Learning Objectives

• Increase knowledge and awareness of FDA approved tobacco treatment pharmacotherapies
• Understand interactions between tobacco smoke and psychiatric medications
• To understand key aspects of tobacco assessment necessary for developing treatment plans
• To identify barriers related to the use of tobacco treatments in behavioral health treatment settings

Assessment

• Level of Tobacco/Nicotine Dependence
• Motivation to Quit
**Tobacco Use Disorder**

Most tobacco users are addicted (2 or more)
- withdrawal
- tolerance
- desire or efforts to cut down/ control use
- great time spent in obtaining/using
- reduced occupational, recreational activities
- use despite problems
- larger amounts consumed than intended
- Craving; strong urges to use

**Tobacco Withdrawal**

Emerge hours after last cigarette
Can last for (4) weeks

Depressed mood
Insomnia
Irritability, frustration or anger
Anxiety
Difficulty concentrating
Restlessness
Increased appetite or weight gain
Heaviness of Smoking Index=
Measure of Dependence

Number of cigarettes per day (cpd)

AM Time to first cigarette (TTFC)
\[\leq 30 \text{ minutes} = \text{moderate}\]
\[\leq 5 \text{ minutes} = \text{severe}\]

Heatherton 1991

Smokers with depression smoke more cpd and are more dependent

Smokers in NJ Addiction Treatment are Moderately to Severely Addicted to Nicotine

N=1882 smokers in NJ addictions treatment, 2001-2002;
Williams et al., 2005
80% of Smokers with SMI report smoking within 30min of awakening

![Bar chart]

N=100

Williams et al. CMHJ 2010

Individuals with schizophrenia highly addicted

![Graph]

4 minute Nicotine Boost (ng/mL)

25.2 vs. 11.1; p<0.01

Greater nicotine intake per cigarette

Williams NTR 2010

NRT and Agitation in Smokers With Schizophrenia:

- 40 smokers in psych ER
- 21mg patch vs placebo patch
- Usual care for psychosis
- Agitated Behavior was 33% less at 4 hours and 23% ↓ at 24 h for NRT group
- Better response in lower dependence
- Same magnitude of response as antipsychotic studies

Allen 2011; Am J Psych
Reduced Success Quitting in Smokers with Anxiety Disorders

More withdrawal symptoms

panic, social anxiety or GAD

Piper et al., 2010

Smokers with MI or SMI
Reduced Quitting over Lifetime

E= N x S

Exsmokers = (number trying to quit) x (success of attempts)

Smokers with mental illness = anxiety, MDE, PTSD, psychoses, bipolar, drug dependence
SMI= measured by K6

Hagman 2007; McClave 2010; Lasser 2000; Pratt & Brody 2010

READINESS to QUIT in SPECIAL POPULATIONS

Intend to quit in next 6 mo  Intend to quit in next 30 days

General Population 40% 20%
General Psych Outpts 43% 28%
Depressed Outpatients 55% 24%
Psych. Inpatients 43% 24%
Methadone Clients 48% 22%

* No relationship between psychiatric symptom severity and readiness to quit

Smokers with mental illness or addictive disorders are just as ready to quit smoking as the general population of smokers.

Slide Courtesy J Prochaska; Acton 2001; Prochaska 2004; Prochaska 2006; Nahvi 2006
Access to Clinical Treatment

- Engaging Smokers
  - Motivational Techniques
- Wellness Curriculum
  - Learning about Healthy Living
- Adapted Cessation
  - High Levels of Dependence
  - Aggressive Medications and Counseling

Pharmacological Treatment

Rationale
- Reduce or eliminate withdrawal
- Block reinforcing effects of nicotine
- Manage negative mood states
- Unlearn smoking behaviors
- Cost-effective treatment
- Lessen/delay weight gain

Hard to Quit Without Treatment

70% of smokers report wanting to quit someday
Few people quit successfully without treatment
Only 1/3 of quitters (without treatment) remain abstinent for 2 days
< 5% ultimately successful on a given quit attempt
Need for Pharmacotherapy

