Smoking, Mental Illness and Other Addictions

A Biopsychosocial Understanding of CoMorbidity

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Robert Wood Johnson Medical School
Learning Objectives

The participants will be able to:

- Discuss the high prevalence of tobacco use in persons with mental illness or other addictions.
- List the numerous medical and non-medical consequences of tobacco use in the population.
- Review evidence for treatment research in smokers with comorbidity including techniques for assessment and brief intervention.
- Identify barriers in the mental health system that makes it difficult for smokers to access tobacco dependence treatment.
Cigarette Smoking, Adults 18 Years and Over

I = 95% confidence interval. Note: Data are for persons who have smoked at least 100 cigarettes in lifetime and currently report smoking everyday or some days. American Indian includes Alaska Native. The categories black and white exclude persons of Hispanic origin. Persons of Hispanic origin may be any race. Respondents were asked to select one race prior to 1999. For 1999 and later years, persons were asked to select one or more races. Data for the single race categories shown are for persons who reported only one racial group. Data are age adjusted to the 2000 standard population. Data prior to 1997 are not strictly comparable with data for later years due to the 1997 questionnaire redesign.

SOURCE: National Health Interview Survey, CDC, NCHS.
Cigarette Smoking, Adults 18 Years and Over

2007

Age-adjusted percent

11.7 - 17.1
17.2 - 19.3
19.4 - 20.8
20.9 - 22.6
22.7 - 28.2

Note: Data are for persons who have smoked at least 100 cigarettes in lifetime and currently report smoking everyday or some days. Data are age adjusted to the 2000 standard population. Legend represents quintiles of the percents.

SOURCE: Behavioral Risk Factor Surveillance Survey, NCCDPHP, CDC.
Hardening Hypothesis

• Leveling in smoking prevalence 1990s
• Remaining smokers are more resistant to quitting
  – Increased dependence
  – Reduced cessation
• Smokers not being reached by TC messages
  – Poverty, low SES
  – Mental illness
• No current definitions of hardening include comorbidity of mental illness or addiction
Tobacco Priority/ Disparities Groups

- Disproportionate consumption
- Disproportionate consequences
- Disadvantaged group
- Limited access to tobacco-related health care
- Targeted marketing by the tobacco industry
Are Tobacco Control Techniques Targeting this Population?

- Prevention: None
- Treatment: State-level, minimal
- Policy/ Clean Indoor Air: Not known
- Surveillance and Research: NSDUH
- Price and Access: Not part of universal assessments
- Litigation against Tobacco Industry: Not known, None- None of MSA Funds
Current Smokers by Mental Illness History  

Lasser et al, JAMA, 2000

- 41% Past Month
- 35% Ever Ill
- 23% None
Three Fourths of Smokers have a Past or Present Problem with Mental Illness or Addiction

Lasser et al., 2000; Data from National Comorbidity Study
## Increased Smoking

<table>
<thead>
<tr>
<th></th>
<th>EVER/DAILY</th>
<th>HEAVY (&gt;25)</th>
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<tbody>
<tr>
<td>Maj Depression</td>
<td>X</td>
<td></td>
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<tr>
<td>Bipolar Disorder</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Panic/agoraphobia</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Alcohol Depend</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Drug Depend</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Hughes et al., 1986; Williams & Ziedonis, 2004*
<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Smoking</td>
<td>30.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Lifetime</td>
<td>71.3</td>
<td>59.9</td>
</tr>
</tbody>
</table>

Data from 2002 NSDUH

Hagman et al., 2007; Williams et al., in press
Increased severity of SPD ↑ likelihood of being a current smoker

2002 National Survey on Drug Use and Health
<table>
<thead>
<tr>
<th></th>
<th>%</th>
<th>AOR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– YES</td>
<td>26.0</td>
<td>1.82</td>
<td>(1.61-2.06)</td>
</tr>
<tr>
<td>– NO</td>
<td>44.9</td>
<td>1.0</td>
<td>referent</td>
</tr>
<tr>
<td><strong>Alcohol/ Drug Use Disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– YES</td>
<td>57.9</td>
<td>3.09</td>
<td>(2.78-3.45)</td>
</tr>
<tr>
<td>– NO</td>
<td>24.4</td>
<td>1.0</td>
<td>referent</td>
</tr>
</tbody>
</table>

