Treatment of Tobacco Use Disorder in Primary Care

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Jill M. Williams Disclosures

• Grant Support from Pfizer
• Grant Support from NCI, NIDA, NIMH, NJDMHAS, ABPN
• Consultant and Speaker for American Lung Association

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.
Target Audience

• The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.
Educational Objectives

• Statement of Need: Although tobacco use rates are declining, smoking is still a leading cause of preventable death and rates are higher in low income and behavioral health populations.

• At the conclusion of this activity participants should be able to:
  ▪ Recognize the effect of toxicity from combustible tobacco
  ▪ Identify the available quick forms of clinical assessment, including the utility of the Time to First Cigarette measure (TTFC)
  ▪ Demonstrate knowledge of pharmacotherapies for tobacco use disorder treatment, highlighting the safety and efficacy of each
  ▪ Describe nicotine replacement treatment dosing and how to enhance its effectiveness in patients
  ▪ Review the role of counseling in increasing the success of quit attempts and describe the Ask, Advise and Refer model for Primary Care
Tobacco = #1 Cause of Preventable Death in US

30% of all cancer deaths

It’s the Smoke that Kills

- **Cigarette smoke > 7000 compounds**
  - Acetone, Cyanide, Carbon Monoxide, Formaldehyde

- **>65 Carcinogens**
  - Benzene, Nitrosamines
Sources of Tobacco Toxins

Nicotine; nitrosamines

More than 600; Ammonia, cellulose acetate; flavors

Thousands; carbon monoxide; formaldehyde; benzene; arsenic, lead; polycyclic aromatic hydrocarbons

CDC 2014
Tobacco Associated Problems

- Barrier to Recovery
- Financial Hardships
- More Employment Difficulties
- More Housing Difficulties
- Poorer Mental Health
- More Relapse to Drugs and Alcohol
- Social Stigma
- Poorer Appearance
- More Fires in Home
# Improved Mental Health with Quitting Smoking

Meta-analysis 26 studies (gen pop and mental health)

## Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of studies included</th>
<th>No of studies excluded</th>
<th>Standardised mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>0</td>
<td>-0.37 (-0.70 to -0.03)</td>
</tr>
<tr>
<td>Depression</td>
<td>9</td>
<td>1</td>
<td>-0.29 (-0.42 to -0.15)</td>
</tr>
<tr>
<td>Mixed anxiety and depression</td>
<td>4</td>
<td>1</td>
<td>-0.36 (-0.58 to -0.14)</td>
</tr>
<tr>
<td>Psychological quality of life</td>
<td>4</td>
<td>4</td>
<td>0.17 (-0.02 to 0.35)</td>
</tr>
<tr>
<td>Positive affect</td>
<td>1</td>
<td>2</td>
<td>0.68 (0.24 to 1.12)</td>
</tr>
<tr>
<td>Stress</td>
<td>2</td>
<td>1</td>
<td>-0.23 (-0.39 to -0.07)</td>
</tr>
</tbody>
</table>

Taylor et al, 2014
Smoking is a Social Justice Issue

www.thetruth.com
Tobacco Use Disorder is in DSM-5. Therefore it is a Behavioral Health condition.
Smoking is Fastest Route of Drug Administration
Best Measure of Nicotine Dependence Severity

Heaviness of Smoking Index

• AM (upon awakening) Time to First Cigarette (TTFC)
  ▪ \( \leq 30 \text{ minutes} = \text{moderate} \)
  ▪ \( \leq 5 \text{ minutes} = \text{severe} \)

• Implications for Treatment Outcome
• Need for Medications
• Implications for dose

Heatherton 1991
Assessment of Carbon Monoxide

- CO = product of combustion
- Expired CO in smokers
  - > 10 parts per million (ppm)
- Displaces oxygen on RBCs
- Strain on heart
  - Risk factor for CVD
- Can be assessed with a meter
- Reversible effect
  - Normal levels 2-3 days (0-3ppm)
Tobacco Withdrawal Symptoms

Emerges hours after last cigarette
Can last up to (4) weeks

• Depressed mood
• Insomnia
• Irritability, frustration or anger
• Anxiety
• Difficulty concentrating
• Restlessness
• Increased appetite or weight gain
Limited Access to Tobacco Treatment

