD and is still smoking tend to need aggressive, long term pharmacotherapy.
- Bupropion, as well as varenicline, has proven to be both safe and effective in those with mild-moderate COPD.
- "Harm reduction" as shown by Jimenez study might be a course of action for those not willing to quit. Using NRT and reducing cigarette intake has been shown to help lung funct ion.
- New labeling states that recent evidence shows varenicline was effective in this population, with no increase in adverse events demonstrated and no new safety concerns REFERENCES: National Lung Study; Tashkin, 2001; Jiménez-Ruiz, 2002; Wagena, 2003; GOLD 2019



KEY POINTS:

- Smoking increases the risk of the development of diabetes.
- We know that nicotine, itself, impairs the cells response to insulin. Another way of saying this is that it increases insulin resistance. So this is technically the case with NRT. Keep in mind, the levels of nicotine in NRT are most often much less than what the smoker had previously taken in.
- Bupropion has been studied in mice which demonstrated an increase in insulin level. This, *in theory,* could lead to hypoglycemia (low blood sugar)
- A recent review of pooled studies found that the effectiveness and safety of varenicline was the same for those with and without diabetes
- Be wary of the sugar content of the lozenges (some are sugar free, such as Nicorette) in patients with diabetes who are taking lozenges every 1-2 hours. This is not a reason not to use, but something to be aware of.

REFERENCES: Bornemisza, 1980; Eliasson, 2003; Epifano, 1992; Chang, 2012; Tonstad & Lawrence, 2017.

Pregnancy and Lactation

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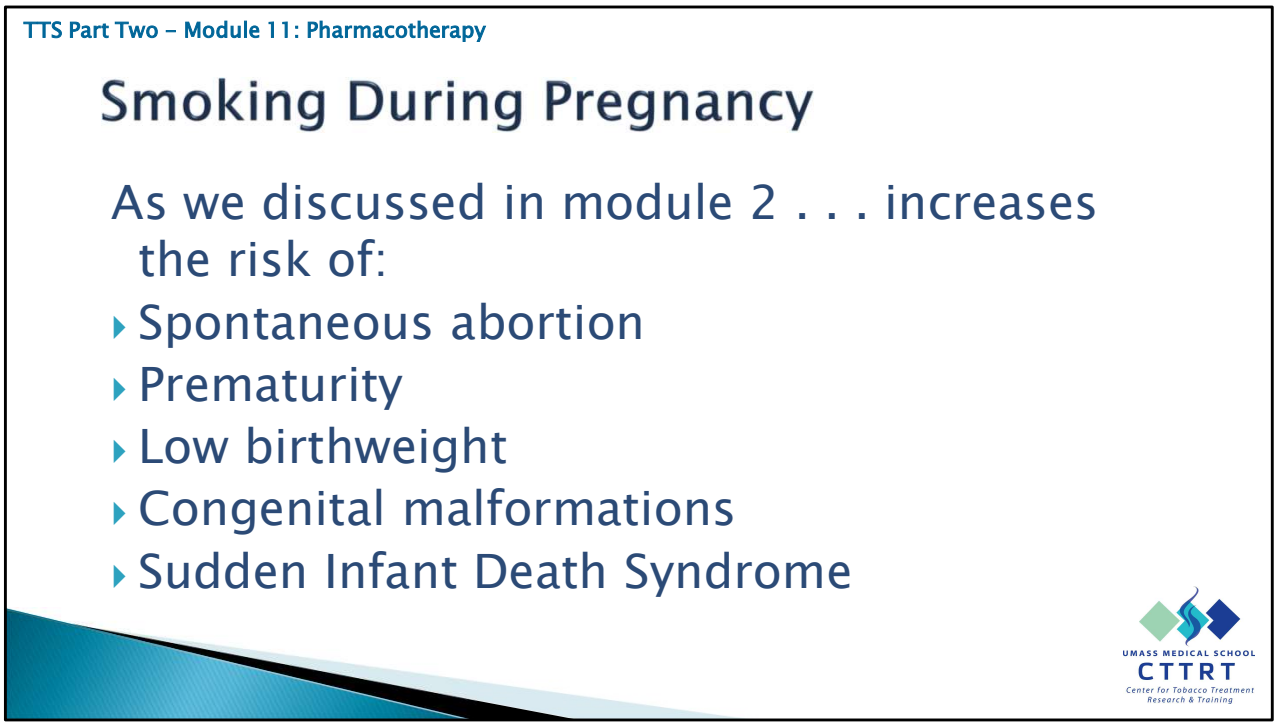
KEY POINTS:

Women who smoke during pregnancy risk the following:

- Ectopic pregnancy
- Miscarriage
- Low birth-weight baby
- Stillbirth
- Complications of the placenta
- Premature birth
- Certain fetal malformations

Cessation of smoking during pregnancy is important for both maternal and fetal health

REFERENCES: (for all slides on pregnancy)
Benowitz, 2000; Lambers, 1996; Oncken, 1997; Slotkin, 1995; Wright, 1997; Coleman, 2012



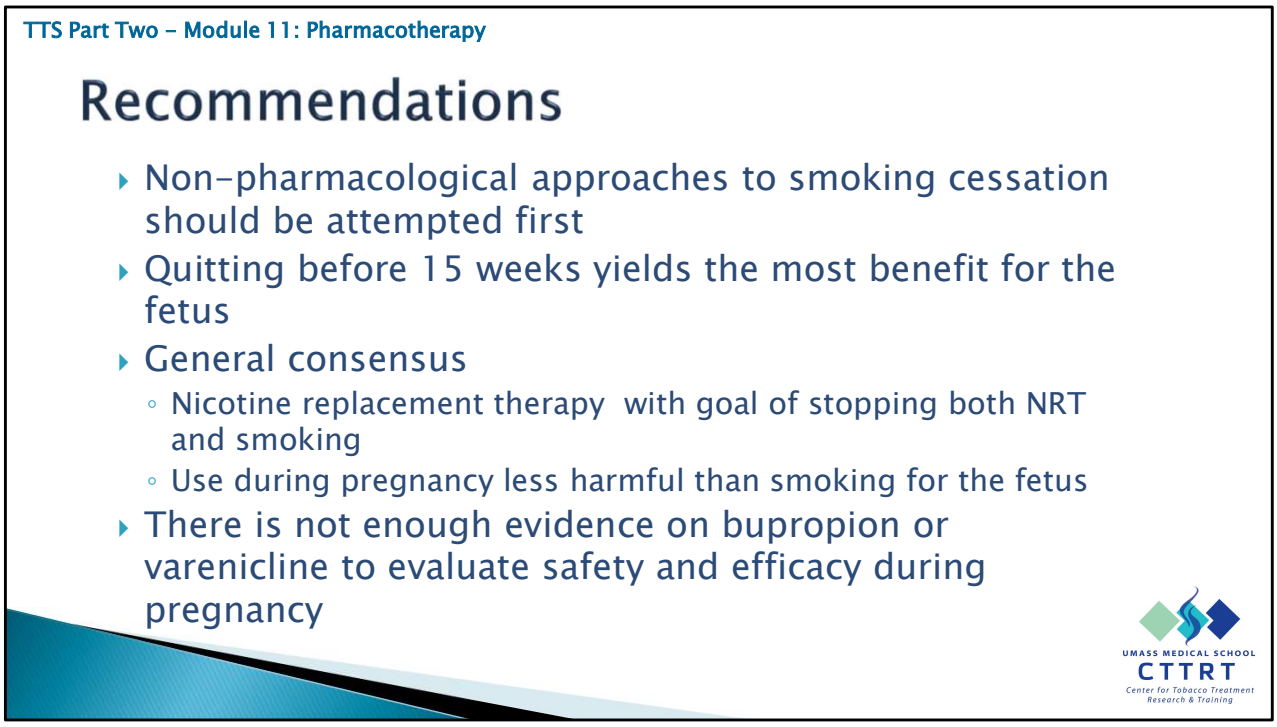
KEY POINTS:

- Up to 45% of women who smoke before pregnancy stop before their first prenatal visit. Women who quit spontaneously are more likely to have higher social status, no smoking partner, a lower degree of nicotine dependence, and less concern about weight gain.
- Most mothers who quit smoking during pregnancy resume smoking within 6 months of delivery and about 70% relapse by 12 months.
- Nicotine readily gains access to the fetal compartment via placental blood flow.
- In fact, nicotine blood levels are higher in the fetus than in the mother
- Although precise mechanisms that underlie the various effects of smoking on pregnancy are not completely understood, several major processes have been implicated:

1. Nicotine induces vasoconstriction, restricts blood flow and reduces the supply of nutrients and oxygen to the fetus
2. Carbon monoxide in tobacco smoke inhaled by the mother displaces oxygen in the circulation further reducing the amount available to the fetus
3. It affects the placenta, as smoking disrupts the growth and proliferation of blood vessels in it

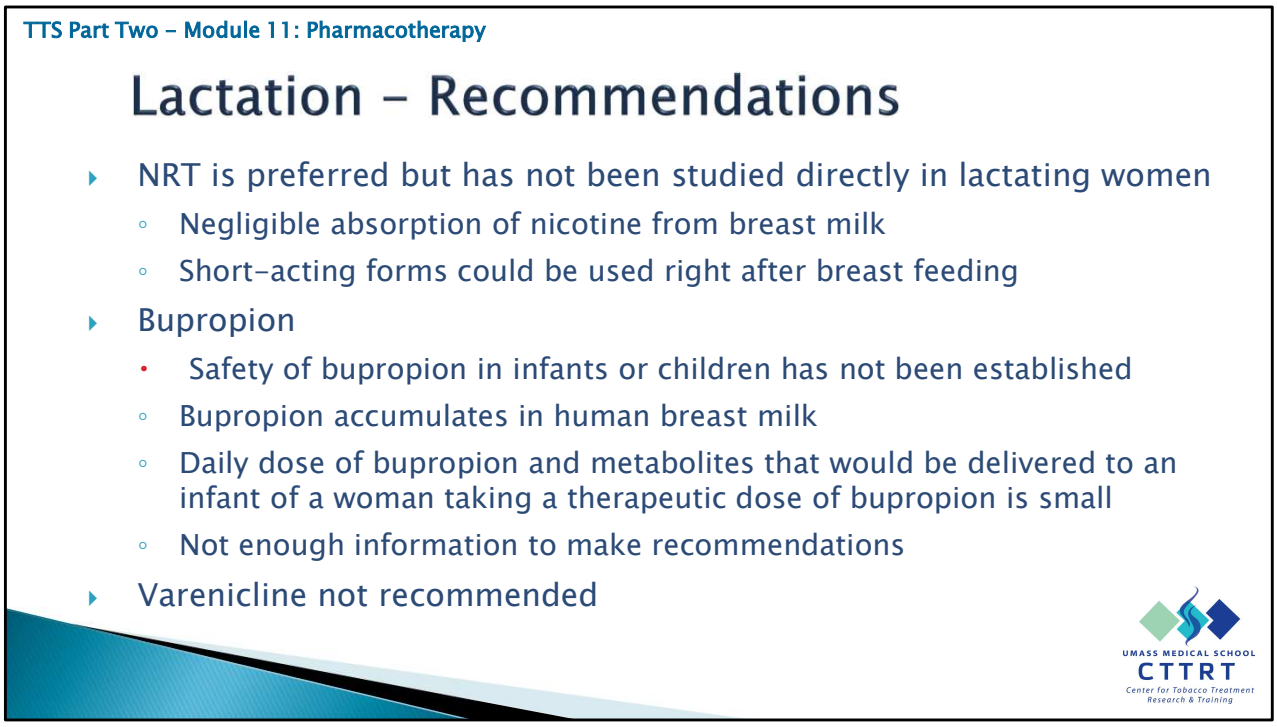
KEY POINTS:

- Cochrane review looked at 6 randomized control trials with 1745 subjects.
- The success of higher dosing should be discussed as possible reason for moderate success and low adherence in earlier trials
- American College of Obstetricians and Gynecologists (ACOG)- studies on NRT were stopped early due to adverse drug reactions or lack of effectiveness. Discuss risks with patients and use with goal of getting off NRT rather than using throughout pregnancy.
- Small studies in varenicline have not shown teratogenicity, but it is not recommended by ACOG at this time.
- Bupropion has limited data. There is conflicting data regarding malformations. There have been non-congenital malformations, but the jury is still out on cardiovascular. From a mental health care standpoint, benefits may outweigh risks, but there is a different risk benefit analysis that would need to occur to start a new med during pregnancy rather than continue an existing one.



KEY POINTS:

- Try non-pharmacologic first.
- Quitting before 15 weeks is of most benefit to the fetus (ACOG 2017). If non pharmacological intervention in unsuccessful, it may be best to try NRT to achieve a quit prior to this time rather than persisting with behavioral interventions alone. Successful quit prior to the third trimester can help reduce the risk of low birthweight due to maternal smoking.
- If that does not work, exposure to nicotine in NRT is likely safer than exposure to nicotine from other tobacco products.



KEY POINTS:

- Mothers who smoke are less likely to breastfeed
- Those who do breastfeed do so for a shorter time
- We know that in breastfeeding mothers who smoke produce poorer quality milk
- The effect of smoking on breastfeeding may be mediated by nicotine regulation of the hormone prolactin. Prolactin is essential for the initiation and maintenance of milk production. Breastfeeding mothers who smoke have lower levels of prolactin than those who do not smoke. This results in poorer milk supply

Again, in terms of pharmacotherapy the same applies.

- varenicline avoided because safety of varenicline in infants and children has not been studied
- May try lozenges/gum first