Controlled for age, gender, race, education
### Nicotine dependence and SPD status according to the NDSS and FTND, NSDUH 2002

<table>
<thead>
<tr>
<th>SPD status</th>
<th>Weighted %</th>
<th>95% CI</th>
<th>Weighted %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicotine Dependence based on NDSS score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (SPD score ≥ 13)</td>
<td>49.7%</td>
<td>+ 3.67</td>
<td>33.3%</td>
<td>+ 1.39</td>
</tr>
<tr>
<td>No (SPD score &lt; 12.99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nicotine Dependence based on FTND score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (SPD score ≥ 13)</td>
<td>57.6%</td>
<td>+ 3.53</td>
<td>42.1%</td>
<td>+ 1.47</td>
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<tr>
<td>No (SPD score &lt; 12.99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nicotine Dependence in the past month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (SPD score ≥ 13)</td>
<td>66.5%</td>
<td>+ 3.24</td>
<td>49.5%</td>
<td>+ 1.48</td>
</tr>
<tr>
<td>No (SPD score &lt; 12.99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoked first cigarette within five minutes from waking</strong></td>
<td>29.2%</td>
<td>+ 3.61</td>
<td>19.3%</td>
<td>+ 1.29</td>
</tr>
</tbody>
</table>

*Hagman et al., Addict Behav. 2008*
81% of Smokers Seeking Cessation Treatment have Lifetime Co-morbidity

Piper et al., Addiction 2010

N=1504
Persons with a mental disorder/addiction in the past month purchase/consume 30-44% of cigarettes in the U.S.

Disproportionate consumption= disparity group

Is this group price sensitive?

Lasser et al, 2000; Grant et al., 2004
Tobacco excise taxes

- ↑ Price  ↑ Cessation and ↓ Initiation

- Smokers with mental illness are responsive to price, although the **price elasticities** may differ somewhat. (model controlled for poverty, stressful life events, and family history of addiction)

- Did not include level of dependence.

Saffer and Dave (2002)
Smokers with Serious Mental Illness may **not** be Price Sensitive

• Smoke more generic/ discount value brands vs controls \( (p < 0.01) \)

• Discount/generic cigarette use ↑ nationally from 6% (1988) to 26% (2004)

  Lower household income

  Higher cpd

  Lower cessation

(Maxwell Report 2004; Cummings et al., 1997; Harris & Chan, 1999)
Monthly Budget as a Percentage of Median Public Assistance Received
(N=68)

- 73% Food, Shelter, Misc. Living Expenses
- 27% Cigarettes

61% of Mental Health Consumers Report that Their Families Buy Them Tobacco
It’s the Smoke that Kills
Cigarette smoke > 4000 compounds
Acetone, Cyanide, Carbon Monoxide, Formaldehyde
>60 Carcinogens
Benzene, Nitrosamines
Tobacco-Caused Illness

~90% of all lung cancers
~100% COPD
2X death from stroke/ CAD

Half of all smokers die from a tobacco-caused disease

CDC Surgeon General, 2004
Recent data from several states have found that people with SMI die, on average, 25 years earlier than the general population.

National Association of State Mental Health Program Directors (NSMHPD) 2006; Miller et al., 2006

Disproportionate consequences=

disparity group
Cardiovascular risk factors – overview

BMI = body mass index; TC = total cholesterol; DM = diabetes mellitus; HTN = hypertension


Cause of Death in Patients with Psychosis

For those aged 35-54 years, the odds of cardiac related death was increased by 12X in smokers vs. nonsmokers

Kelly et al., 2009

BMI = body mass index; TC = total cholesterol; DM = diabetes mellitus; HTN = hypertension

Fewer consequences / Not as disruptive to patients’ life

• More alcoholics die from smoking related diseases than alcohol related diseases

• Synergistic effects of alcohol and tobacco ↑ risk of developing pancreatitis and oral cancers

• Smoking reduces recovery from cognitive deficits during alcohol abstinence

Stigma: Smoking is a Barrier to Community Integration

Jobs
- Only about 1 in 3 employed
- Consumers Need Employment Support

Housing
- The lack of decent, safe, affordable housing is one of the most significant barriers to community life for people with SMI.