ASAM Levels of Care for SUD

~99% of tobacco treatment occurs ≤ level 1

Williams et al., JAM, 2016

1% Use Quitlines

Lichtenstein et al, 2010
## Limited Access to Tobacco Treatment

### Tobacco Related Policies and Practices (2016 data)

<table>
<thead>
<tr>
<th>Mental health treatment facilities (%)</th>
<th>Substance abuse treatment facilities (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>48.9</td>
<td>64.0</td>
<td>Reported screening patients for tobacco use</td>
</tr>
<tr>
<td>37.6</td>
<td>47.4</td>
<td>Offered tobacco cessation counseling</td>
</tr>
<tr>
<td>25.2</td>
<td>26.2</td>
<td>Offered nicotine replacement therapy</td>
</tr>
<tr>
<td>21.5</td>
<td>20.3</td>
<td>Offered non-nicotine cessation medications</td>
</tr>
<tr>
<td>48.6</td>
<td>34.5</td>
<td>Had a smoke free campus policy</td>
</tr>
</tbody>
</table>

Marynak et al., MMWR, 2018
Brief Interventions

2As and R (Ask, Advise and Refer)

• Do you use Tobacco?
  ▪ How much? What kinds?
  ▪ Document tobacco use at visits
• How do you feel about quitting?
• Can I give your name to someone to get more information?
Treatment for Tobacco Use Disorder Works

• Brief Assessment

• Counseling + Medications

• Approach like a Co-occurring Disorder

• “Treatment” not “Cessation”
Principles of Co-occurring Disorders Treatment

- Integrated mental health and addiction services
- Comprehensive services
- Treatment matched to motivational level
- Long-term treatment perspective
- Continuous Assessment of substance use
- Motivational interventions
- Psychopharmacology
- Case management
- Housing
Hard to Quit

- 55% make a serious quit attempt/year (>1d)
- <5% ultimately successful on a given quit attempt without treatment
- 6 month quit rates usually ~ 25% with treatment
Why so Hard to Quit?

- Smoking a drug is highly addicting

- Treatment options are limited
  - Few medication types
  - Limited (brief) counseling support
  - No levels of care

- Utilization of treatment is poor
  - Most don’t use counseling
  - Medications-too low dose, not enough time
Predictors of Abstinence

• Lower level of dependence
• Higher socioeconomic status: education, insured
• Older age
• No behavioral health comorbidity
• Fewer smokers in social networks
• Quit in first 7 days / # days quit
• Use of cessation treatment

Foulds et al., 2006; Ashare 2013; Twyman et al., 2017
## Counseling + Medications = Best Treatment Plan

Effectiveness of meds or counseling alone vs. combination

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No of Studies</th>
<th>Est Odds Ratio (95%cl)</th>
<th>Estimated Quit Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication alone</td>
<td>8</td>
<td>1.0</td>
<td>22</td>
</tr>
<tr>
<td><strong>Meds plus counseling</strong></td>
<td><strong>39</strong></td>
<td><strong>1.4 (1.2-1.6)</strong></td>
<td><strong>28</strong></td>
</tr>
<tr>
<td>Counseling alone</td>
<td>11</td>
<td>1.0</td>
<td>15</td>
</tr>
<tr>
<td><strong>Meds plus counseling</strong></td>
<td><strong>13</strong></td>
<td><strong>1.5 (1.3-2.1)</strong></td>
<td><strong>22</strong></td>
</tr>
</tbody>
</table>
Psychosocial Treatment

*Individual or Group*

- Skills training
- Relapse prevention
- Problem solving
- Coping skills
- Stress management

- Change cognitions about smoking
- Reinforce nonsmoking
- Avoid high risk situations
Quitline

- Telephone counseling
- Toll-free / state funded
- Assessment
- 4 follow-up calls
- Good for transportation issues
- Scheduled calls from tobacco specialist
- Good success rate in smoking cessation
Maximizing Social Support

- **Intra-treatment support**
  - GROUP members
  - Clinician

- **Extra-treatment**
  - Friends
  - Family
  - Self-help
  - Internet

Both ↑ success in making a quit attempt
Pharmacological Treatment

• Rationale
  ▪ Cost-effective
  ▪ Reduce or eliminate withdrawal
  ▪ Lessen/delay weight gain
  ▪ Block reinforcing effects of nicotine

