Tobacco Treatment in Serious Mental Illness: Integrating Medications with Behavioural Therapies

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<th>Disclosures: Dr. Tony P. George</th>
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Learning Objectives

At the conclusion of this lecture, participants should be able to:

• Describe the prevalence and potential etiologies for tobacco smoking in persons with serious mental illnesses.

• Describe pharmacological and behavioral treatments for co-morbid tobacco addiction in persons with mental illness.

• Discuss an approach to tobacco bans in psychiatric inpatient settings.
ALL RIGHT AMERICA—
YOU ARE SMOKING MORE*

*Government figures show smoking at all-time peak.

And You're SAFER
Smoking

PHILIP MORRIS

A FINER cigarette—scientifically proved less irritating to nose and throat...

When smokers changed to PHILIP MORRIS, every case of irritation of the nose or throat—due to smoking—cleared up completely or definitely improved!

—findings reported in medical journals by a group of distinguished doctors.

We do not claim curative powers for PHILIP MORRIS. But this evidence proves they are far less irritating for your nose and throat.

PROTECTION ADDED TO
FINER SMOKING PLEASURE

CALL FOR
PHILIP MORRIS

America's FINEST Cigarette
“Quitting smoking is easy – I’ve done it several hundred times ...”

- Mark Twain
Case Review

• 47 year old white male with schizophrenia
• Smoking 2 ppd x 31 years, multiple failed quit attempts “too many to count”
• First cigarette smoked <1 minute after waking
• Many antipsychotic, refractory positive symptoms, now on Clozapine 525 mg/day
• +Metabolic Syndrome, COPD, +EST, poor diet
• Lives in group home with 20 other heavy smokers
• What do we do?
Tobacco Smoking and Persons with Psychiatric Disorders

• One epidemiological study suggests that while nicotine-dependent mentally ill smokers make up 7.1% of the population of smokers, they consume 34.7% of all cigarettes (Grant et al., 2004)

• A major cause of death of people with SPMI and addictions is tobacco-related illness (Hurt et al., 1996; Hennekens et al., 2005; George and Ziedonis, 2009)

• A substantial portion of disability income (up to 25%) may be spent by heavily-dependent mentally ill smokers on tobacco products each month (Ziedonis et al., 2005)
A 1986 Advertisement for Philip Morris' Merit Cigarettes Suggests Evidence of Direct Marketing of Tobacco Products to Individuals with Schizophrenia.
Prevalence of Smoking in Clinical Samples of Persons with Psychiatric and Substance Use Disorders

Reasons Why Individuals with Mental Health and Addictions (MHA) May Have Higher Rates of Smoking

• The pathophysiology of these disorders increases vulnerability to initiation and maintenance of smoking behaviors.
• Individuals with MHA are self-medicating affective and cognitive symptoms.
• Social factors common to both MHA and smoking (e.g., peer modeling, poverty, stress, availability)

Neurocircuits Involved In Drug Dependence
Nicotine Effects on DA Dysregulation in Schizophrenia

Schizophrenia

- PFC
- NAc
- VTA
- DA

Type of firing of VTA--PFC DA neurons
- Regular basal firing
- Burst firing

Type of firing of VTA--NAc DA neurons
- Regular basal firing
- Burst firing

Dysfunctional mesocortical system
Dysfunctional mesolimbic system

DA-mediated reward-system deficiency

Nicotine

Smoking in Schizophrenia?

- PFC
- NAc
- VTA
- DA

Type of firing of VTA--PFC DA neurons
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Dysfunctional mesocortical system
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Nicotine improves DA-mediated reward-system deficiency

Effects of Smoking Abstinence on Visuospatial Working Memory in Schizophrenia (n=23) vs. Controls (n=29)

Genetics
CHRNA7, CHRNA3, CHRNA5, BDNF, DRD1, DRD3

Environmental insults
e.g. nicotine exposure during neurodevelopment

Pathophysiology
DA, GLU, GABA, nACh aberrations

Prefrontal cortex

Nucleus Accumbens
DA modulation a482

Hippocampus

Ventral Tegmental Area

Clinical manifestation
↑ initiation of smoking, addiction severity, relapse

Wing, VC et al. (2012)
Ann. NY Acad. Sci. 1248: 89-106
The 5 A’s
For Patients Willing To Quit

**ASK** about tobacco use.

**ADVISE** to quit.

**ASSESS** willingness to make a quit attempt.

**ASSIST** in quit attempt.

**ARRANGE** for follow-up.

USPHS Tobacco Clinical Practice Guidelines, 2008
Reduced Smoking –
A Viable Target or Not?