REFERENCES: ACOG 2017

Psychiatric and Substance Use Disorders

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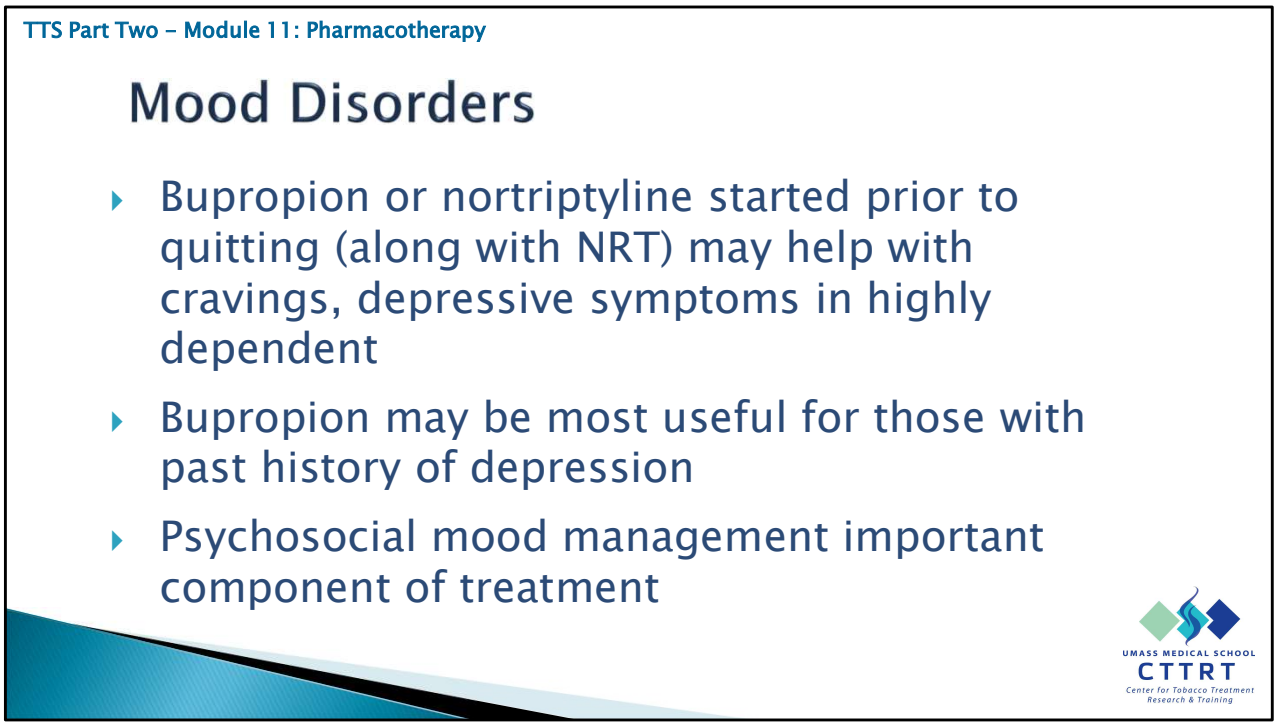
KEY POINTS:

Smokers are over represented in psychiatric populations

- Psychiatric patients are 2-3 times more likely to smoke
- 40-50% of pts. with depression and anxiety disorders smoke.
- 70-90% of pts. with schizophrenia smoke.
- 75-100% of substance abusers smoke.
- 44% of all cigarettes smoked in US are by individuals with psychiatric or substance abuse disorders

- We also know that smokers in this population have even worse risks than others.
- Among treated narcotic addicts, smokers' death rates were 4X that of nonsmokers.
- Among treated alcoholics who died, 51% of mortality attributed to smoking-related illness.
- It appears there is a synergistic effect between smoking and other substances.

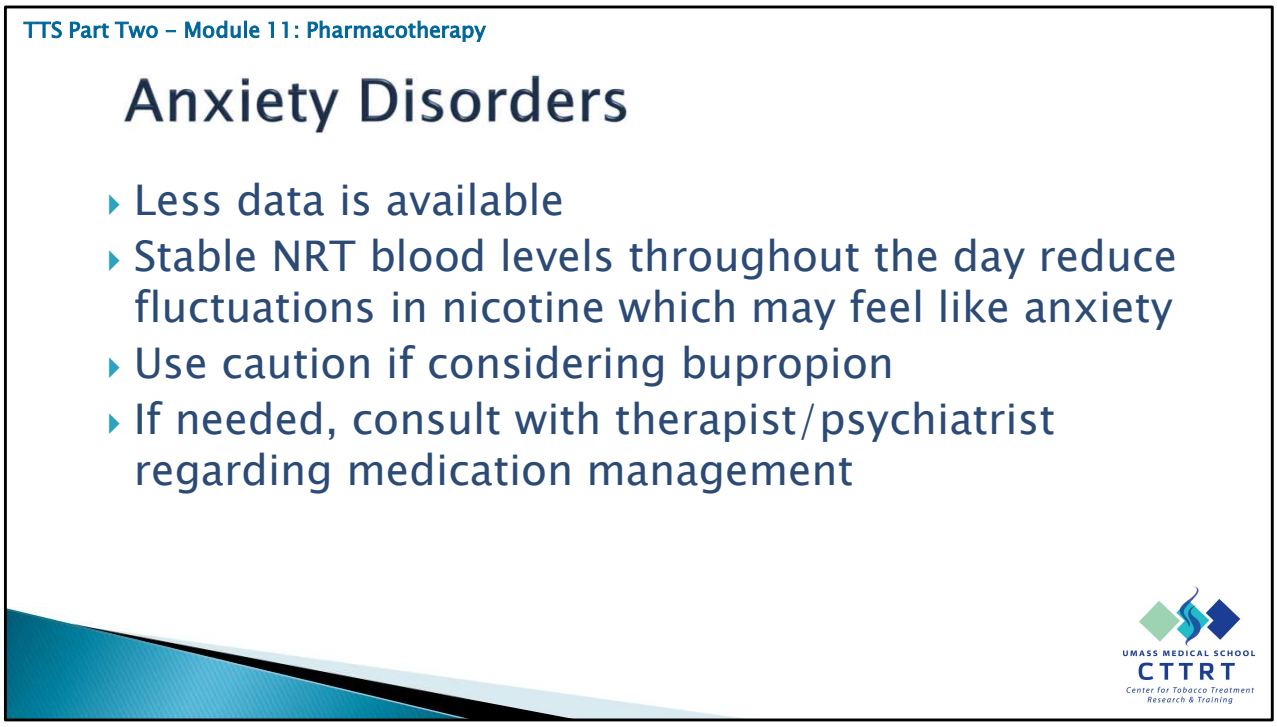
REFERENCES: Hurt, 1996; Grant , 2004



KEY POINTS:

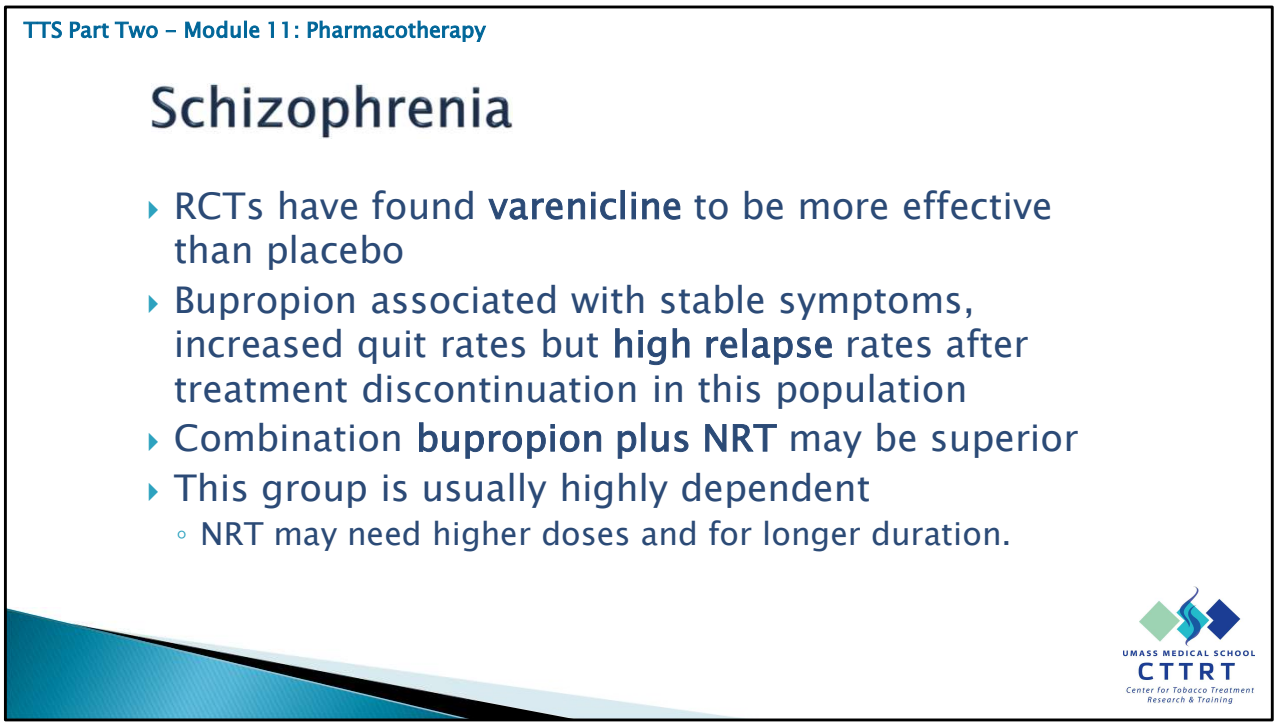
- It is important to emphasize that a common myth/misconception is that quitting smoking worsens psychiatric symptoms.
- Coordination of pharmacotherapy with prescriber of psychiatric medications is critical.
- People with mental health disorders can quit successfully and at rates similar to the general population.
- A new meta-analysis published 2014 in BMJ that contrary to common perception, smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with those continuing to smoke. The effect size is equal and even larger than that seen with antidepressant treatment.

