Updates in the Treatment of Tobacco Use Disorder

PCSS-MAT, Smoking Cessation Leadership Center and American Psychiatric Association

Jill M Williams, MD
Professor Psychiatry
Director, Division Addiction Psychiatry
Robert Wood Johnson Medical School

Disclosures

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

US Smoking Prevalence

16 million smokers with current mental illness
~ 1/3 of 51 million smokers in US

NCS-R 2001-2003; Diagnoses using CIDI
Smoking Rates among Illicit Drug Users
Data from 1997 National Household Survey on Drug Abuse (n=16661)

Richter, et al. 2002

Smoking associated with Opioid Misuse

- Smokers 3X more likely to have past-year prescription opioid misuse vs. never smokers (men and women)
  
  Daily (AOR = 3.79); Intermittent (AOR = 3.12)

- Daily Smokers ~ 5X more likely met criteria for past-year opioid abuse/dependence, vs. never smokers (men and women)
  - Intermittent smokers ~ 3x

- Daily smokers high nicotine dependence 2.5X more likely to have past-year prescription opioid abuse/dependence (men and women)

Zale et al., NTR 2014

Causes of Death in Opioid Using Population

Veldhuizen et al., 2014

Veldhuizen et al., 2014

N=68,066 hospitalized in CA for opioid 1990-2005
Addressing Tobacco in SUD

- **TREATMENT** - No negative impact on SUD treatment
  - Same LOS
  - No worsening of craving or abstinence rates

- **POLICY** - No negative impact on SUD treatment
  - No early discharges
  - Clients interested in treatment
  - No reductions in admissions (NYOASAS)

- Smoking Cessation Interventions Provided during Addictions Treatment Associated with **A 25% INCREASED LIKELIHOOD OF LONG-TERM ABstinence FROM ALCOHOL AND ILLICIT DRUGS**

  Williams 2004; Reid et al., 2008; Prochaska JCCP 2004
**Tobacco Use Disorder**

Many 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, social activities
- use despite problems (interpersonal; physical)
- larger amounts consumed than intended
- use when physically hazardous
- craving; strong urges to use

*DSM-5*

---

**Tobacco Withdrawal**

Abrupt tobacco cessation or reduction

4 or more (in 24 hours)

Depressed mood
Insomnia
Irritability, frustration or anger
Anxiety
Difficulty concentrating
Restlessness
Increased appetite or weight gain

*DSM-5*

---

**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 Addiction Treatment are Moderately to Severely Addicted to Nicotine

Less than Half of US Substance Abuse Facilities Treat this Substance

Friedmann et al., JSAT 2008
Need for Pharmacotherapy in Tobacco Use and Behavioral Health

No reason not to use
NRT is not a “new drug”
First line treatment/ Recommended all smokers
Comfortable detox for temporary abstinence
Higher levels of nicotine dependence

Patients with SUD Quit Smoking Successfully

• H/o ETOH Just as likely to succeed in quitting smoking as other smokers
• Usual treatments effective
• Smokers learned skills in recovering from alcohol that helped them quit smoking

Hughes & Kalmann, 2006

First-line Treatments (FDA Approved)

• Nicotine Replacement
• Bupropion
  Zyban/ Wellbutrin
• Varenicline
  Chantix

Counseling + Medications
  = Best treatment plan
Pharmacological Treatment

Nicotine Replacement
- Patch: Available OTC but may be covered with prescription with state Medicaid
- Gum
- Lozenge
- Inhaler
- Nasal Spray
- 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
- Safe enough to be OTC

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

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

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
Rx needed

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**: a selective a4B2 nicotinic receptor partial agonist

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

- **“Antagonist”**
  - Blocks nicotine binding a4B2

---

**Varenicline**

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

- **“Antagonist”**
  - Blocks nicotine binding a4B2

No drug-drug interactions
Excreted by kidney (urine)
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% Cl</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>

Varenicline Labeling Updates

- Warning
  - 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


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

Thomas et al., 2015; BMJ
Cardiovascular Review

SUMMARY:
Low risk of harm
Benefits outweigh low risk of serious adverse CVS events associated with use of tobacco treatment medications

Sharma et al., Curr Cardiology Reports (Review)
2015

Combination Therapies

Improve abstinence rates
Decrease withdrawal
Well tolerated

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch + gum or spray</td>
<td>1.9 (1.3 – 2.7)</td>
</tr>
<tr>
<td>Patch + bupropion</td>
<td>1.3 (1.0 – 1.8)</td>
</tr>
</tbody>
</table>

Fiore 2008

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

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

Varenicline - Major Depression
- 525 past h/o or stable, treated MDE; ≥10 cpd
- MADRS, HAM, C-SSRS, SBQ
- 73% on antidepressants (SSRI or SNRI)
- VAR More effective vs placebo
- Week 12 CAR: 35.9% vs 15.6% for placebo (OR 3.35; p<0.001)
- 24 and 52 week outcomes also significant

Anthenelli et al., Ann Int Med, 2013
No Worsening of Depression Scores

No difference in AEs (abnormal dreams, anxiety, agitation, restlessness, SI)

MADRS total scores mean change from baseline; Slight improvement in depression and anxiety in both groups

Studied in Methadone Maintenance

- 4 RCTs
- Motivated to quit/ reduce
- 35% patients quit on quit date
- Reduced quit rates from Varenicline or NRT (10% 7dPP 12 weeks)
- Lower medication adherence
- High rates personality disorders (poor emotion regulation)

Cubell et al., 2011; Tsukahara et al., 2010; DeDios 2014; Stein 2013; Cooperman in press

Other Medications

With Efficacy Data but not FDA Approved
- Nortriptyline
- Clonidine
- Cytisine (not available in US)

Not Shown to be Effective
- SSRIs
- Naltrexone
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 (Zyprexa)
- Clozapine (Clozaril)
- Fluphenazine, Haloperidol, Chlorpromazine, Perphenazine

Antidepressants

- Amitriptyline, doxepin, clomipramine, desipramine, imipramine, Fluvoxemine (Luvox)

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
### Medication Interaction Tobacco Treatments

- **Nicotine**
  - CYP2A6: None

- **Bupropion**
  - CYP2B6: Many
  - CYP2D6 inhibitor

- **Varenicline**
  - Excreted in urine: None

---

### Conclusions

Tobacco number one cause of death – mental health and addictions

Treatments increase the success rates and should be used in all smokers

Nicotine treatments are effective and well tolerated

Combinations improve outcomes

Varenicline greater efficacy than prior monotherapy treatments

**jill.williams@rutgers.edu**

---

### Resources


[http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf](http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf)

**Smoking Cessation Leadership Center (UCSF)**

[https://smokingcessationleadership.ucsf.edu/behavioral-health](https://smokingcessationleadership.ucsf.edu/behavioral-health)

Williams JM, Stroup S, Brunette MF, Raney L. Tobacco Use and Mental Illness: a Wake-up Call for Psychiatrists. Psychiatic Services 2014

TREATING TOBACCO DEPENDENCE IN BEHAVIORAL HEALTH SETTINGS 2 day CME/ CE Activity