- First line treatment/ recommended all smokers
- Comfortable detox for temporary abstinence
- Higher levels of nicotine dependence
- Risk benefit ratio supports NIC > TOB
- Psychiatric inpatients not given NRT were > 2X likely to be discharged from the hospital AMA

Fiore 2008; Prochaska 2004

Pharmacological Treatment
FDA Approved

Nicotine Replacement (NRT)
- Patch
- Gum
- Lozenge
- Inhaler
- Nasal Spray
- Counseling +
- Medications =
- Best treatment plan
- Bupropion
- Varenicline

Nicotine Medications
- Not a carcinogen
- Use high enough dose
- Scheduled better than PRN
- Use long enough time period
- Can be combined with bupropion
- Can be combined with each other
- Have almost no contraindications
- Have no drug-drug interactions
- Not introducing a “new drug”
Nicotine Replacement

- Smokers misinformed about safety/efficacy
- Risk-benefit ratio nicotine > tobacco

Few Contraindications to NRT

OTC labeling
With caution if:
- Recent MI
- Smokes < 10 cpd
- Pregnant/breastfeeding
- Adolescents (Not FDA approved)

Mild side effects
- Mostly local
- Systemic, less common

Nicotine Patch

- Slow onset of action
- Continuous nicotine delivery
- 24 or 16 hour dosing
- Easy, good compliance
- No strict tapering or timeline
- Side effects- skin reaction, insomnia
- OTC
Nicotine Gum
Use every 1 hour
Bite and “park” method
Slow, buccal absorption
Acidic foods ↓ absorption
Side effects- mouth, throat burning
Dose: 2mg < 25 cpd
  4mg > 25 cpd
OTC

Nicotine Lozenge
Don’t chew
2 and 4mg dose
More discreet than gum
Up to 20 lozenges/ daily
Dose based on TTFC
  2mg if > 30 mins TTFC
  4 mg< 30 mins TTFC
OTC; Mini lozenge

Nicotine Inhaler
6-16 cartridges/day
Puff for 20-30 minutes
Oral puffer
Acidic beverages decrease absorption
Side effects- throat irritation or coughing
Rx needed
First-line Treatments
(FDA Approved)

- **Nicotine Replacement**
- **Bupropion**
  - Zyban/ Wellbutrin
- **Varenicline**
  - Chantix

Bupropion SR

- Start 150mg/day to dose of 150mg bid
- Nonsedating, activating antidepressant with effects on NE and DA systems
- Start 10-14 days prior to quit date
- Side effects- headache, insomnia
- Contraindicated in h/o seizures or bulimia
- Noncompetitive nicotinic receptor antagonist
- Similar efficacy to NRT

  *Slemmer 2000*

Bupropion Effective in Schizophrenia

- 8 published studies vs placebo
- Although 6 month outcomes of bupropion treatment are similar whether or not NRT was given concomitantly
- Shorter outcomes (4 weeks of continuous abstinence (CA) measured 8 weeks after TQD), bupropion plus NRT yielded quit rates which are the highest ever reported in SS
  - 28 % CA (George 2008)
  - 52% CA (Evins 2007).

  *Tsou 2013; Dixon 2010*
Combination Therapies
Improves abstinence rates
Decreased withdrawal
Well tolerated

Kornitzer 1995

Number of medications predicted abstinence in a tobacco clinic

A randomized placebo-controlled clinical trial of five smoking cessation pharmacotherapies
• 1504 smokers
• 5 treatments and 5 placebo groups
  – nicotine lozenge
  – nicotine patch
  – bupropion SR
  – nicotine patch + nicotine lozenge
  – bupropion + nicotine lozenge

Piper et al., 2009

Steinberg MB et al., 2006
Smoking with NRT

- Relatively safe
- Harm Reduction
- Less reinforcing effects
- Withdrawal of treatment = punishment for relapsing