- Many smokers (esp. with SPMI) are simply unable to quit smoking.
- Should sustained reductions in smoking been considered a goal of tobacco treatment or should reduction be a transitional goal towards eventual smoking abstinence (Hughes, 2002; George and Vessicchio, 2002; McChargue et al., 2002)?
- One study suggests that sustained smoking reductions (50% reduction) do not reduce cancer or cardiac disease risk (Tverdall and Bjartveit, 2006).
Assessment of Tobacco Addiction

- Get a detailed history
- Motivation to quit
- Number of Previous Quit Attempts and Longest Period of Abstinence (what was the context?).
- Previous Treatment (medications, behavioral interventions)
- Effects of abstinence on MH symptoms and drug use/craving
- Objective verification of tobacco use (Expired Breath CO, cotinine)
- Tobacco-related health problems
Which Smokers are Candidates for Pharmacotherapy?

- Daily smokers (typically smoking >10 cpd)
- Evidence for moderate to heavy levels of dependence on nicotine (e.g. FTND score >5).
- Willingness to comply with daily medication dosing.
- Willingness to accept basic smoking cessation counseling (to learn the behavioral skills required to quit smoking) during the trial of medication.
## Pharmacotherapies for Tobacco Dependence

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Examples</th>
<th>How used</th>
<th>Efficacy vs. PLO</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT: Slow-acting</td>
<td>Transdermal Patch</td>
<td>Daily application</td>
<td>2-fold</td>
<td>Local irritation</td>
</tr>
<tr>
<td>NRT: Fast-acting</td>
<td>Gum, lozenge, inhaler, nasal spray</td>
<td>Multiple uses as needed</td>
<td>1.5-2.5-fold</td>
<td>Oropharyngeal irritation</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>Sustained-release (SR) Bupropion</td>
<td>150 mg po BID after induction</td>
<td>2.0-fold</td>
<td>Insomnia, activation, dry mouth</td>
</tr>
<tr>
<td>Nicotinic Partial Agonist</td>
<td>Varenicline</td>
<td>1 mg po BID after induction</td>
<td>3.0-fold (1.5-fold vs. Bupropion)</td>
<td>GI, Insomnia</td>
</tr>
</tbody>
</table>
Nicotine Delivery by Cigarettes and Nicotine Replacement Therapy (NRT)

- Cigarette (nicotine delivery, 1-2mg)
- Gum (nicotine delivery, 4mg)
- Nasal spray (nicotine delivery, 1mg)
- Transdermal patch (nicotine delivery, 15-21mg)

Plasma Nicotine Concentration (μg/L)

Time Post-administration (minutes)

NRT has rates of delivery which are all less than that of cigarette smoking.
NRT acts as an agonist alone, mimicking nicotine in its mechanism of action.
Peak levels achieved by NRT are about 30-50% of those achieved by smoking.

Is it Safe to Get Patients to Quit Smoking?

• Short Answer: Yes

• In schizophrenia, smoking cessation does not exacerbate psychotic or depressive symptoms (e.g. George et al., 2000; Evins et al., 2001; George et al., 2002; Baker et al., 2005; Evins et al., 2005; Evins et al., 2007; George et al., 2008; Williams et al., 2012).

• In major depression, some longitudinal studies by the Columbia group (Glassman et al., 1988; 1990) do suggest a small increased risk of depression with smoking cessation (~5%), but several other studies have not supported this conclusion (Niaura et al., 2001; Thorsteinsson et al., 2001).

• In anxiety disorders, little evidence that cessation can exacerbate PTSD or GAD, and in fact severity and frequency of panic attacks in Panic Disorder may be higher in smokers versus non-smokers (Breslau and Klein, 1999).

