Nicotine Dependence In Schizophrenia
All Smoke?

Veena Kumari, PhD
Tonmoy Sharma, MBBS, MSC
Sovereign Health Group
Overview

- Tobacco use - heath and economic consequences
- Tobacco smoking in schizophrenia
- Why do patients with schizophrenia smoke? (mechanisms mediating schizophrenia-smoking associations)
- Ways to promote smoking cessation in schizophrenia
Health Risks

• Tobacco smoke contains > 7,000 chemicals.

• Of these, at least 250 are harmful.

• 69 can cause cancer.

A leading cause of cancer and death from cancers of the lung, esophagus, larynx, mouth, throat, kidney, bladder, liver, pancreas, stomach, cervix, colon, and rectum, as well as acute myeloid leukemia.

Costs of Tobacco Use

• **A leading preventable cause of death**
  - 16% of all non-communicable diseases deaths

• **Economic losses**
  - lost productivity due to illnesses and early death
  - 6-15% of the total health care costs
# Tobacco Smoking in Schizophrenia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rate of smoking</th>
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<tbody>
<tr>
<td>Healthy control</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Schizophrenia</strong></td>
<td><strong>88%</strong></td>
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<tr>
<td>Mania</td>
<td>70%</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>49%</td>
</tr>
<tr>
<td>Anxiety, personality disorder</td>
<td>45-47%</td>
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(Hughes et al. 1986, Am J Psychiatry)

- Supported by meta-analysis of 42 studies
  (de Leon & Diaz, 2005, Schizophrenia Research)

- More recent evidence (e.g. Cooper et al., 2012, ANZJP; Jackson et al. 2015, Bipolar Disorder)

57% *first episode patients*
19.6 cigarettes daily average (vs 11 cigarette/day in the healthy group)
(Hickling et al. 2017, Schizophrenia Research)
Smoking in Schizophrenia

- Smoking associated with a high risk for psychosis (Weiser et al., 2004, Am J Psychiatry). Maternal nicotine exposure also linked to increased risk of schizophrenia (Niemela et al., 2016, Am J Psychiatry)

- Smoked for some years prior to the onset of psychosis (review, Miles et al. 2012, J Clin Psychiatry)

- Higher nicotine dependence and concurrent use of alcohol and substance abuse associated with a younger age at smoking initiation (Baker et al., 2007, Psychiatry Res)
Higher Nicotine Dependence & Nicotine Extraction

- Higher levels of nicotine and cotinine with similar craving and withdrawal
  (Weinberger et al. 2007, Schiz Res; Strand and Nyback, 2005; Williams et al., 2005, Schiz Res; 2010, Nicotine Tob Res)

- More puffs per cigarettes, shorter inter-puff intervals, larger total cigarette puff volumes and higher carbon monoxide boosts
  (Tidey et al., 2005, Drug Alcohol Depend)
Low Cessation Rates

- 9% vs 14 - 49% in the general population
  (Meta-analysis, de Leon and Diaz, 2005, Schiz Res)

- 12%  
  (Culhane et al., 2008, J Clin Psychiatry)

- Poor cessation rate despite persistent attempts to quit
  (Addington et al., 1997, Can J Psychiatry; Lader and Meltzer, 2001, Department of Health, UK)
Why do people with schizophrenia smoke?

Possible Mechanisms Mediating Schizophrenia-Smoking Associations

- Genetic vulnerability
- Reduction in psychiatric symptoms
- Reduction of side effects of antipsychotics
- Improvement in sensorimotor / sensory gating and cognitive deficits
Genetic vulnerability

- Certain genetic variants linked to both smoking and schizophrenia (Hong et al., 2011, Genes, Brain & Behav; Hartz et al., 2017, Schiz Res; Reginsson et al., 2017, Addiction Biology).