Increases chances of successful quit 2-3X
First-line Treatments (FDA Approved)

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

Counseling + Medications = Best treatment plan
Pharmacological Treatment

• Nicotine Replacement Therapy (NRT)
  ▪ Patch
  ▪ Gum
  ▪ Lozenge
  ▪ Inhaler
  ▪ Nasal Spray

Available OTC, but may be covered with prescription with state Medicaid*
Nicotine Medications

- 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
- Safe enough to be OTC
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
Summary:

- Low risk of harm
- Benefits outweigh low risk of serious adverse cardiovascular events associated with use of tobacco treatment medications
Nicotine Patch

- Slow onset of action
- Continuous nicotine delivery
- 24 or 16 hour dosing
- Usual dose 21 mg/day
- Easy, good compliance
- No strict tapering or timeline
- Side effects – skin reaction, insomnia
- OTC
Oral Forms of Nicotine

- Dose frequently – every 1-2 hours
- Slow, buccal absorption
- Acidic foods ↓ absorption
- Mild side effects – mouth, throat burning
- GI upset if swallowed (bite and park gum)
- Rx for Nicotine Inhaler
Prescription Nicotine

- **Nicotine Nasal Spray**
  - Rapid delivery though nasal mucosa
  - Most side effects (nasal irritation, rhinitis, coughing, watering eyes)
  - 2 sprays = 1 dose; up to 40 doses/day
  - Some dependence liability

- **Nicotine Inhaler**
  - 6-16 cartridges/day
  - Puff for 20-30 minutes
  - Oral puffer
  - Acidic beverages decrease absorption
  - Mild side effects – throat irritation or coughing
Smoking with NRT

- Relatively safe (nausea)
- Harm reduction
- Less reinforcing effects
- Withdrawal of treatment = punishment for relapsing
- In unmotivated smokers, 7% quit

LeHouezec et al., 2011; Kozlowski et al., 2007; Zapawa 2011
Bupropion SR

- Effective at 150 to 300mg daily
- 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/ anorexia
- Noncompetitive nicotinic receptor antagonist
- Similar efficacy to NRT
- Effect independent of depression
- Less weight gain with 300mg than placebo

Hughes 2007; Slemmer 2000
Combination NRT

- Long acting (patch) + short acting (gum/lozenge/inhaler)
- Delivers higher dose
- Immediate withdrawal and craving relief

Carpenter et al., 2013

<table>
<thead>
<tr>
<th>References</th>
<th>Combination NRT</th>
<th>Controla</th>
<th>Total N</th>
<th>Treatment duration</th>
<th>Relative risk</th>
<th>Longest follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piper et al. [89]</td>
<td>Patch + lozenge</td>
<td>Patch, lozenge</td>
<td>789</td>
<td>8 weeks (patch); 12 weeks (lozenge)</td>
<td>1.2 (vs. patch)</td>
<td>6 months (see left)</td>
</tr>
<tr>
<td>Smith et al. [90]</td>
<td>Patch + lozenge</td>
<td>Patch, lozenge</td>
<td>822</td>
<td>8 weeks (patch); 12 weeks (lozenge)</td>
<td>1.2 (vs. lozenge)</td>
<td>6 months (see left)</td>
</tr>
<tr>
<td>Puska et al. [92]</td>
<td>Gum + patch</td>
<td>Gum + placebo patch</td>
<td>300</td>
<td>18 weeks (patch); 12 months (gum)</td>
<td>1.3</td>
<td>1.4 (52 weeks)</td>
</tr>
<tr>
<td>Kernitzer et al. [93]</td>
<td>Patch + gum</td>
<td>Patch + placebo gum</td>
<td>299</td>
<td>24 weeks</td>
<td>1.8</td>
<td>1.4 (52 weeks)</td>
</tr>
<tr>
<td>Cooney et al. [94]</td>
<td>Patch + gum</td>
<td>Patch + placebo gum</td>
<td>96</td>
<td>12 weeks (patch); 24 weeks (gum)</td>
<td>1.7</td>
<td>See below4</td>
</tr>
<tr>
<td>Blondal et al. [95]</td>
<td>Patch + spray</td>
<td>Patch + placebo spray</td>
<td>239</td>
<td>5 months (patch); 1 yr (spray)</td>
<td>2.0</td>
<td>1.9 (6 years)</td>
</tr>
<tr>
<td>Croghan et al. [96]</td>
<td>Patch + spray</td>
<td>Patch, spray</td>
<td>1,384</td>
<td>6 weeks</td>
<td>1.2 (vs. patch); 1.3 (vs. spray)</td>
<td>6 months (see left)</td>
</tr>
<tr>
<td>Botadana et al. [97]</td>
<td>Inhaler + patch</td>
<td>Inhaler + placebo patch</td>
<td>400</td>
<td>26 weeks (inhaler); 6 weeks (patch)</td>
<td>1.1</td>
<td>1.4 (52 weeks)</td>
</tr>
<tr>
<td>Tonnesen et al. [98]</td>
<td>Inhaler + patch</td>
<td>Inhaler, patch</td>
<td>337</td>
<td>Up to 9 months</td>
<td>0.6 (vs. patch); 0.7 (vs. inhaler)</td>
<td>(12 months)</td>
</tr>
</tbody>
</table>

