

**The Use of NRTS and other  
FDA Approved Tobacco  
Treatment Pharmacotherapies**  
PBHCI Tobacco Cessation  
Webinar Series

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**Learning Objectives**

- Increase knowledge and awareness of FDA approved tobacco treatment pharmacotherapies
- Understand interactions between tobacco smoke and psychiatric medications
- To understand key aspects of tobacco assessment necessary for developing treatment plans
- To identify barriers related to the use of tobacco treatments in behavioral health treatment settings

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**Assessment**

- **Level of Tobacco/  
Nicotine Dependence**
- **Motivation to Quit**

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## Tobacco Use Disorder

Most 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 activities
- use despite problems
- larger amounts consumed than intended
- Craving; strong urges to use

DSM-5

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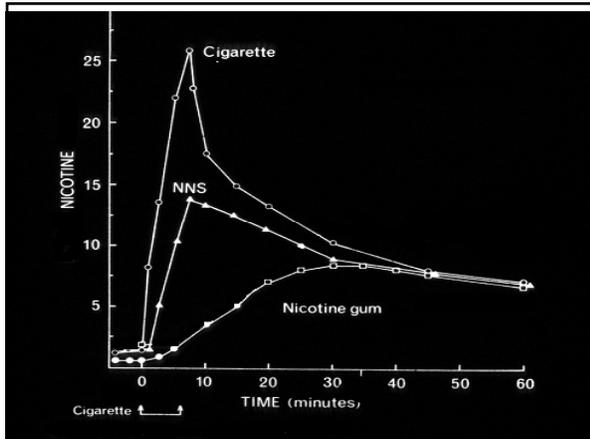
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## Tobacco Withdrawal

Emerges hours after last cigarette  
Can last for (4) weeks

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

DSM-5

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## Heaviness of Smoking Index= Measure of Dependence

Number of cigarettes per day (cpd)

AM Time to first cigarette (TTFC)

≤ 30 minutes = moderate

≤ 5 minutes = severe

*Heatherton 1991*

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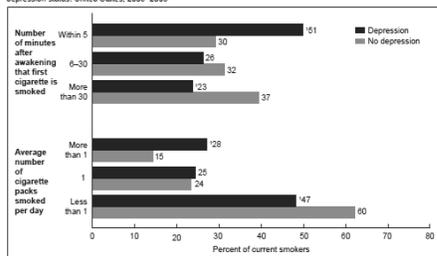
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## Smokers with depression smoke more cpd and are more dependent

Figure 3. Percentage of current smokers aged 20 and over, by time of first cigarette and amount smoked per day, by depression status: United States, 2005-2008



\*Significantly different from no depression.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2005-2008.

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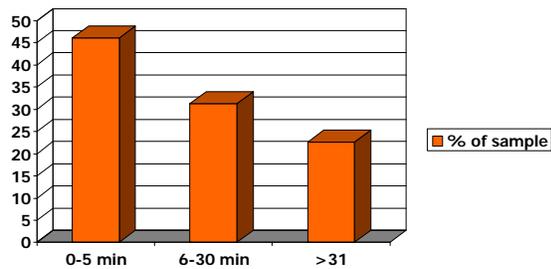
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## Smokers in NJ Addiction Treatment are Moderately to Severely Addicted to Nicotine



N=1882 smokers in NJ addictions treatment, 2001-2002;

*Williams et al., 2005*

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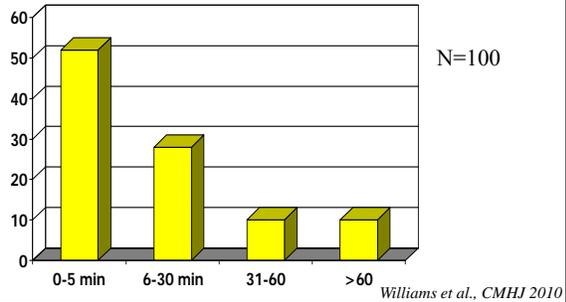
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80% of Smokers with SMI report smoking within 30min of awakening




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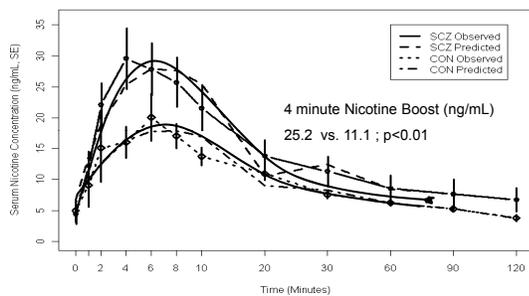
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Individuals with schizophrenia highly addicted