Both highly stigmatize smokers

The President’s New Freedom Commission on Mental Health, Final Report July 2003
Suicide and Smoking

• Daily smoking → predicts suicidal thoughts or attempt (adjusted for prior depression, SUD, prior attempts; OR 1.82)
• ↑ risk in schizophrenia and bipolar disorder
• Heavy smoking
  ↑ Suicide completions
  ↑ Attempts in adolescents (especially girls)

Breslau et al., 2005; Ostacher et al., 2006; Altamura et al., 2006; Iancu et al., 2006; Cho et al., 2007; Oquendo et al., 2007; Riala et al., 2006; Moriya et al., 2006
Benefits of Smoking

Cognition

Nicotine/ Nicotinic Receptors

✓ Alzheimer's disease
✓ Attention deficit disorder
✓ Autism
✓ Schizophrenia

- Tobacco ≠ pharmacological treatment
- Not a rationale for smoking

Depression

MAO Inhibitor Like Substance
Tobacco Dependence is an Axis I Disorder
State level Prevention and Cessation Initiatives

• Risk Factor for Tobacco Use Progression
• Reduced access to tobacco treatment
• May not be helped by community/brief tobacco treatments
CURRENT MENTAL ILLNESS INCREASES SMOKING PROGRESSION

<table>
<thead>
<tr>
<th></th>
<th>DAILY SMOKING</th>
<th>NIC DEPEND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maj Depression</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GAD</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Substance Use Disorder</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ODD</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Breslau et al., 2004a; Breslau 1995; Dierker 2001
Policy Development

• Tobacco-free grounds

• Other Steps
  – No staff smoking with patients
  – No selling tobacco products
  – Getting NRT products on formulary
  – Require assessment at all levels of care

Williams JM, JAMA, 2008
Clean indoor air laws and workplace tobacco bans

- Benefit from TF recreational facilities (bingo), shopping malls, churches, buses
- Not in workplace
- Workers less likely to be covered
  - Blue-collar and food/hospitality service (bartenders, restaurant)
  - Workers who earn ≤$50,000/yr
  - HS education or less

Gerlach et al., 1997; Delnevo et al., 2004
Smoke-Free Hospitals

- Hospitals with a psychiatric or substance abuse unit have lower compliance with 1992 JCAHO tobacco standards
- Tobacco-free psych hospitals do no show increase in violence of incidents
- Policy supports treatment
- Psychiatric inpatients **not** given NRT were >2X likely to be discharged from the hospital AMA
- No Exemptions

Longo et al., 1998; Joseph et al., 1995; Prochaska 2004
Smoke-Free Inpatient Units

- Inpatient units going tobacco-free
  **DO NOT REPORT**
- Increase in disruptive behaviors
- Increase in AMA discharges
- Additional seclusion and restraints
- Increase in use of PRN medications

NASMHPD 2006; Patten et al., 1995; Haller et al., 1996
Smoking in the Home

- Successful quitters were more likely to have rules against smoking in their homes.
- Living with other smokers reduces the chances of successfully quitting.
- Smoking bans in the workplace or the home are predictors of successful quitting.

Lee and Kahende 2007
• 60% of mental health consumers report living with smokers AND smoking indoors

Are mental health workers putting themselves at risk at work?
Anti-tobacco counter-marketing efforts

• None

• Tobacco industry documents reveal evidence of targeting to psychologically vulnerable populations/mentally ill

Prochaska et al., 2008; Apollonio and Malone 2005
Reduced Access to Tobacco Treatment

- Nicotine dependence documented in 2% of mental health records
- Psychiatrists treat tobacco dependence in less than 2% of their outpatient practice
- Psychiatrists have lowest awareness of Quitlines and state tobacco services
- Less than 30% of state psychiatric hospitals offer cessation sessions
- Less than half of outpatient SA treatment programs offer smoking cessation counseling or pharmacotherapy

Peterson 2003; Montoya 2005; Friedmann 2008; Steinberg 2006
Usual Community Treatments or State Funded May not Work

Not ready for cessation
  Target Preparation
Not aware/ not accessing
Too brief
Stigma
Rigid algorithms
Community Cessation Group