- Tobacco use in relatives of people with schizophrenia (Weiser et al., 2004, Am J Psychiatry; Esterberg et al., 2007; Schiz Res; Smith et al., 2008, Schiz Res; Ferchiou et al., 2012, Psychiatry Res)


  Schizotypy personality - close proximity to schizophrenia but free of medication and illness-related issues
Why do people with schizophrenia smoke?

Possible Mechanisms Mediating Schizophrenia-Smoking Associations

- Genetic vulnerability
- **Reduction in psychiatric symptoms**
- Reduction of side effects of antipsychotics
- Improvement in sensorimotor / sensory gating and cognitive deficits
Fewer positive symptoms and/or fewer negative/depressive symptoms (Zhang et al., 2010, Neuropsychopharmacol; 2012, Plos One; 2014, Psychopharmacology; Misiak et al., 2015, Compre Psychiatry; An et al., 2016, Neurosci Bull)

Lower reward-based learning associated with higher dependence; nicotine withdrawal and urge to smoke associated with anhedonia (Ahnallen et al., 2012, Psychiatry Res)

Lower beta(2)*- nicotinic acetylcholine receptor availability in the frontal cortex and other brain areas in SZ smokers. Correlated negatively with negative symptoms (D’Souza et al. 2012, Am J Psychiatry)

Stress reduction/stimulation (Baker et al., 2007, Psychiatry Res)

Calmness (Gurpegui et al., 2007, Compr Psychiatry)
Nicotine dependence associated with depression and childhood trauma (Rey et al., 2017, Eur Arch Psychiatry); also with symptoms and prescribed higher doses of antipsychotics (Krishnadas et al., 2012, Br J Psychiatry)

No relationship between mood and smoking (Martin et al., 2008, J Psychiatric Mental Health Nurs)

Non-linear relationship between negative symptoms and smoking (Aguiler et al., 2005, Br J Psych)
Why do people with schizophrenia smoke?

Possible Mechanisms Mediating Schizophrenia-Smoking Associations

- Genetic vulnerability
- Reduction in psychiatric symptoms
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Reduction of Side Effects of Antipsychotics

- **Less parkinsonism in smokers**
  (Zhang et al., 2012, Plos One; 2014, Psychopharamcology)

- **Lower levels of akathisia**
  (Banes et al., 2006, ANCZJP; but no difference in symptoms)

- **Higher motivation to smoke for pleasure and psychomotor stimulation**
  (Barr et al., 2008, Schiz Res)
Why do people with schizophrenia smoke?

Possible Mechanisms Mediating Schizophrenia-Smoking Associations

- Genetic vulnerability
- Reduction in psychiatric symptoms
- Reduced side effects of antipsychotics
- **Improvement in sensorimotor / sensory gating and cognitive deficits**


Mackowick et al. (2014) Prog Neuropsychopharmacol Biol Psychiatry
Nicotine receptors present in several areas of the brain associated with cognition.

Nicotine/nicotine ligands improve, whereas nicotine antagonists, such as mecamylamine, disrupt performance on a variety of sensory gating and cognitive tasks.
Cognitive Deficits in Schizophrenia

A range of cognitive and sensorimotor gating deficits present:

- Prior to the manifestation of clinical symptoms
- At the first presentation of symptoms

- Some deficits also found in milder form in relatives and people with schizotypal personality traits

- **Increased vulnerability for tobacco and substance use?** (Mackowick et al., 2014, Prog Neuropsychopharmacol Biol Psychiatry)
Cognitive Deficits in Schizophrenia

Wright et al., 2015, Schizophrenia Research
Prepulse Inhibition of the Startle Response

Patients, on average, show less PPI than controls. 
(> 25 studies from Braff and other laboratories across the world)
Nicotine enhances Prepulse Inhibition in Animals


- Reversal of apomorphine-induced disruption of PPI by nicotine - blocked by mecamylamine (Suemaru et al. 2004 Br J Pharmacol).