Carpenter et al., 2013
Combination Therapies

- Improve abstinence rates
- Decrease withdrawal
- Well tolerated

<table>
<thead>
<tr>
<th>Therapy Combination</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch + gum or spray</td>
<td><strong>1.9</strong> (1.3-2.7)</td>
</tr>
<tr>
<td>Patch + bupropion</td>
<td><strong>1.3</strong> (1.0-1.85)</td>
</tr>
</tbody>
</table>

Varenicline and NRT **NOT** recommended
Varenicline Summary

- a4B2 partial nicotinic agonist
- No drug-drug interactions
- Excreted by kidney (urine)
- Only precaution in severe kidney disease (reduced dose)
Varenicline: A selective α4β2 nicotinic receptor partial agonist
Varenicline

• Partial Agonist
  ▪ Partially stimulates receptor
  ▪ Some dopamine release at nucleus accumbens
  ▪ Prevents withdrawal

• “Antagonist”
  ▪ Blocks nicotine binding a4B2
Most Common Varenicline Side Effects

- Nausea
- Insomnia
- Abnormal dreams
- Constipation
- Flatulence
- Vomiting

Dosed twice a day with food to reduce nausea

Increasing dose in week one to 1mg BID
Effectiveness of First Line Medications

Results from meta-analyses comparing to placebo (6 month F/U)

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. Studies</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nic. Patch (6-14 wks)</td>
<td>32</td>
<td>1.9</td>
<td>1.7-2.2</td>
</tr>
<tr>
<td>Nic. Gum (6-14 wks)</td>
<td>15</td>
<td>1.5</td>
<td>1.2-1.7</td>
</tr>
<tr>
<td>Nic. Inhaler</td>
<td>6</td>
<td>2.1</td>
<td>1.5-2.9</td>
</tr>
<tr>
<td>Nic. Spray</td>
<td>4</td>
<td>2.3</td>
<td>1.7-3.0</td>
</tr>
<tr>
<td>Bupropion</td>
<td>26</td>
<td>2.0</td>
<td>1.8-2.2</td>
</tr>
<tr>
<td>Varenicline (2mg/day)</td>
<td>5</td>
<td>3.1</td>
<td>2.5-3.8</td>
</tr>
</tbody>
</table>

2008 PHS Guideline Update; Hartmann-Boyce et al., 2013
Varenicline and Neuropsychiatric Side Effects

- Meta analysis 39 RCT (10,761 participants)
- Study not sponsored by Pfizer
- Industry and non-industry funded studies

- **No** increased risk of suicide
- **No** increased risk of suicidal ideation
- **No** increased risk of depression
- **No** increased risk of irritability
- **No** increased risk of aggression
- Increased risk of sleep disorders
- Increased risk of insomnia
- Increased risk of abnormal dreams
- Reduced risk of anxiety

- Warning (OLD)
- Reported from case reports of individuals taking varenicline
  - Observe patients for serious neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal thoughts or behavior