6 or 8 weeks
Once weekly
Everyone quit together (Week 2)
Group support and coping
Quitline

Toll-free telephone counseling
Good for transportation issues
Assessment & 4 Follow up calls

• Lack of stable phone service
• Limited access
  – Group home
  – Boarding home
• Crisis/ problem calls
• Mental health issues and symptoms
Behavioral Health Should Take a Lead in Tobacco Treatment

- High prevalence of tobacco use
- Nicotine Dependence in DSM-IV
- Knowledge of addictions co-occurring disorders
- Familiar with some medications for tobacco
- Tobacco interactions with psych meds
- Longer and more treatment sessions
- Experts in psychosocial treatment
- Trained in addictions
- Tremendous patient need
- Experts in psychosocial treatment
- Relationship to mental symptoms

Williams & Ziedonis. Behavioral Healthcare 2006
APA Practice Guidelines for Treatment of Patients with Nicotine Dependence, 1996

• Patients who smoke and are being seen by a psychiatrist for a psychiatric disorder
• Smokers who have failed initial treatments for smoking cessation and need more intensive treatments
• Psychiatric patients who smoke and are temporarily confined to smoke-free wards
<table>
<thead>
<tr>
<th>Primary Care</th>
<th>Behavioral Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Intervention</td>
<td>Intensive</td>
</tr>
<tr>
<td>Shorter visits</td>
<td>↑ Addictions Experience</td>
</tr>
<tr>
<td>15 vs 30 min visits</td>
<td>↑ Addictions Training</td>
</tr>
<tr>
<td>Access</td>
<td>More Visits</td>
</tr>
<tr>
<td></td>
<td>Experts Psychosocial Tx</td>
</tr>
<tr>
<td></td>
<td>Assessment Mood</td>
</tr>
</tbody>
</table>
My mental health center, counselor or psychiatrist should give me treatment to quit smoking.
Reduced Access to Tobacco Treatment

- Nicotine dependence documented in 2% of mental health records
- Only 1.5% of patients seeing an outpt psychiatrist received treatment for smoking
- Psychiatrists have lowest awareness of Quitlines and state tobacco services
- Less than half of outpt SA treatment programs offer smoking cessation counseling or pharmacotherapy

Peterson 2003; Montoya 2005; Friedmann 2008; Steinberg 2006
Tobacco Treatment Availability in SATP

  - 88% response rate
- 41% offer smoking cessation counseling or pharmacotherapy
- 38% offer individual/group counseling
- 17% provide quit-smoking medication
- More likely: medically oriented, more comprehensive services, recognize the health burden of smoking

Friedmann et al., JSAT 2008
Does your mental health program offer any tobacco treatment?

- Yes: 30%
- Don't Know: 12%
- No: 58%

(CHOICES)
Where is the Outrage?

- Mental health professionals and advocacy groups have not been vocal in demanding tobacco treatment services.
- Virtually none of MSA money ($206 billion) helping smokers with mental illness.
Barriers to Addressing Tobacco in Mental Health

- Undervalue of tobacco use as a problem
- Consumers/ families minimize the health risks of tobacco
- Professionals/ MH systems have been slow to change in addressing tobacco
- Lack the knowledge about effectiveness of treatment
- Lack of advocating for treatment

*Williams & Ziedonis, Addictive Behaviors, 2004*
Removing Barriers to Providing Treatment

- Training health professionals can ↑ delivery of tobacco treatments
- More favorable attitudes are associated with higher rates of tobacco treatments
- Nurses who use tobacco
  - provide ↓ cessation services
  - rate their ability to help patients as lower

Slater et al., 2006; Braun et al., 2004; Reeve et al., 1996; Lancaster et al, 2008
Addressing Tobacco Requires Attention to Multiple Domains

- Neurobiological
- Psychological
- Social & Environmental
- Spiritual & Advocacy
- Treatment System & Institutional

- Greater dependence
- Poor coping; low confidence
- Live with smokers
- Seeing peers succeed; having hope
- Provider bias; No access to help
Mental Health Tobacco Recovery in NJ

Community
- Access to medications
- Peer services
- Advocacy

Clinical Treatment
- Engaging smokers
- Wellness curriculum
- Adapted cessation

Environment
- Increase Demand for Services
- Staff development
- Tobacco-free policy
- Other policy