- Nicotine attenuates disruption of PPI by phencyclidine (PCP) in some strains (Spielewoy and Markou, 1995, Behav Genet; Andreasen et al. 2006, Behab Brain Res; Terry et al. 2005 CNS Drugs Rev).
Cigarette smoking increases PPI in smoking-deprived healthy smokers.

Also reported by:
- Della Casa et al. (1998) Psychopharmacology
- Duncan et al. (2001) Psychopharmacology

Kumari et al. (1996) Psychopharmacology
Cigarette Smoking and PPI in Schizophrenia

More PPI in smoking than non-smoking patients
Swerdlow et al. (2006) Arch Gen Psychiatry

No PPI deficit under ad lib smoking
Woznica et al. (2009) Schiz Res
Subcutaneous Nicotine and PPI in Healthy Non-smokers

Kumari et al. (1997) Psychopharmacology
Nicotine Effect on PPI in Schizophrenia

Enhancement associated with symptom severity

Hong et al. (2007) Neuropsychopharmacology
Nicotine Effect on PPI in Schizophrenia

George et al. (2006) Schizophrenia Research

(A)

<table>
<thead>
<tr>
<th>Study Session</th>
<th>% Pre-Pulse Inhibition</th>
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<tbody>
<tr>
<td>D2AM</td>
<td>0 mg/day</td>
</tr>
<tr>
<td>D3AM</td>
<td>5 mg/day</td>
</tr>
<tr>
<td>D3PM</td>
<td>10 mg/day</td>
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* p < 0.01 and # p < 0.05 vs. Day 2AM; ** p < 0.01 vs. Day 3AM

(B)

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## p = 0.053 vs. Day 2AM (0.0 mg/day) in SZ smokers
Nicotine Effect on Tactile PPI in SZ

Postma et al. (2006) Psychopharmacology
Greater activation in schizophrenia patients compared to controls under nicotine.

Postma et al. (2006) Psychopharmacology
Psychosis Proneness x Smoking Status

Kumari et al. (1997) Personality & Individual Differences

Replicated by Evans et al. (2005) Psychophysiology
Clozapine reduces *ad lib* smoking.


Clozapine also improves PPI.

(Kumari et al., 1999, Am J Psychiatry; Vollenweider et al., 2006, Biol Psychiatry)
Nicotine Effects on Antisaccade
Recordings – Prosaccade
Anti-saccade
Nicotine Effects on Antisaccade

- Reduces error rate in smoking and non-smoking patients
  (Petrovsky et al. 2013, Int J Neuropsychopharmacol)

- Also in smoking and non-smoking high schizotypals
  (Schmechtig et al. 2014, Psychopharmacology)
Nicotine Effects on Other Cognitive Tasks

Impaired following nicotine withdrawal in smokers

- Attention
- Inhibitory control
- Processing speed
  
  (AhnAllen et al., 2015, Nicotine, Tobacco Res)

Inconsistent relationship between chronic smoking and cognitive performance (i.e. difference between smoking and non-smoking patients)

  (Hickling et al. 2017, Schiz Res)
Cannabis and Tobacco

• Frequently co-administered together (Hindocha et al., 2016, Front Psychiatry)

• Cigarette smoking mediates the relationship between frequency of cannabis use and dependence (Hindocha et al., 2015, Drug Alcohol Depend)

• Both cigarette smoking and cannabis use highly prevalent in schizophrenia (Koskinen et al., 2010, Schiz Bull.

• Cannabis produces impairments, similar to that seen in schizophrenia, especially in working and verbal memory domains (Broyd et al., 2016, Biol Psychiatry; Curran et al., 2016, Nat Rev Neurosci)
Cannabis and Tobacco

Nicotine (acutely) improves memory in

- Smokers and non-smokers
  (meta-analysis; Heishman et al., 2010, Psychopharmacology)

- People with schizophrenia
  (Sacco et al, 2005, Arch Gen Psychiatry; Smith et al, 2006, Neuropsychopharmacol)
The individual and interactive effects of cannabis and tobacco on cognition

- Cannabis alone impaired verbal memory but not when combined with tobacco
- Cannabis load-dependently impaired manipulation of information in working memory
- Performance improved after tobacco, compared with placebo.