Greater nicotine intake per cigarette

Williams NTR 2010

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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% ↓ at 24 h for NRT group
- Better response in lower dependence
- Same magnitude of response as antipsychotic studies

Allen 2011; Am J Psych

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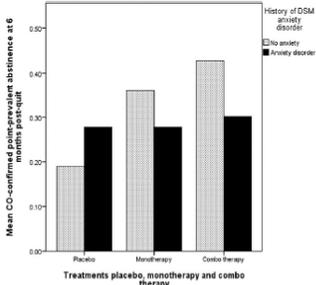
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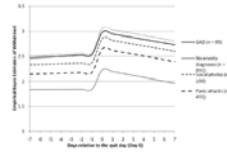
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## Reduced Success Quitting in Smokers with Anxiety Disorders



### More withdrawal symptoms



panic, social anxiety or GAD

Piper et al., 2010

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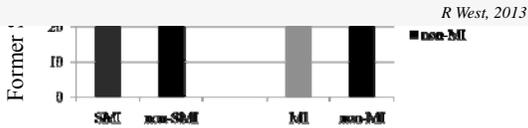
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## Smokers with MI or SMI Reduced Quitting over Lifetime

$$E = N \times S$$

Exsmokers = (number trying to quit) x (success of attempts)



R West, 2013

mental illness = anxiety, MDE, PTSD, psychoses, bipolar, drug dependence  
SMI= measured by K6

Hagman 2007; McClave 2010; Lasser 2000; Pratt & Brody 2010

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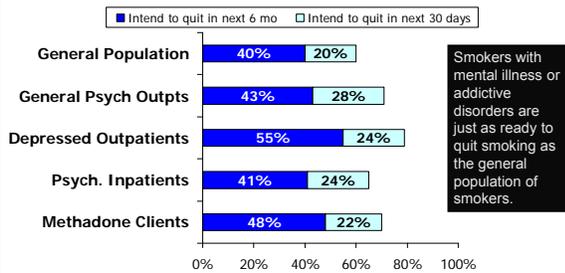
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## READINESS to QUIT in SPECIAL POPULATIONS



Smokers with mental illness or addictive disorders are just as ready to quit smoking as the general population of smokers.

\* No relationship between psychiatric symptom severity and readiness to quit

Slide Courtesy J Prochaska; Acton 2001; Prochaska 2004; Prochaska 2006; Nahvi 2006

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## Access to Clinical Treatment

- Engaging Smokers
  - Motivational Techniques
- Wellness Curriculum
  - Learning about Healthy Living
- Adapted Cessation
  - High Levels of Dependence
  - Aggressive Medications and Counseling

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## Pharmacological Treatment

### Rationale

- Reduce or eliminate withdrawal
- Block reinforcing effects of nicotine
- Manage negative mood states
- Unlearn smoking behaviors
- Cost-effective treatment
- Lessen/delay weight gain

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## Hard to Quit Without Treatment

70% of smokers report wanting to quit someday  
Few people quit successfully without treatment  
Only 1/3 of quitters (without treatment) remain  
abstinent for 2 days

**< 5% ultimately successful on a  
given quit attempt**

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## 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

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## Pharmacological Treatment

FDA Approved

### Nicotine Replacement (NRT)

Patch

Gum

Lozenge

Inhaler

Nasal Spray

**Counseling +  
Medications =  
Best treatment  
plan**

**Bupropion**

**Varenicline**

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## 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
- Not introducing a “new drug”

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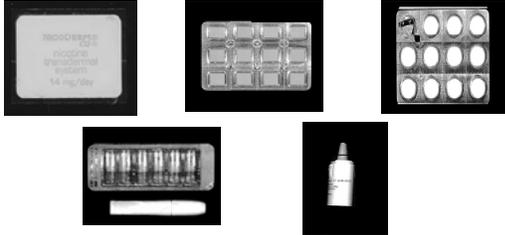
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## Nicotine Replacement

- Smokers misinformed about safety/efficacy
- Risk-benefit ratio nicotine > tobacco



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## Few Contraindications to NRT

OTC labeling

With caution if:

- Recent MI
- Smokes < 10 cpd
- Pregnant/breastfeeding
- Adolescents (Not FDA approved)

Mild side effects

- Mostly local
- Systemic, less common

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## 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

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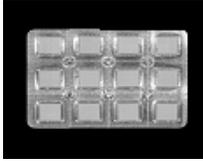
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## Nicotine Gum