Help More Smokers Quit

Williams et al, Administration & Policy in Mental Health and Mental Health Services Research, 2010
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
Principles of Co-occurring Disorders Treatment

• Dual diagnosis patient develop stable remission at a rate of about **10-15%** achieving remission per year

• Programs need to take a long term, outpatient perspective

*Drake & Mueser, 2001; Drake 2000*
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
80% of Smokers with SMI report smoking within 30min of awakening

Williams et al., CMHJ 2010

N=100
Higher Nicotine Levels in SCZ not Due to Metabolic Differences

[Box plots showing the distribution of Nicotine levels (ng/mL) and COT RATIO for control smokers and smokers with schizophrenia.]
Schizophrenia

- High prevalence of smoking
- High nicotine dependence
- Increased nicotine intake per cigarette
- Altered puff topography
- Half as successful in quit attempts as other smokers

Bipolar Disorder

- Less known
- High prevalence of smoking
- Heavy smoking linked to psychosis
- Correlates with SUD and suicide

de Leon & Diaz, 2005; Tidey et al., 2005; Weinberger et al., 2007; Sacco et al., 2005; Williams et al., 2005; George et al., 2006; Lasser 2000; Hughes 1986; Corvin 2001; Gonzalez-Pinto 1998; Itkin 2001; Uck 2004; Diaz 2009
Measurement of smoking topography and nicotine intake

• N=236 subjects
  – 75 schizophrenia; SCZ
  – 75 bipolar, BPD
  – 86 controls; CON

• CON- no mental illness in last year; no psych meds for any reason last 6 months; heavy smoking, low SES controls

• Schizoaffective disorder excluded

• All smokers with mental illness stable on psychiatric medications
Methods

• 24 hour topography- 3pm Day 1 to 3pm Day 2 (includes 1st cig of day)
• Ad lib smoking, outside of lab; own cigs
• CReSSmicro device
• 3 blood draws for nicotine and cotinine
  – 10am (Trough- 60 mins after last cig)
  – 10am (Peak- After a single cigarette)
  – 3pm (Steady-state)
## Sample Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SCZ (n=75)</th>
<th>BPD (n=75)</th>
<th>CON (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPD</td>
<td>22.3</td>
<td>19.7</td>
<td>20.0</td>
</tr>
<tr>
<td>CO (ppm)</td>
<td>23.1</td>
<td>19.7</td>
<td>19.5</td>
</tr>
<tr>
<td>FTND</td>
<td>5.9</td>
<td>5.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Age*</td>
<td>45.7</td>
<td>38.9</td>
<td>38.0</td>
</tr>
<tr>
<td>Age first smoke</td>
<td>14.7</td>
<td>14.2</td>
<td>14.7</td>
</tr>
<tr>
<td>TTFC ≤30 min (%)</td>
<td>95</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>Male gender (%)*</td>
<td>73</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td>African American Race (%)*</td>
<td>47</td>
<td>16</td>
<td>29</td>
</tr>
</tbody>
</table>
Higher Nicotine and Cotinine Levels in Schizophrenia; No Difference in Values Between Bipolar Smokers and Controls; N=226

*** p < 0.001 vs both groups; ** p<0.01 vs both

Williams et al, DAD, 2011
HIGHER AND EARLIER NICOTINE PEAK IN SCHIZOPHRENIA

Williams NTR 2010

4 minute Nicotine Boost (ng/mL)
25.2 vs. 11.1 ; p<0.01
Rapid Smoking May not be Aversive in Schizophrenia

- SS smoke more puffs per cigarette (15.8 vs. 12.3 puffs, \( p<0.001 \))
- Interpuff interval (IPI) shorter by 6.5 sec in SS (\( p<0.001 \))
- Greater total puff volume in SS (681.8 vs. 540.5, \( p<0.001 \))
- SS smokers 2X more likely to have IPI’s of \( \leq 6 \) sec (\( OR=2.05; 95\% \) CI 1.47, 2.88; \( p<0.001 \))
- More SS smoked \( \geq 3 \) cigarettes sequentially in 30 min vs CON (45.3 vs. 19.7%; \( p<0.001 \))
- Maximum number of cigarettes smoked during a 30 minute period was 7 for SS