REFERENCE: Taylor, 2014; Wilhelm, 2004; Lerman, 2004; Cook, 2004; van der Meer et al, 2013



KEY POINTS:

- Remember to keep NRT doses stable over the course of the day to reduce fluctuations in nicotine which may feel like anxiety.
- In some individuals, bupropion can increase anxiety. However, there is no determining beforehand who that might be.



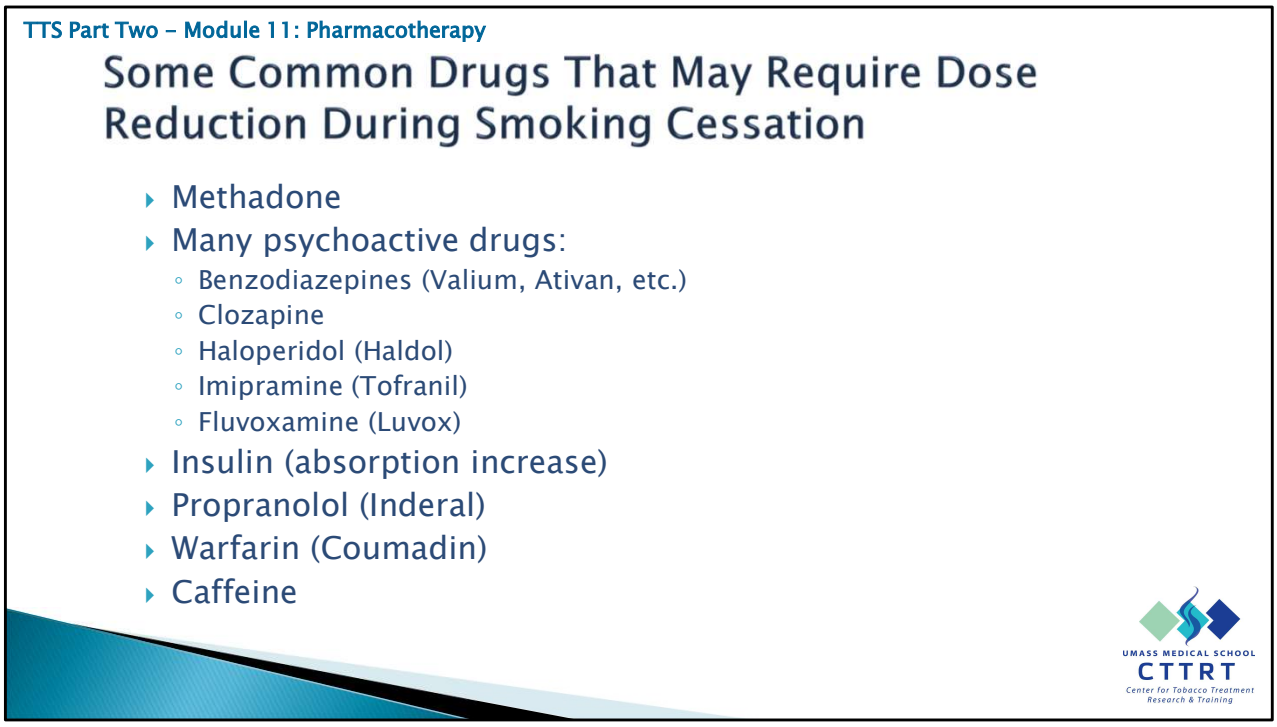
KEY POINTS:

- We have seen what a high percentage of this population smokes
- Data also shows that people with mental illness are at greater risk of dying early from smoking than of dying from their mental health conditions
- The most effective cessation strategies for the general public, a combination of medication and counseling also apply to people with mental health conditions.
- None of the meds are contraindicated in this group. As always in those with active mental health diagnosis the psychiatrist should be consulted and worked with closely.
- This population often need greater intensity and duration of services. Many in the field believe that some will need indefinite duration of treatment- maybe even lifetime.

REFERENCES: Williams, et al 2012; Stapleton , 2007; Turner, 2004; Gibbons , 2013

These authors reanalyzed data from 17 studies previously conducted by Pfizer (n= >8000) plus a large DOD data set to look at any neuropsychiatric symptoms from varenicline or NRT (n= >35,000). The analysis revealed no evidence that

varenicline is associated with these adverse events in either individuals with and without a recent history of a psychiatric disorder.



KEY POINTS:

- Smoking affects enzymes involved in the metabolism of many drugs
- Smoke has polycyclic aromatic hydrocarbons that induce these enzymes. When one quits smoking, this enzyme activity goes down and it could result in higher levels of certain drugs (since they aren't being metabolized as well). There are drugs that may need to be adjusted.
- Many of the psychoactive drugs, And even caffeine.
- Also both Coumadin and insulin can be affected by smoking cessation. Anyone on Coumadin already should have a schedule of blood draws to test their levels. Likewise with insulin, close blood sugar monitoring should be done by the patient.

REFERENCES: Murray, 2010; Clair, 2013; Wahawisan, 2011

Drug Interactions– Bupropion

- Levadopa
- MAO inhibitors
- Tricyclic antidepressants
- SSRIs (fluoxetine, paroxetine)
- Cimetidine (Tagamet)
- Ritonavir (HIV med)