Use every 1 hour  
Bite and “park” method  
Slow, buccal absorption  
Acidic foods ↓ absorption  
Side effects- mouth, throat  
burning  
Dose: 2mg < 25 cpd  
4mg > 25 cpd  
OTC

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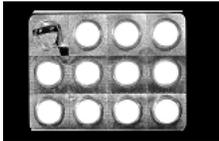
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## Nicotine Lozenge



Don't chew  
2 and 4mg dose  
More discreet than gum  
Up to 20 lozenges/ daily  
Dose based on TTFC  
2mg if > 30 mins TTFC  
4 mg < 30 mins TTFC  
OTC; Mini lozenge

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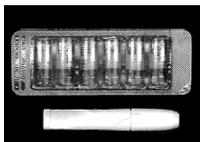
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## Nicotine Inhaler



6-16 cartridges/day  
Puff for 20-30 minutes  
Oral puffer  
Acidic beverages decrease  
absorption  
Side effects- throat irritation  
or coughing  
Rx needed

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**First-line Treatments**  
(FDA Approved)

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

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**Bupropion SR**

- Start 150mg/day to dose of 150mg bid
- 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
- Noncompetitive nicotinic receptor antagonist
- Similar efficacy to NRT

*Slemmer 2000*

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**Bupropion Effective in Schizophrenia**

- 8 published studies vs placebo
- Although 6 month outcomes of bupropion treatment are similar whether or not NRT was given concomitantly
- Shorter outcomes (4 weeks of continuous abstinence (CA) measured 8 weeks after TQD), bupropion plus NRT yielded quit rates which are the highest ever reported in SS
  - 28 % CA (George 2008)
  - 52% CA (Evins 2007).

*Tsoi 2013; Dixon 2010*

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## Combination Therapies

Improves abstinence rates  
Decreased withdrawal  
Well tolerated

*Kornitzer 1995*

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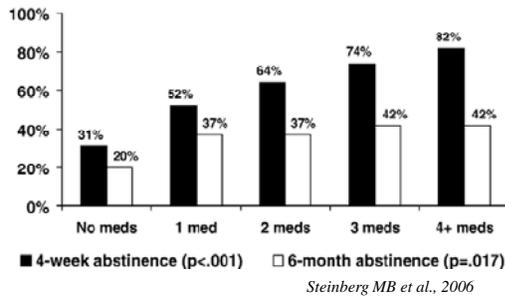
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## Number of medications predicted abstinence in a tobacco clinic



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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*

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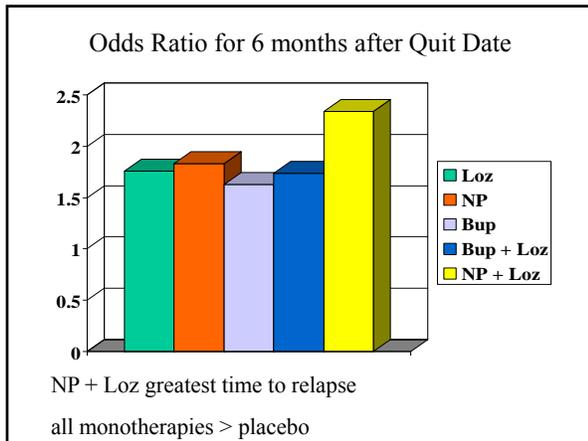
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### Smoking with NRT

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

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### Cut Down To Quit (CDTQ)

- NRT previously licensed in the UK for quitting have recently been granted a new licensed indication called 'cut down to quit' (CDTQ).
- Aims at smokers unwilling or unable to stop smoking in the short term
- Gradually to cut down smoking over an extended period while taking NRT
- Gum and inhaler

*Wang et al., 2008*

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### NRT Assisted Reduction

- 7 Smoking Reduction trials (four Nicotine gum, two inhaler, and one free choice NRT)
- 2767 smokers
- NRT for 6-18 months
- 6.75% of smokers receiving NRT had sustained abstinence for six months, 2X more those receiving placebo
- No statistically significant differences in adverse events and discontinuation because of adverse events except nausea →more with NRT
- **Whether smokers are motivated to reduce then quit or simply motivated to reduce may make little difference to the efficacy of NRT for smoking cessation**

*Moore et al., BMJ, 2009*

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### 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

APRIL2013  
[www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm](http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm)

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### Varenicline Summary

- Selective  $\alpha 4\beta 2$  nicotinic receptor partial agonist
- No drug-drug interactions
- Precaution in ESRD
- Dosed with food to reduce nausea