Median IPI was 9.5 sec in SCZ and 16.4 sec in CON

Williams et al., NTR 2011
Higher 3HC/Cotinine Ratio in Bipolar Smokers; N=226

*** $p < 0.01$ vs both groups
Medication Effects - Antipsychotic

• About half of BPD sample (49.3%) had a history of psychotic symptoms
• 76% of BPD sample taking antipsychotic medications (95% atypical)
• No effect of these on nicotine, cotinine levels or 3HC/COT ratios
## Medications Taken By Smokers with Mental Illness

<table>
<thead>
<tr>
<th></th>
<th>SCZ (n=73) N (%)</th>
<th>BPD (n=74) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>27 (37)</td>
<td>33 (45)</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>73 (100)</td>
<td>56 (76)</td>
</tr>
<tr>
<td>Atypical antipsychotic</td>
<td>65/73 (89)</td>
<td>53/56 (95)</td>
</tr>
<tr>
<td>Mood stabilizer</td>
<td>22 (30)</td>
<td>51 (69)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>14 (19)</td>
<td>21 (28)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>3 (4)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Carbamazepine/oxcarbazepine</td>
<td>4 (6)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Lithium</td>
<td>4 (6)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1 (2)</td>
<td>7 (10)</td>
</tr>
</tbody>
</table>
Carbamazepine but Not Valproate Induces CYP2A6 Activity (Nicotine Metabolism)

The 3HC/cotinine ratio was significantly higher in smokers taking carbamazepine or oxcarbazepine (combined, n = 14) vs those not taking either mean 0.993 versus 0.503; P < 0.001

Williams et al., 2010
3HC/COT Ratios in Med Subgroups

- Carb/Ox
- Top
- Lam
- Val
- Lithium
- More than one
- Control

14 subjects taking Carb/ox removed
Major Depression

- Conflicting evidence if more difficulty quitting
- Past history of depression, not factor
- Current symptoms, recurrent illness may be important
- Antidepressants treat both
- 30% risk of relapse to MDE after quitting if past history +

Niaura 2001; Anda 1990; Glassman 2001
Is history of MDE associated with failure to quit smoking?

• Meta-analysis – 15 studies
• No differences for smokers + or – h/o MDE
  – short-term (≤ 3 mos) or
  – long-term abstinence rates (≥ 6 mos)

Hitsman et al., 2003
Current Depression

• N=600 Smokers
• 15% quit rate at 12 weeks (88/600)
• BDI≥10 less likely to quit vs BDI< 10 (OR 6.4)
• Coping skills and personality traits did not predict outcome

Berlin & Covey, 2006
Smokers with Anxiety

• ~39% of smokers seeking treatment
• Higher nicotine dependence: Panic attack, GAD, Social Anxiety
• More withdrawal symptoms
• Reduced cessation at 8 weeks, 6 months (vs no diagnosis)

Piper et al., Addiction 2010
Serious Mental Illness

REDUCED CESSATION

• Schizophrenia/ Schizoaffective disorder
• Bipolar disorder
• PTSD
• ADHD
Quit Ratios by SPD

Ratio of former to ever smokers/ estimation of cessation in population

- Non-SPD 0.47
- SPD 0.29

SPD= serious psychological distress

Hagman et al., 2008
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% lower at 24 hours for NRT group
• Better response in lower dependence
• Same magnitude of response as antipsychotic studies  

Allen 2011; Am J Psych
High-Dose Patch Rationale

- Recommended doses of nicotine replacement therapy are inadequate for many smokers
- In heavy smokers, underdosing may limit limited effectiveness of patch
High Dose Nicotine Patch Study

- Randomized trial
  42mg (double patch) vs. 21mg patch in smokers with schizophrenia/schizoaffective disorder
  - Patch doses decreased in an 8-week tapering schedule
  - All subjects participated in 15 minute weekly individual sessions
Abstinence Outcomes

7-day PP abstinence rates at 8 weeks was 24% (n=11) in total sample.