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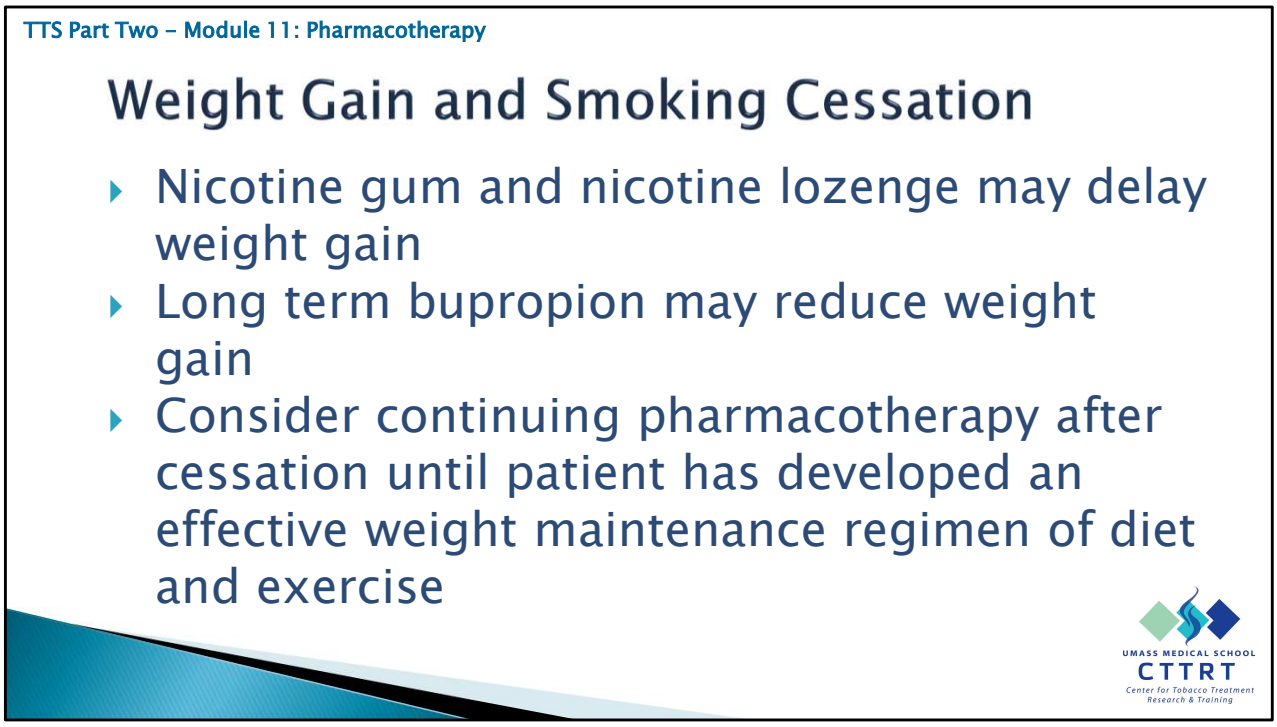
KEY POINTS:

- Bupropion can interact with these meds.
- A patient's physician would be part of the decision in prescribing bupropion.



KEY POINTS:

- Many smokers (particularly women) are concerned about their weight and fear that quitting will produce weight gain.
- Evidence does show that the majority of smokers who quit smoking do gain weight. Most will gain fewer than 10lbs. But it can vary quite a bit, with some gaining as much as 30lbs.
- As a clinician, we should not deny that weight gain may happen nor should we minimize the significance to that individual
- Of course, we also have to inform the smoker, that smoking presents a far greater health risk than even a significant weight gain
- Both nicotine gum/lozenge as well as bupropion have shown a delay in weight gain and this may prove to be helpful to some. It could provide time in which they could increase their exercise and change eating habits.
- Please emphasize new study below.
- Smoking cessation was associated with a lower risk of CVD events among both diabetics and non diabetics even in the presence of significant weight gain.

REFERENCES: Clair, 2013

NRT and Adolescents: PHS Recommendations

- NRT should be considered only when there is clear evidence of nicotine dependence and a clear desire to quit
- Factors such as degree of dependence and body weight should be considered when selecting NRT dosage
- Meta-analysis showed varying benefit with patch, gum or lozenge
- Policy in U.K.: Use of NRT in children age 12-18 acceptable. Recommend limit of 12 weeks unless medical professional approves longer treatment

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KEY POINTS:

- The evidence thus far shows NRT is safe to use in adolescents with varying efficacy.
- Meta-analysis of 8 trials in 13-19 year olds smoking > 1 to 20 cigarettes per day using NRT gum patch or lozenge for 4-12 weeks. Quit rate ranged from 7-47%. Most were self-reported.
- It is approved for use in children in the UK.
- You would want to engage the adolescent's pediatrician. With vaping there is a renewed call for studies of NRT in adolescents.

Reference: King 2016

AAP Resources – Youth Tobacco Cessation

- Website: aap.org/helpkidsquit
  - Assessment tool
  - Behavioral support (texting, tobacco quitlines, online)
  - Pharmacologic support
- Completing the assessment tool results in treatment recommendations based on the severity of nicotine dependence

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Case Study Examples

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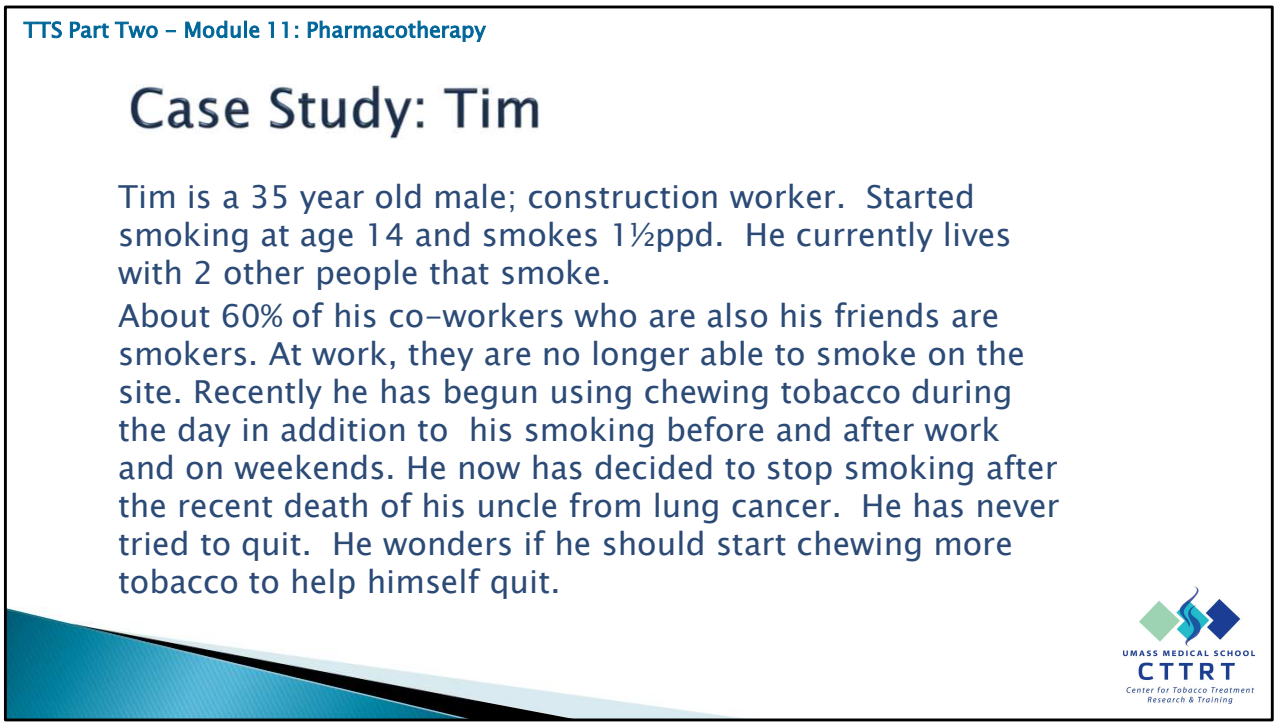