• In SUDs, little evidence that quitting smoking and drinking concurrently may increase alcohol or drug use relapse – a meta-analysis suggests enhanced SUD treatment outcomes (Prochaska et al., 2004).
Cigarette Smoking, Cytochrome P450 and Psychotropic Drug Plasma Levels

- Metabolized by CYP 1A2/3A4
  - Clozapine
  - Olanzapine
  - Haloperidol
  - Chlorpromazine
  - Caffeine

- Not Metabolized
  - Risperidone
  - Ziprasidone
  - Aripiprazole
  - Quetiapine
  - Bupropion

Treatment of Tobacco Dependence in People with SPMIs

• Cessation rates in SPMI (e.g. schizophrenia, bipolar disorder, PTSD) are 1/2 to 1/3 of those in the general population.

• Need to exploit pathophysiological relationships between the mental illness and tobacco dependence – this could improve treatment outcomes.

• Need to combine medications with behavioral therapies, and extend length of treatment (Hall et al., 2008)

• Need to integrate tobacco dependence treatments into psychiatric settings

Hitsman, B et al., 2009. Can. J. Psychiatry
Components of Smoking Cessation Group Therapy Program for SPMI Smokers

• 10 weekly sessions of manualized group smoking cessation counseling (Ziedonis and George, 1997; George et al, 2000; 2002; 2008).
• Flexibility in setting a target quit date (TQD) if unsuccessful on initial attempt.
• Emphasis on motivational interviewing (MI) and psychoeducation pre-TQD
• Modified cognitive behavioral therapy (CBT) emphasizing small amounts of material at each session with frequent repetition, to compensate for cognitive deficits of subjects.
• Focus on building social skills, emphasis on relapse prevention skills post-TQD.
Atypical Versus Typical Antipsychotic Drugs and Nicotine Patch for Smoking Cessation in Schizophrenia (n=45)


*p<0.05 vs. Typical
Combination Therapy with Nicotine Patch and Bupropion SR is Superior to Placebo + Patch for Smoking Cessation in Schizophrenia (N=58)

Fisher’s Exact Test + p = 0.056 * p < 0.05 # p=0.11

Active versus Sham High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) may Reduce Tobacco Craving in Schizophrenia

Wing, VC et al. (2012). Under Review

![Graph showing change in TQSU score over weeks for different treatments and factors.]

Factor 1: Intention to Smoke; Anticipation of Positive Effects
- Week 1: Real rTMS > Sham rTMS
- Week 2: Real rTMS > Sham rTMS
- Week 3: Real rTMS > Sham rTMS
- Week 4: Real rTMS > Sham rTMS

Factor 2: Anticipation of relief from withdrawal; Desire to Smoke
- Week 1: Real rTMS > Sham rTMS
- Week 2: Real rTMS > Sham rTMS
- Week 3: Real rTMS > Sham rTMS
- Week 4: Real rTMS > Sham rTMS

*p<0.05 vs Sham TMS
Varenicline and Safety

• Several case reports both published (Freedman, 2007; Kohen and Kremen, 2007) and unpublished (FDA Medwatch) implicating varenicline in neuropsychiatric treatment-emergent adverse events (TEAEs), including suicidality, homicidality, psychosis and mania.

• However, clinical studies comparing Psychiatric Hx+ to Hx- smokers in varenicline treatment suggest that treatment outcomes and adverse events are comparable (e.g. Stapleton et al., 2008; McClure et al., 2010).

• Open-label trial in schizophrenia suggests its safety and effectiveness (Evins et al., 2008)

• Several recent (FDA-mandated) studies of varenicline in schizophrenia, bipolar disorder and depression (e.g. Williams et al., 2012; Wu et al., 2012).
“I had no idea this is what the FDA meant by putting the pill through a clinical trial.”
Varenicline for Smoking Cessation in People with Schizophrenia


www.clinicaltrials.gov

Analysis population = ITT minus 1 subject randomized to varenicline who did not receive treatment.