Continuous abstinence at 8 weeks was 15.6% (n=7)

Abstinence rates and time to first smoking were not different between dose groups.
NNS Case Series

- 12 SA/SCZ (6 M; 6F)
- Average age 45
- Smoked ~ 26 yrs
- FTND 8 (severe dependence)
- Smoked 27 cpd
- Baseline CO 22
- Failed patch treatment

Williams et al, Sept 2004, Psychiatric Services
NNS Case Series

• 11 tolerated NNS well; 9 used > 30 dose/day
• High users (Four 10ml bottles/ q 14 days)
• Mean treatment 255 days (2-811 d)
• Five (42%) were abstinent for longer than 90 days
• Four had substantial ↓ in cpd and CO
• Before NNS CO=21; After NNS CO= 3.5

Williams 2004, Psych Serv
NNS for Craving Study in SCZ

• 26 smokers with SCZ or SA
• Cue-induced craving smoking vs. on NRT
• Paid $85 to complete Day 3
• 81% (21/26) of subjects abstinent for 3 days
• Compliance: NNS and NP excellent
• No drops outs due to medication side effects
• Average self-reported NNS use 20 doses/day (first 2 full days of use)
• Limitation: Open Label
Mean urges to smoke less in NNS vs. Patch at Day 3 (N=21)

Williams et al., J Dual Diagnosis 2008
Safety and Efficacy of Varenicline for Smoking Cessation in Patients with Schizophrenia and Schizoaffective Disorder

• Primary objective
  – Assess the safety and tolerability of varenicline in patients with stable schizophrenia or schizoaffective disorder motivated to quit smoking

• Secondary objective
  – Assess efficacy of varenicline in smoking cessation and reduction

Study Design

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

12-week treatment phase

Varenicline 1 mg BID
starting with 1-week titration (0.5 mg QD x3 days; 0.5 mg BID x4 days)

2:1 randomization

Placebo

12-week non-treatment follow-up

Assessments: CGI-I, CGI-S, CSSRS, AEs, NUI, PANSS

AEs, adverse events; BID, twice daily; CGI-I, Clinical Global Impression Improvement; CGI-S, Clinical Global Impression Severity of Illness scale; CSSRS, Columbia-Suicide Severity Rating Scale; NUI, nicotine use inventory; PANSS, Positive and Negative Symptom Scale; QD, once daily; T, telephone visit; TQD, target quit date
Subject Disposition

Screened: 214

Screen failures: 86 (40.2%)

Assigned to study treatment: 128

Varenicline: 84

Discontinued: 23 (27.4%)

Treatment phase
- AE: 3 (3.6%)
- Death: 0 (0%)
- Lost to follow-up: 2 (2.4%)
- Declined to participate further: 4 (4.8%)
- Other: 4 (4.8%)

Follow-up phase
- AE: 0 (0%)
- Death: 1 (1.2%)
- Lost to follow-up: 4 (4.8%)
- Declined to participate further: 4 (4.8%)
- Other: 1 (1.2%)

Completed: 61 (72.6%)

Placebo: 43

Discontinued: 6 (14.0%)

Treatment phase
- AE: 0 (0%)
- Death: 0 (0%)
- Lost to follow-up: 2 (4.7%)
- Declined to participate further: 0 (0%)
- Other: 1 (2.3%)

Follow-up phase
- AE: 0 (0%)
- Death: 0 (0%)
- Lost to follow-up: 1 (2.3%)
- Declined to participate further: 2 (4.7%)
- Other: 0 (0%)

Completed: 37 (86.0%)
## Baseline Characteristics and Smoking History

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Varenicline (n=84)</th>
<th>Placebo (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, n (%)</td>
<td>65 (77.4)</td>
<td>33 (76.7)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>40.2 (11.9)</td>
<td>43.0 (10.2)</td>
</tr>
<tr>
<td>Race, White (%)</td>
<td>59.5</td>
<td>58.1</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>30.0 (4.6)</td>
<td>28.7 (4.8)</td>
</tr>
<tr>
<td>Current psychiatric diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>59 (70.2)</td>
<td>32 (74.4)</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>25 (29.8)</td>
<td>11 (25.6)</td>
</tr>
<tr>
<td>Atypical antipsychotic use, n (%)</td>
<td>74 (88.1)</td>
<td>35 (81.4)</td>
</tr>
<tr>
<td>PANSS, total score, mean (SD)</td>
<td>55.9 (9.5)</td>
<td>54.5 (10.7)</td>
</tr>
</tbody>
</table>