Cut Down To Quit (CDTQ)

- NRT previously licensed in the UK for quitting have recently been granted a new licensed indication called ‘cut down to quit’ (CDTQ).
- Aims at smokers unwilling or unable to stop smoking in the short term
- Gradually to cut down smoking over an extended period while taking NRT
- Gum and inhaler

Wang et al., 2008
**NRT Assisted Reduction**

- 7 Smoking Reduction trials (four Nicotine gum, two inhaler, and one free choice NRT)
- 2767 smokers
- NRT for 6-18 months
- 6.75% of smokers receiving NRT had sustained abstinence for six months, 2X more than those receiving placebo
- No statistically significant differences in adverse events and discontinuation because of adverse events except nausea — more with NRT

  *Whether smokers are motivated to reduce then quit or simply motivated to reduce may make little difference to the efficacy of NRT for smoking cessation*

  Moore et al., BMJ, 2009

**FDA Labeling Updates**

- No significant safety concerns associated with using more than one NRT
- No significant safety concerns associated with using NRT at the same time as a cigarette.
- Use longer than 12 weeks is safe

APRIL 2013

www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm

**Varenicline Summary**

- Selective a4B2 nicotinic receptor partial agonist
- No drug-drug interactions
- Precaution in ESRD
- Dosed with food to reduce nausea
Varenicline: a selective a4B2 nicotinic receptor partial agonist

Varenicline

Partial Agonist
- Partially stimulates receptor
- Some DA release at NAcc
- Prevents withdrawal

“Antagonist”
- Blocks nicotine binding a4B2

**Don’t use as combination

Chantix™ (varenicline) Phase 3 Studies: Efficacy Measurements: CO-Confirmed 4-Wk Continuous Abstinence Rates Wks 9–12

The 4-Wk period of continuous abstinence is defined as the percentage of subjects who abstained from smoking not even a puff from Week 9 through 12 of the study as confirmed by both subject self-report and by end-expiratory carbon monoxide CO3 measurements.

The most frequently reported adverse events (>10%) with Chantix were nasopharyngitis, headache, insomnia, and abnormal dreams.
Varenicline vs Nicotine Patch
- Open label (N=776)
- 12 Week varenicline vs 10 week NP
- Nausea: varenicline (37%) > NP (10%)

Aubin et al., 2008

Continuous Abstinence, Week 9-12

Week 52

Varenicline Labeling Updates
- Warning (Reported with Chantix)
  - Observe patients for serious neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal thoughts or behavior
  - Worsening of preexisting psychiatric illness
  - Causal relationship not established
  - Clinical trials (N>5000; SI rate = placebo)
  - Sleep disturbance/ vivid dream

www.PfizerPRO.com/chantix

Varenicline and Suicide
- 80,660 smokers prescribed NRT (~63k), varenicline (~11k), and bupropion (~6k), UK, primary care
- Compared with NRT, the hazard ratio for self harm among people prescribed varenicline was 1.12 (95% CI 0.67 to 1.88), and it was 1.17 (0.59 to 2.32) for people prescribed bupropion.
- No clear evidence that varenicline was associated with an increased risk of fatal (n=2) or non-fatal (n=166) self harm
- No evidence that varenicline was associated with an increased risk of depression or suicidal thoughts

Gunnell et al., 2009; BMJ
Bupropion Adverse Effects

- French dataset: 700,000 patients
- 1682 cases of adverse reactions were reported
  - 1/3 of these involved SAR
  - Allergic reactions (31.2%), including angioedema and serum sickness-like reactions.
  - Serious neurological reactions were frequent (22.5%), mostly comprising seizures; almost half of these patients had history seizures or other risk factors.
  - Serious neuropsychiatric adverse events reported (17.3%), suicide attempts/suicides were a cause for concern, although risk factors (history of depression, suicide attempts, etc.) were described for 66% of patients experiencing these events.