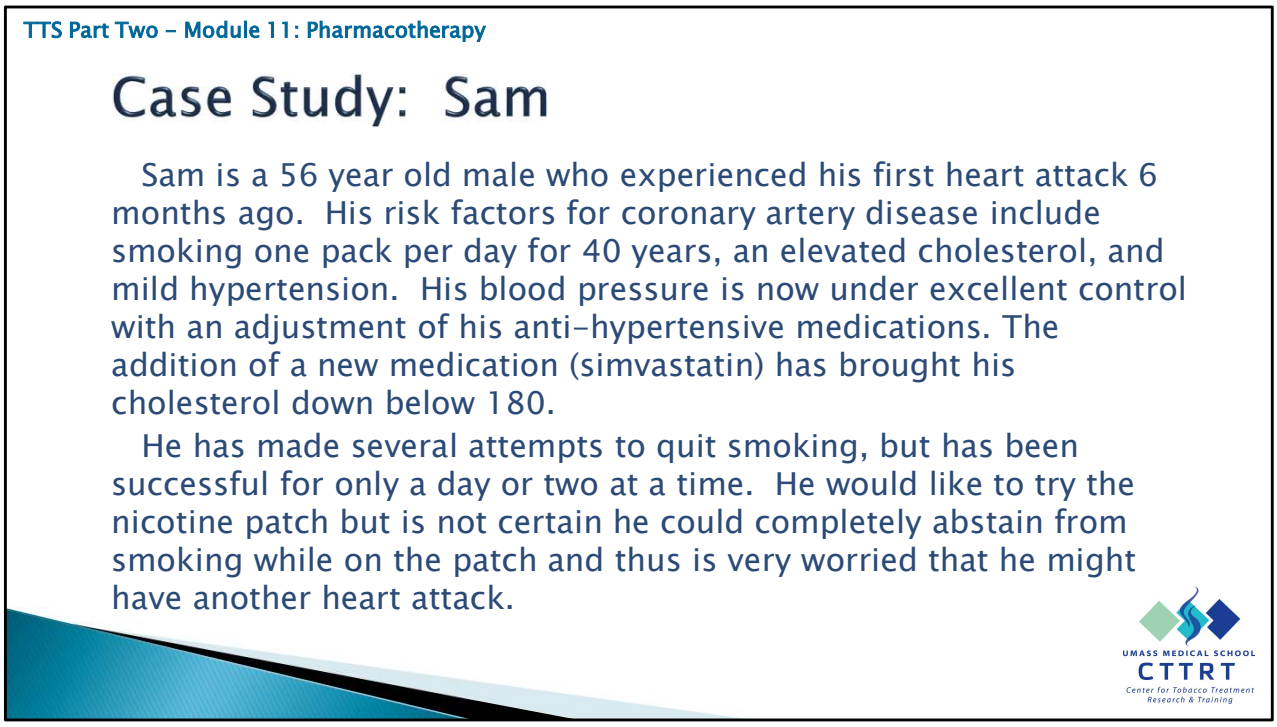
Let's begin to apply some of this to real life type of cases. We'll start with a rather uncomplicated case.
Read the case study or ask participant to read aloud.

Invite the class ask more questions about Tim that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Tim and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- For Tim typical answers might be: "Yes, we smoke in the house. I smoke my first cig when within 10mins", " I smoke more on the weekends…sometimes over a pack. During the week, I smoke less but I chew tobacco in between"
- There are no real wrong answers here but hopefully their thinking will be to go with NRT first. Less complicated and OTC. Hopefully with his concurrent chewing they will come to combo NRT…..
- Having said that, it is perfectly acceptable if they considered any of the meds.

- Just get them thinking about Tim!
- Try to keep this discussion on the shorter side since there are no significant issues to consider.

Goal time: 10 minutes



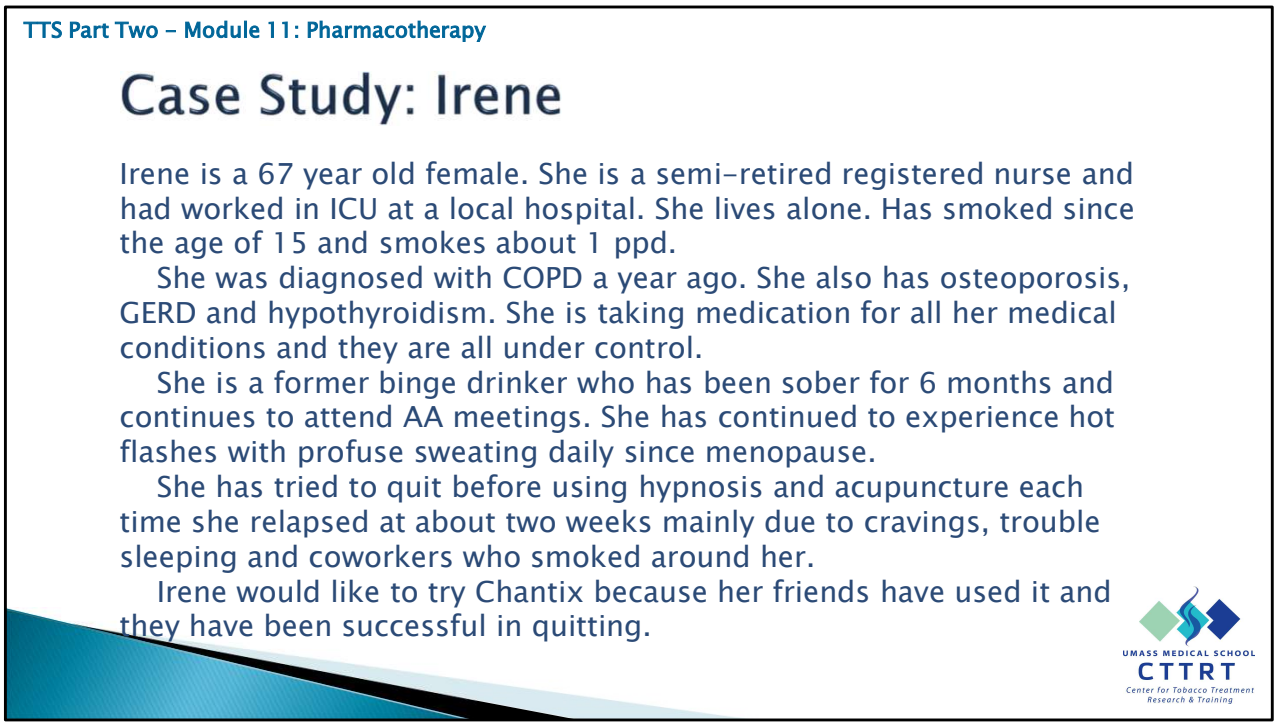
Read the case study or ask participant to read aloud.

Invite the class ask more questions about Sam that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Sam and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- In Sam's case, since he has stated he is interested in the patch it probably makes since to start there. Adding a short acting would also make sense.
- Elicit from the group a discussion re risk for another heart attack if he smokes on the patch. You want them to mention how important education is around this and that it needs to be imparted to Sam. That there is no increase in risk if he smokes on the patch , however, the goal is to become smoke free and the importance of having a plan in place for a "safety net" should he experience breakthrough cravings on patch….e.g., have lozenge, gum, or inhaler with him at all times.
- Remind group that there is data to support continuing to wear patch even after a lapse.

<u>Goal time: 10 minutes</u>

REFERENCES: Ferguson, 2012; Hubbard, 2005



Read the case study or ask participant to read aloud.