## Smoking History

<table>
<thead>
<tr>
<th>Smoking History</th>
<th>Varenicline (n=84)</th>
<th>Placebo (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagerström Test for Nicotine Dependence score, mean (SD)</td>
<td>6.6 (1.7)</td>
<td>6.3 (1.6)</td>
</tr>
<tr>
<td>Total number of years smoking, mean (range)</td>
<td>23.7 (2–48)</td>
<td>24.9 (3–44)</td>
</tr>
<tr>
<td>Number of cigarettes/day, mean (range)</td>
<td>23.5 (15–50)</td>
<td>22.3 (15–50)</td>
</tr>
<tr>
<td>Proportion of subjects with 3+ serious quit attempts (%)</td>
<td>51.2</td>
<td>62.8</td>
</tr>
</tbody>
</table>
7-Day Point Prevalence of Abstinence from Smoking

At Weeks 12 and 24

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

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

Participants (%)
10/83 (11.9%)
2/43 (4.7%)
16/83 (19.0%)
1/43 (2.3%)

Analysis population = ITT minus one subject randomized to varenicline who did not receive treatment.
CI=confidence interval; ITT, intent to treat; OR=odds ratio
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
Clinical Global Impression of Severity (CGI-S); Summary of CGI-I by Treatment and Study Visit

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Varenicline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>3.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Week 12</td>
<td>15</td>
<td>74</td>
</tr>
<tr>
<td>Week 24</td>
<td>103</td>
<td>131</td>
</tr>
</tbody>
</table>

Participants (%)

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
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>Adverse Event (All Causalities)</th>
<th>Varenicline (N=84) %</th>
<th>Placebo (N=43) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>9.5</td>
<td>4.7</td>
</tr>
<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>9.3</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
Lifetime History of Suicidality as Measured by C-SSRS

<table>
<thead>
<tr>
<th>Category</th>
<th>Varenicline (n=84)</th>
<th>Placebo (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number assessed</td>
<td>84 (100%)</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>Suicidal behavior or ideation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>52 (62.9%)</td>
<td>22 (51.2%)</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>36 (42.9%)</td>
<td>15 (34.9%)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>35 (41.7%)</td>
<td>14 (32.8%)</td>
</tr>
<tr>
<td>Preparatory acts towards imminent suicidal behavior</td>
<td>25 (29.8%)</td>
<td>11 (25.6%)</td>
</tr>
<tr>
<td>Aborted</td>
<td>14 (16.7%)</td>
<td>10 (23.3%)</td>
</tr>
<tr>
<td>Interrupted attempt</td>
<td>11 (13.1%)</td>
<td>5 (11.6%)</td>
</tr>
<tr>
<td>Preparatory acts or behavior</td>
<td>18 (21.4%)</td>
<td>5 (11.6%)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-injurious behavior, no suicidal intent</td>
<td>12 (14.3%)</td>
<td>12 (27.9%)</td>
</tr>
</tbody>
</table>
## Columbia Suicide-Severity Rating Scale Summary of “Yes” Answers

<table>
<thead>
<tr>
<th></th>
<th>Varenicline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suicidal behavior and/or ideation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lifetime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number assessed</td>
<td>84</td>
<td>43</td>
</tr>
<tr>
<td>n (%) of “yes” answers</td>
<td>52 (61.9)</td>
<td>22 (51.2)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number assessed</td>
<td>84</td>
<td>42</td>
</tr>
<tr>
<td>n (%) of “yes” answers</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td><strong>Treatment phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number assessed</td>
<td>82</td>
<td>43</td>
</tr>
<tr>
<td>n (%) of “yes” answers</td>
<td>9 (11.0)</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td><strong>Post treatment follow-up phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number assessed</td>
<td>70</td>
<td>39</td>
</tr>
<tr>
<td>n (%) of “yes” answers</td>
<td>8 (11.4)</td>
<td>2 (5.1)</td>
</tr>
</tbody>
</table>
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 mental illness or addictions comorbidity are a Disparity Group that should be a higher priority
- Not clear that current Tobacco Control Strategies are helping this group of smokers
- Working with Mental Health Systems and Providers is an Effective Approach
References