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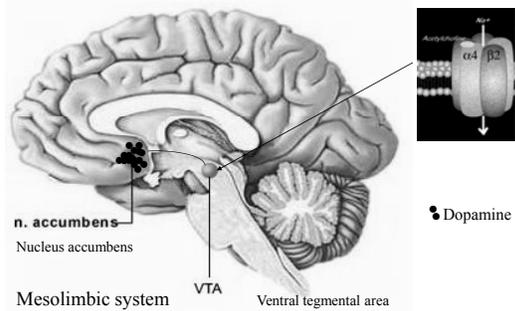
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## Varenicline: a selective $\alpha 4\beta 2$ nicotinic receptor partial agonist




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## Varenicline

### Partial Agonist

- Partially stimulates receptor
- Some DA release at NAcc
- Prevents withdrawal

### “Antagonist”

- Blocks nicotine binding  $\alpha 4\beta 2$
- \*\*Don't use as combination

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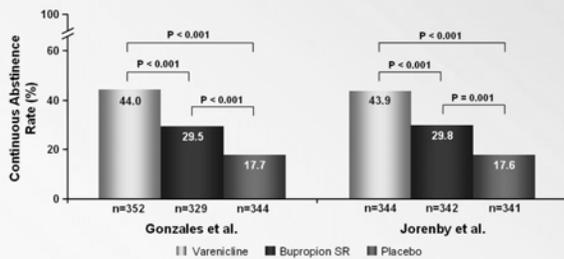
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## Chantix™ (varenicline) Phase 3 Studies: Efficacy Measurements: CO-Confirmed 4-Wk Continuous Abstinence Rates Wks 9–12



The 9-12 week Continuous Abstinence Rate is defined as the percentage of subjects who abstained from smoking (not even a puff) from Week 9 through Week 12 of the study as confirmed by both subject self-report and by end-expiratory carbon monoxide (CO) measurement.  
 The most frequently reported adverse events (>10%) with Chantix were nausea, headache, insomnia, and abnormal dreams.  
 1. Gonzalez D et al. JAMA. 2006;296:47-55. 2. Jorenby DE et al. JAMA. 2006;296:56-63.

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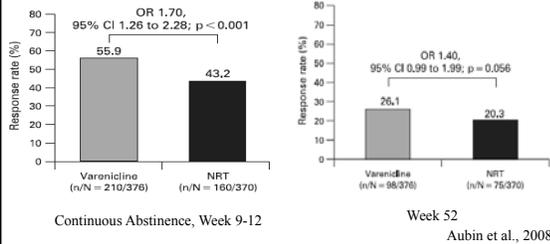
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## Varenicline vs Nicotine Patch

- Open label (N=776)
- 12 Week varenicline vs 10 week NP
- Nausea: varenicline (37%) > NP (10%)




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## Varenicline Labeling Updates

- Warning (Reported with Chantix)
  - 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

[www.PfizerPRO.com/chantix](http://www.PfizerPRO.com/chantix)

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## Varenicline and Suicide

- 80,660 smokers prescribed NRT (~63k), varenicline (~11k), and bupropion (~6k); UK, primary care
- Compared with NRT, the hazard ratio for self harm among people prescribed varenicline was 1.12 (95% CI 0.67 to 1.88), and it was 1.17 (0.59 to 2.32) for people prescribed bupropion.
- **No clear evidence that varenicline was associated with an increased risk of fatal (n=2) or non-fatal (n=166) self harm**
- **No evidence that varenicline was associated with an increased risk of depression or suicidal thoughts**

Gunnell et al., 2009; BMJ

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## 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

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## 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*

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## 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**

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## Conclusions

- Smokers with addictions and mental illness comorbidity need increased access to tobacco treatments
- Usual treatments work although efficacy can be reduced
- Important interactions between tobacco smoke and psychiatric medications
- Varenicline more effective than other treatments
- Combinations more effective

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## References

- Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C and George TP. A Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Varenicline for Smoking Cessation in Patients with Schizophrenia or Schizoaffective Disorder. *J Clin Psychiatry* 2012 May; 73(5): 654-660
- Williams JM, Gandhi KK, Lu SE, Kumar S, Steinberg ML, Cottler B, Benowitz NL. Shorter interpuff interval is associated with higher nicotine intake in smokers with schizophrenia. *Drug Alcohol Depend*, 2011 Nov 1;118(2-3):313-9. Epub 2011 May 18.

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