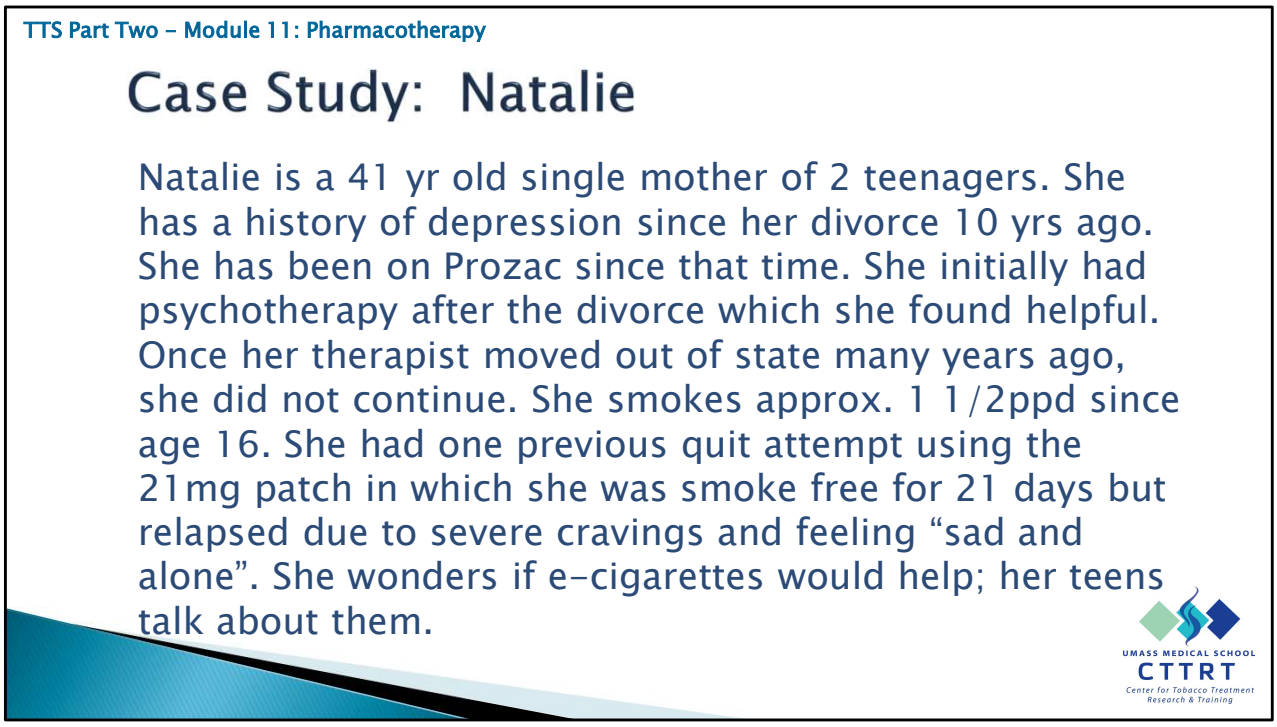
Invite the class ask more questions about Irene that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Irene and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- Given this case, it would make sense to have her begin varenicline given her preference. Education re how to use, i.e., take with water and food, don't take too late at night, stop med and tell MD if experiencing any changes in behavior or thoughts, etc."
- May encourage class to consider also selecting a short acting NRT to have available after quit date.
- If time, you may also throw out question. "Is there any med you would not recommend and why?"
- Some thoughts, but not necessarily conclusions, include…She does have a history of GERD, maybe avoid gum as could upset her stomach. She has a history of binge drinking which, in theory, could put her at risk for seizures and therefore would avoid bupropion. However, she is sober x

6mths and has support. Not all patients who binge drink are at risk of seizures, it is important to keep in mind. Note that varenicline can increase sensitivity to alcohol.

- And of course, no reason she couldn't use NRT other than her preference is varenicline.

Goal time: 10 minutes



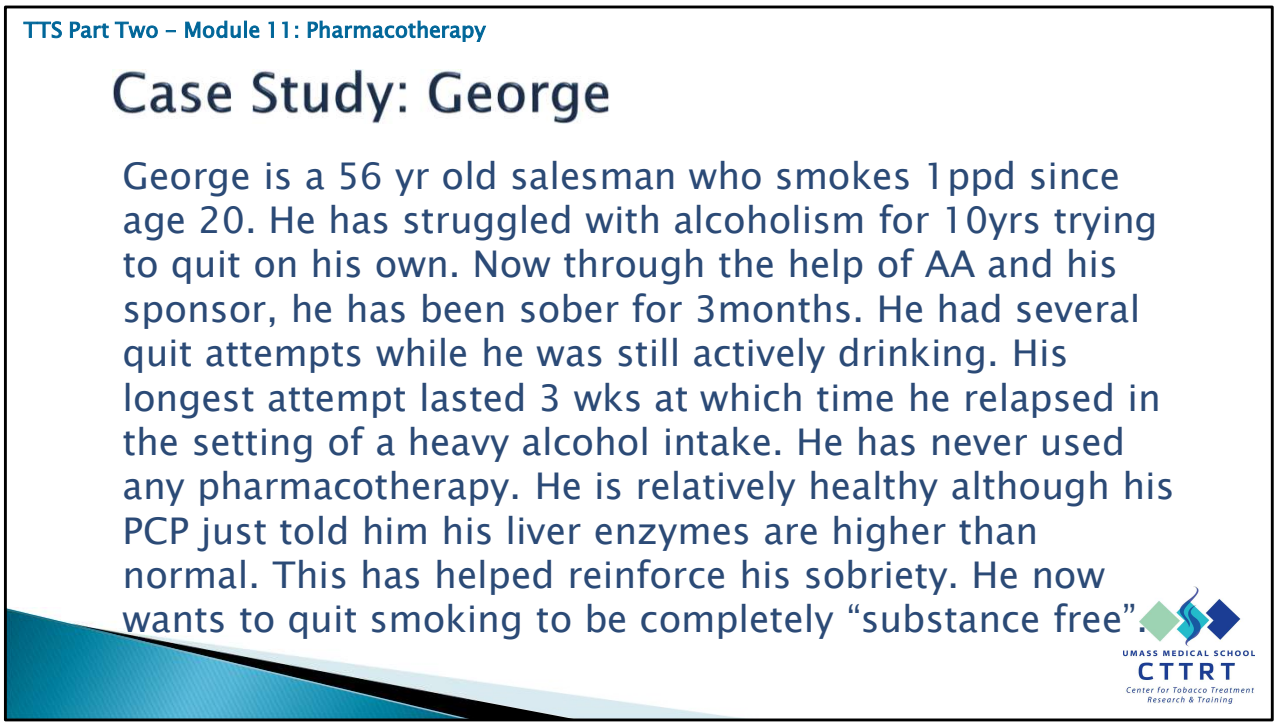
Let's discuss a couple of cases to look at this area of mental health and substance abuse.
Read the case study or ask participant to read aloud.

Invite the class ask more questions about Natalie that pertain to Agent, Patient or Medical factors in decision making. As the instructor, you will pretend you are Natalie and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- Again, there are no right or wrong recommendations
- Discuss lack of knowledge of content of ENDS devices and variability between devices as well as lack of evidence supporting efficacy for cessation.
- Hopefully, the discussion will include some of these concepts:
    - She needed more NRT….If she is to use that, she needs at least 21mg patch plus prn short acting. An alternative would be wearing more than 1 patch (21 plus 14 mg).
    - If her mental health becomes more stable or if her provider concurs, varenicline may be an option
    - Perhaps bupropion plus NRT. Of course her md would need to be involved. There is an interaction between fluoxetine and bupropion; fluoxetine blood concentrations may be increased.
- Encourage re-engaging in therapy, and other support systems-

groups, quitlines, etc.