Thomas et al., 2015; BMJ
Neuropsychiatric Safety and Efficacy

Varenicline, Bupropion, Nicotine Patch
Smokers with and without Psych Disorders (EAGLES)

- 8144 (4416 psych and 4028, non psych by SCID)
- Triple dummy (DB-PC) x 12 weeks
  - Nicotine patch 21mg (NP)
  - Varenicline 1 mg BID
  - Bupropion 150 mg BID (BUP)
- Largest smoking cessation study
- 33% lifetime suicidal ideation (12% behavior); 50% on psych meds
  - 70% depression/bipolar
  - 20% anxiety d/o
  - 10% psychotic
  - 1% personality disorder
- Brief weekly counseling
- Funded Pfizer and Glaxo (GSK)

Anthenelli et al., Lancet 2016
Varenicline superior to BUP and NP in psych and nonpsych cohorts

Anthenelli et al., Lancet 2016
Neuropsychiatric Composite

Side Effect Measure

- Anxiety/panic
- Depression
- Feeling abnormal
- Hostility
- Agitation
- Aggression
- Delusions
- Hallucinations/paranoia/psychosis
- Homicidal ideation
- Mania
- Suicidal ideation or behavior
Rates of Neuropsychiatric Adverse Events

Varenicline ➤ Side effects: Nausea, insomnia, abnormal dreams, headaches

Anthenelli et al., Lancet 2016
FDA Approves **Removal** of Boxed Warning Regarding Serious Neuropsychiatric Events from CHANTIX® (varenicline) Labeling

- Based on a U.S. Food and Drug Administration (FDA) review of a large clinical trial that we required the drug companies to conduct, 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 results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines (December 2016)

http://www.fda.gov/Drugs/DrugSafety/ucm532221.htm
Varenicline and Alcohol

- a4B2 may modulate rewarding effects of alcohol
- Varenicline reduces alcohol consumption and craving
  - In heavy drinkers
  - In smokers trying to quit smoking
  - In lab studies of animals and humans

Erwin & Slaton, 2014; Mitchell JM et al., 2012
Smoking Reduction with Varenicline

- 52-week double blind placebo controlled study of 1,510 subjects who were not able/willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over 12 weeks
- Varenicline 1 mg BID (N=760) or placebo (N=750) for 24 weeks
- Subjects instructed to reduce cigarettes per day by 50% end of first four weeks of treatment, followed by further 50% reduction from week 4-8, with the goal of reaching complete abstinence by 12 weeks.

Ebbert et al., JAMA 2015
Reduction with Varenicline had a significantly \( \uparrow \) Quit Rate

Consider a gradual approach to quitting smoking for patients who are sure that they are not able or willing to quit abruptly.

Chantix Package Insert (on label)

Ebbert et al., JAMA 2015
Conclusions

• It’s the smoke that kills
• Approach tobacco use as a co-occurring disorder
• Ask, Advise, Refer
• Medications + counseling
• Think about medications for anyone TTFC < 30 mins
• Varenicline OR combination NRT two very good medication options
References

References


PCSS Mentor Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.

- PCSS mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medication-assisted treatment.

- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.

- No cost.

For more information visit: pcssNOW.org/mentoring
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague
A simple and direct way to receive an answer related to medication-assisted treatment. Designed to provide a prompt response to simple practice-related questions.

Ask Now
PCSS-MAT is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with the: Addiction Technology Transfer Center (ATTC); American Academy of Family Physicians (AAFP); American Academy of Neurology (AAN); American Academy of Pain Medicine (AAPM); American Academy of Pediatrics (AAP); American College of Emergency Physicians (ACEP); American College of Physicians (ACP); American Dental Association (ADA); American Medical Association (AMA); American Osteopathic Academy of Addiction Medicine (AOAAM); American Psychiatric Association (APA); American Psychiatric Nurses Association (APNA); American Society of Addiction Medicine (ASAM); American Society for Pain Management Nursing (ASPMN); Association for Medical Education and Research in Substance Abuse (AMERSA); International Nurses Society on Addictions (IntNSA); National Association of Community Health Centers (NACHC); National Association of Drug Court Professionals (NADCP), and the Southeast Consortium for Substance Abuse Training (SECSAT).

For more information: www.pcssNOW.org

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