Varenicline Effects on Positive and Negative Symptoms in Smokers with Schizophrenia


www.clinicaltrials.gov
## Treating Tobacco in Other Psychiatric Disorders

<table>
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<tr>
<th>Study</th>
<th>Psychiatric Disorder</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Chengappa et al. (2001)</td>
<td>Major Depression (N=31)</td>
<td>Open-label bupropion SR (300 mg/d) well-tolerated and produced 30% abstinence rate in smokers with MDD stabilized on SSRIs.</td>
</tr>
<tr>
<td>Hertzberg et al. (2001)</td>
<td>PTSD (N=10)</td>
<td>Abstinence rate with bupropion (300 mg/d) of 60% versus placebo (0%), well-tolerated.</td>
</tr>
<tr>
<td>McFall et al. (2005)</td>
<td>PTSD (N=109)</td>
<td>Integrated treatment of PTSD and tobacco dependence in same setting led to better outcomes than non-integrated care.</td>
</tr>
<tr>
<td>Weinberger et al. (2008)</td>
<td>Bipolar I Disorder (N=5)</td>
<td>Double-blind PLO-controlled randomized trial, bupropion (up to 300 mg/d) well-tolerated and increased smoking abstinence rates.</td>
</tr>
<tr>
<td>Wu and George (2012)</td>
<td>Bipolar I Disorder (N=5)</td>
<td>Double-blind PLO-controlled randomized trial of varenicline (up to 2 mg/day), drug was well-tolerated, with higher smoking abstinence/reduction in VAR versus PLO groups.</td>
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• Tobacco Reconceptualization in Psychiatry (TRIP)

Tobacco Control Host-Vector-Agent Model

Host (Smoking Client)

Environment
(Psychiatric Hospitals, Cultural, Economic, Social, Political, Media, Historical)

Agent (Tobacco)

Vector
(Cigarettes, Smoking Policy, Tobacco Manufacturers, Sales)

Moss, T.G. et al., 2010. Am. J. Addictions. 19: 293-311
Tobacco Control Host-Vector-Agent Model

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Moss et al., 2010. Am. J. Addict., 19: 293-311
Advantages of Tobacco Bans in Inpatient Settings

- Great opportunity to provide motivational interventions for those not initially willing to try to quit (a “teachable moment”).

- Effects of interventions can be monitored in controlled therapeutic setting.

- Reduction in episodes of seclusion and restraint, decreased PRN use and length of stay (LOS).

- The goals of a smoke-free work environment are promoted, and consistent with wellness interventions that are being implemented in most inpatient settings.

Lawn and Pols, 2005; Moss et al., 2010
Disadvantages of Tobacco Bans in Inpatient Settings

- Inpatients generally not interested in quitting, as this is low on their “hierarchy of needs”.

- Staff and administration are often reluctant as this can be perceived as a distraction to treatment plans, and is a critical “positive” reinforcer. This may be especially true amongst staff and administration that are smokers themselves.

- Lack of training of unit staff or other qualified people to conduct smoking cessation counseling.

- Unmotivated inpatients pose a barrier to success of those few patients wanting to quit.

Moss et al., 2010
Principles of creating a smoke-free environment in inpatient psychiatry settings

• Strict enforcement of the smoking ban – no smoking can be tolerated ("no ifs, and or butts"!)

• Staff need adequate training to deal with the consequences of the smoking ban.

• To promote a tobacco-free environment, patients need a combination of behavioral support and pharmacotherapies (to manage withdrawal and cravings on the unit).

• Patients need to be taught relapse-prevention methods when they are discharged – tobacco treatment needs to be part of the outpatient treatment plan.

Moss et al., 2010
Take Home Messages

• Tobacco dependence is a leading cause of morbidity and mortality in psychiatric patients.

• It is possible to get smokers with psychiatric disorders to quit smoking in the short-term, with a combination of standard medications and behavioral treatments.

• Long-term success rates have been low and requires integrated and extended treatment approaches.

• Implementation of tobacco-free treatment settings improves quality of treatment and safety, and may even encourage tobacco cessation.

• **We need to do a better job identifying smokers and changing attitudes towards tobacco use in psychiatric and addictions settings.**
Thank you!

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