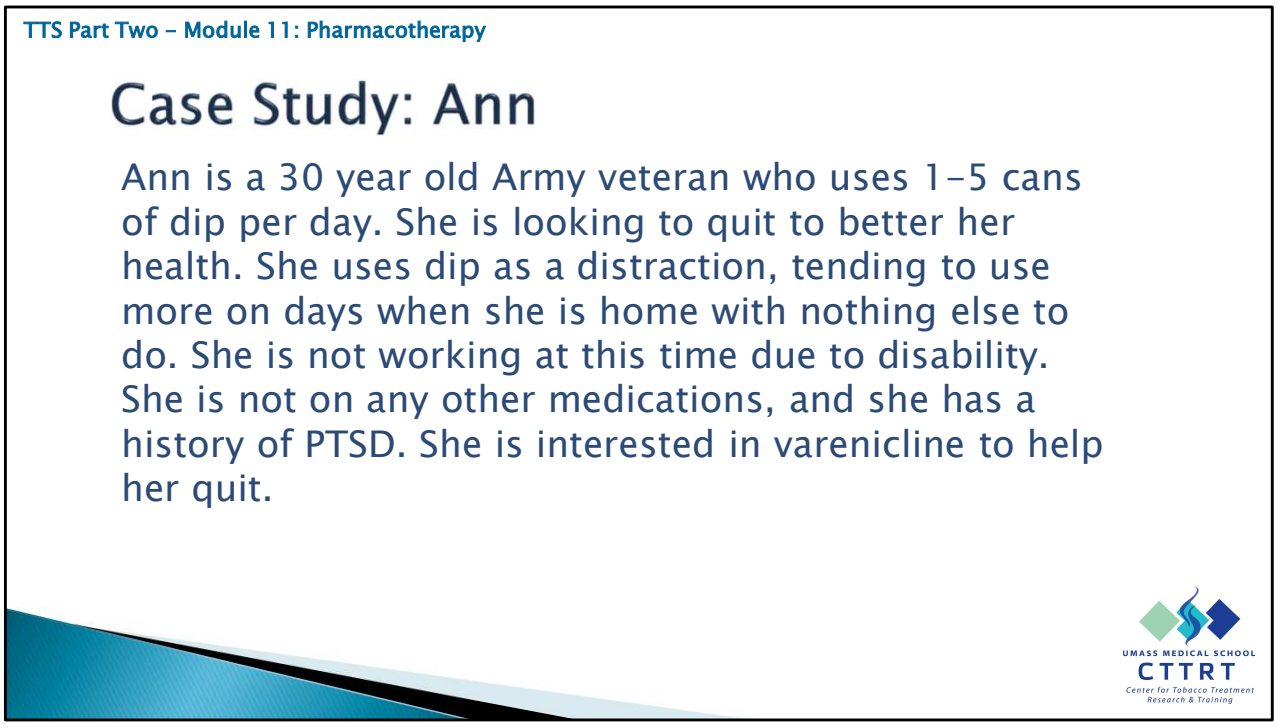
Time goal of 2 cases= 15”



Read the case study or ask participant to read aloud.

Invite the class ask more questions about George that pertain to medication, Patient or Medical factors in decision making. As the instructor, you will pretend you are George and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- Discuss how wanting to be "substance free" may affect his view of medications
- Bupropion would not be an initial choice due to elevated liver enzymes and recent history of alcohol abuse and relapse. Patient is at risk for seizures, too.
- Encourage combo NRT
- Consider varenicline (excreted through the kidney, not the liver). Note that varenicline can increases sensitivity to alcohol.



Read the case study or ask participant to read aloud.

Invite the class ask more questions about Ann that pertain to medication, Patient or Medical factors in decision making. As the instructor, you will pretend you are Ann and can answer any way you like. If there is time after providing more information have class discuss in small groups and provide a recommendation.

- Discuss varying nicotine exposure given variation in dip use.
- PTSD presents in a variety of ways, so it would be good to investigate further.
- Consider varenicline as this is patient preference and has been shown as effective.
- High dose patch per Mayo clinic recommendations; zyban is also an option
- Lozenge high dose would be useful as well, given administration mode.

TTS Part Two – Module 11: Pharmacotherapy

Summary

- FDA has approved 7 first line medications to use in smoking cessation
- Use of combination therapy is increasing
  - Combo NRT use may be more effective for highly addicted patients
  - Those with psych history first try combination NRT

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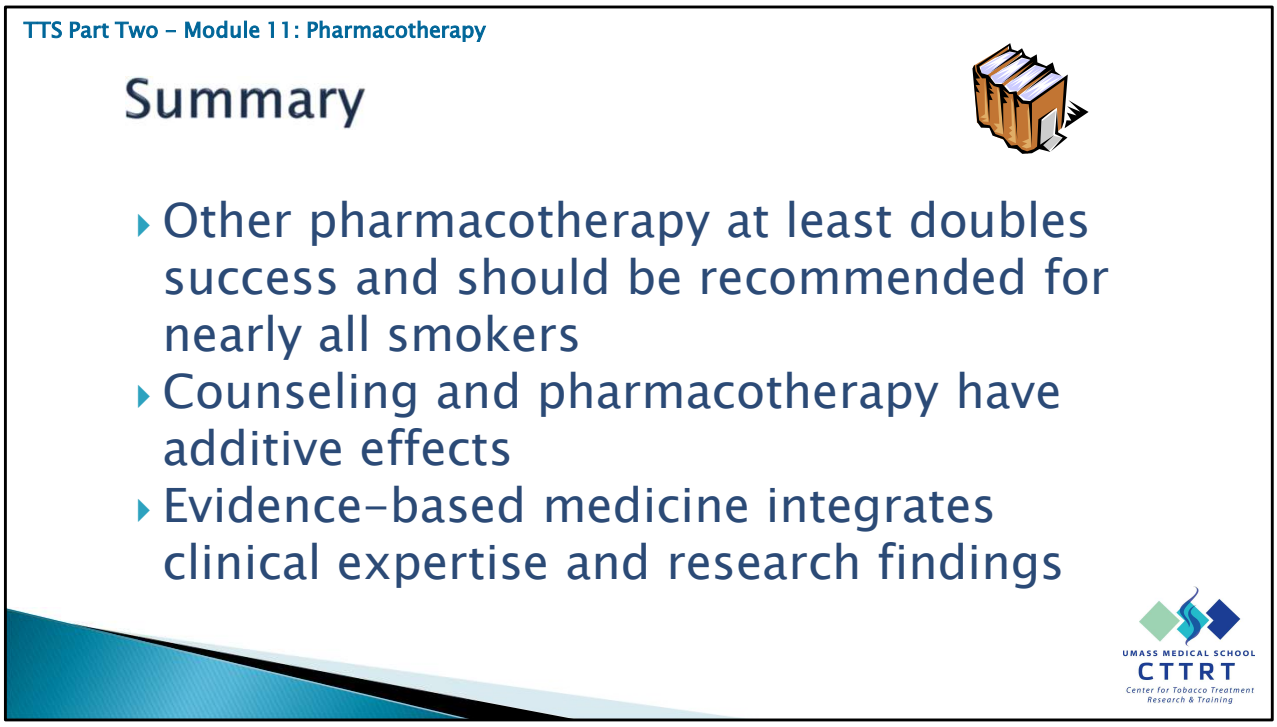
KEY POINTS:

- Meds more than double one's chance for success
- Combination therapy is quickly becoming a standard for many. Although some data has shown it to have the same efficacy as Chantix or monotherapy. It may be best to use for patients with high levels of addiction or report high levels of cravings.



KEY POINTS:

- Meds more than double one's chance for success
- The gold standard = counseling + meds. Consistently across studies the use of both pharm and non-pharm therapy have been proven to be better than either alone. This makes since given the biopsychosocial model of tobacco addiction.

KEY POINTS:

- Consider several factors with each individual
- Choice of therapy may vary according to the underlying medical conditions. Some medical conditions may exclude some of the meds
- Those with mental health/substance abuse history may need more aggressive therapy and for longer duration
- Let the individual be “the captain”. Their preference (after education about meds) most often will drive the recommendation