Beyens et al., 2008

Black Box Warnings

- Antidepressants- suicidal ideation in children
- Lithium - toxicity
- Divalproex (Depakote) – hepatic failure
- Carbamazepine (Tegretol)- aplastic anemia
- Lamotrigine (Lamictal) – Toxic epidermal necrolysis
- Bupropion (Wellbutrin)- serious allergy, seizure
- Methylphenidate (Ritalin/ Concerta)
- Clozapine (Clozaril) agranulocytosis
- Antipsychotics– mortality elderly dementia-psychosis

http://blackboxrx.com/index.php

Safety and Efficacy of Varenicline for Smoking Cessation in Patients with Schizophrenia and Schizoaffective Disorder

Randomized, placebo-controlled, double-blind, multicenter study (conducted in USA/ Canada)

- 12-week treatment phase
- 12-week non-treatment follow-up

Screened: N=214

<table>
<thead>
<tr>
<th>Randomization</th>
<th>2:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Varenicline 1 mg BID starting with 1-week titration (0.5 mg QD x 10 days, 0.5 mg BID x 4 days)</td>
<td></td>
</tr>
</tbody>
</table>

Assessments: CGI-I, CGI-S, CSSRS, AEs, NUI, PANSS
7-Day Point Prevalence of Abstinence from Smoking

At Weeks 12 and 24

By week

Week 12

Week 24

OR: 6.18
95% CI: 0.75, 50.71
P=0.09

OR: 4.74
95% CI: 1.03, 21.78
P=0.046

PANSS by Week Mean Score (Total and Sub-scales)

Mean baseline total score:
Varenicline: 55.8
Placebo: 54.4

No significant changes in PANSS from baseline in any treatment arm in total score or sub-scores

General and Neuropsychiatric AEs

The most common AEs in participants taking varenicline were:
- Nausea (23.8% vs. 14.0% on placebo)
- Headache (10.7% vs. 18.6% on placebo)
- Vomiting (10.7% vs. 9.3% on placebo)

Treatment-emergent neuropsychiatric AEs reported in ≥5% of participants in either treatment group:

<table>
<thead>
<tr>
<th>AEs</th>
<th>Varenicline (%)</th>
<th>Placebo (%)</th>
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</thead>
<tbody>
<tr>
<td>Abnormal dreams</td>
<td>7.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Irritability</td>
<td>6.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>6.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.8</td>
<td>6.3</td>
</tr>
<tr>
<td>Depression</td>
<td>4.8</td>
<td>7.0</td>
</tr>
</tbody>
</table>

There was one suicide attempt by a varenicline patient with a lifetime history of similar attempts.
Medication Interactions with Tobacco Smoke

- Smoking ↑ P450 enzyme system
- Polynuclear aromatic hydrocarbons (tar)
- ↑ 1A2 isoenzyme activity
- Smoking ↑ metabolism of meds
  - ↓ serum levels
- Smokers on higher medication doses

Drugs Reduced by Smoking

Antipsychotics
- Olanzapine, Clozapine
- Fluphenazine, Haloperidol, Chlorpromazine

Antidepressants
- Amitriptyline, doxepin, clomipramine, desipramine, imipramine, Fluvoxemine

Others
- Caffeine, theophylline, warfarin, propranolol, acetaminophen

Desai et al., 2001; Zevin & Benowitz 1999

Quitting Smoking

- Risk for medication toxicity
- May ↑ levels acutely
- Consider dose adjustment
- Clozapine toxicity
  - Seizures
- Reduce caffeine intake

- Nicotine (or NRT) Does Not Change Medication Levels

- Nicotine metabolized by CYP2A6
Conclusions

• Smokers with addictions and mental illness comorbidity need increased access to tobacco treatments
• Usual treatments work although efficacy can be reduced
• Important interactions between tobacco smoke and psychiatric medications
• Varenicline more effective than other treatments
• Combinations more effective

References