Hindocha et al., 2017, Psychological Medicine
Promoting Smoking Cessation in Schizophrenia

- Nicotine Replacement Therapy
- Varenicline
- Bupropion
- Behavioural and Psychosocial Interventions

Stubbs et al., 2016, Acta Psychiatrica Scand
Roberts et al. 2016, Addiction

Tsoi et al. (2013) Cochrane Database Syst Rev
Contingency reinforcement with money effective in the short term.
Promoting Smoking Cessation in Schizophrenia

Garcia-Portilla et al. (2016), Schiz Res

• Transdermal nicotine patches (TNP) or Varenicline
• Non-randomized, open-label, prospective with a 9-month follow-up
• 12-week 7 day smoking cessation rate: 50% (TNP) vs 49.33% (varencline)
• At weeks 24 and 36: 41.3% and 37.3% abstinent
• No worsening of symptoms
Promoting Smoking Cessation in Schizophrenia

Cather et al. (2017) J Dual Diagnoses
- Varenicline and behavior therapy
- 12 weeks trial
- 74/179 (41%) achieved 2 or more weeks of continuous abstinence

Jeon et al. (2016) Schiz Res
- Varenicline vs placebo
- 8 weeks trial
- Smoking reduced in the active arm only
Effect of Varenicline

Independent of smoking status

Also improved P50 gating.

Hong et al. (2011) Arch Gen Psychiatry
Promoting Smoking Cessation in Schizophrenia

Brody et al. (2017) Nicotine Tob Res

- Combination (CBT, bupropion, nicotine patches & lozenge) + bi-weekly home visits with brief behavior therapy for 26 weeks OR
- Combination without home visits  OR
- Treatment-as-usual (CBT + serial single or combination as per standard care)

**Combination + home visits most effective**

(success rate 45%, 20% and 8%)
Promoting Smoking Cessation in Schizophrenia

Evins et al. (2017) Schiz Res

- >12 weeks of *maintenance therapy* with varenicline or placebo to smokers abstinent after 12 weeks of open varenicline treatment (pooled analysis of 2 RCTs)

Maintenance pharmacotherapy normalized relapse curve.
Predictors of Smoking Reduction / Early Abstinence in Schizophrenia

- Later age at smoking initiation and attention performance predict early abstinence (Culhane et al., 2008, J Clin Psychiatry)

- Fewer cigarettes/day, better attention and remitted alcohol dependence predict abstinence (Schuster et al., 2017, Addict Behav)

- Readiness to quit (Chou et al., 2015, Eur Arch Psychiatry Clin Neurosci)

Poor recognition of health risks of smoking in SZs (40.3% vs 62.5%) (Kowalczyk et al., 2017, J Dual Diagnoses)
Number of years since last cigarette controlling for pack-years, age and gender

Karama et al. (2015) Molecular Psychiatry
Smoking Cessation in Schizophrenia

- A combination of drug and psychological therapies

- **Relapse prevention**

  (Baker et al. 2007 Psychiatry Res)
Smoking Cessation in Schizophrenia

- Develop nicotinic agonist (and other) treatments capable of improving gating and attention at least for a subgroup

- Tobacco x Cannabis (other drugs)

- Attention to co-morbid issues (e.g. PTSD or depressive symptoms) which appear linked to different aspects of smoking behaviour

(Besson and Forget, 2016, Front Psychiatry)
Open for Discussion

Questions & Comments Please.

Veena Kumari, PhD
v.kumari@sovhealth.com

Tonmoy Sharma, MBBS, MSC
t.Sharma@sovhealth.com

24/7 Admissions Line
866-594-3271

www.sovcal.com