

Pharmacological Approaches for Treating Tobacco

Jill Williams, MD
Professor of Psychiatry
Director, Division of Addiction Psychiatry
Rutgers-Robert Wood Johnson Medical School

Free Resources

US PHS Clinical Practice Guidelines
[www.surgeongeneral.gov/
tobacco/treating_tobacco_use08.pdf](http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf)

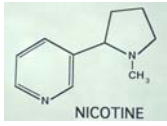


Tobacco Use Disorder

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



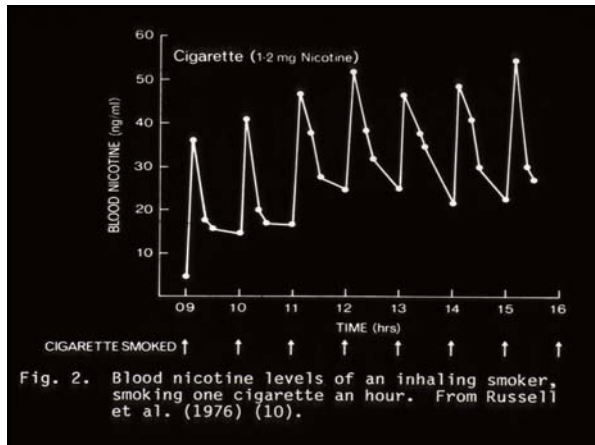
Nicotine Pharmacology

Pharmacology depends on delivery route

Reaches brain in 10 sec

Half-life 2 hours

Metabolized to cotinine in liver



Tobacco Withdrawal

4 or more

Depressed mood

Insomnia

Irritability, frustration or anger

Anxiety

Difficulty concentrating

Restlessness

Increased appetite or weight gain

Heaviness of Smoking Index= Measure of Dependence

Number of cigarettes per day (cpd)

AM Time to first cigarette (TTFC)

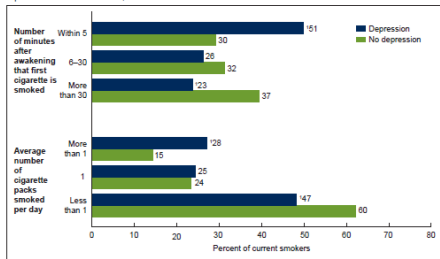
≤ 30 minutes = moderate

≤ 5 minutes = severe

Heatherton 1991

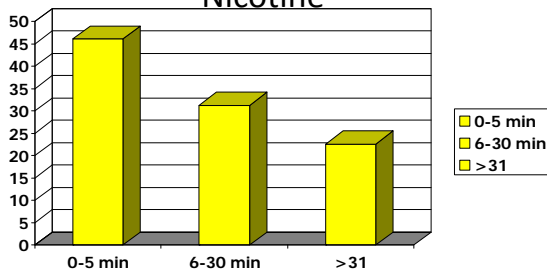
Smokers with depression smoke more cpd and are more dependent

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.

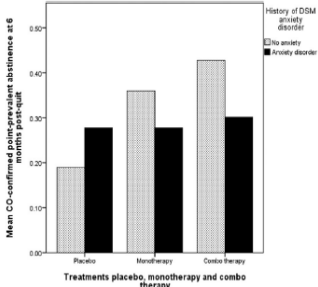
Smokers in Addiction Treatment are Moderately to Severely Addicted to Nicotine



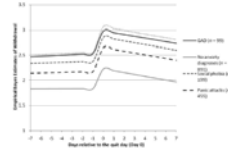
N=1882 smokers in NJ addictions treatment, 2001-2002;

Williams et al., 2005

Reduced Success Quitting in Smokers with Anxiety Disorders



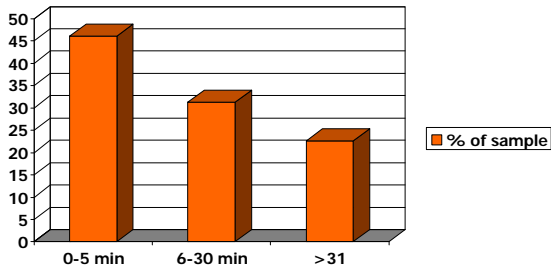
More withdrawal symptoms



panic, social anxiety or GAD

Piper et al., 2010

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

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

Pharmacological Treatment

Rationale

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

First-line Treatments (FDA Approved)

- **Nicotine Replacement**

- **Bupropion**

Zyban/ Wellbutrin

- **Varenicline**

Chantix

Counseling + Medications =
Best treatment plan

Pharmacological Treatment

Nicotine Replacement

Patch

Gum

Lozenge

Inhaler

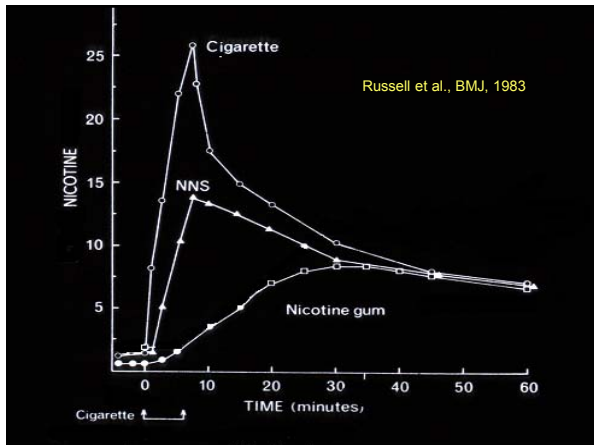
Nasal Spray

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



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

New Directions for Use Flag

- New Directions for Use Flag to be added to the front panel of GSK NRT to highlight changes to consumers
- The flag will be printed on all variants of NRT for a period of 6 months



NRT Cardiovascular Toxicity

- **Nicotine patches are safe to use in smokers with cardiac disease**

- VAMC study of 584 smokers with known CAD
- 21mg nicotine patch vs. placebo
- Abstinence 21% vs. 9%; 1 year 14% vs. 11%
- No difference in MI, death or other endpoints
- Many smoked with the patch

Joseph et al., 1996; Benowitz 1997

Nicotine Patch



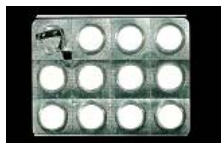
- Slow onset of action
- Continuous nicotine delivery
- 24 or 16 hour dosing
- Easy, good compliance
- No strict tapering or timeline
- Side effects- skin reaction, insomnia
- OTC

Nicotine Gum



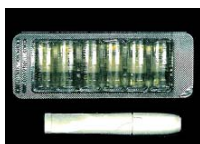
Use every 1 hour
Bite and “park” method
Slow, buccal absorption
Acidic foods ↓ absorption
Side effects- mouth, throat
burning
Dose: 2mg < 25 cpd
4mg > 25 cpd
OTC

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

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

Nicotine Nasal Spray



Rapid delivery through 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

Combination Therapies

Improves abstinence rates

Decreased withdrawal

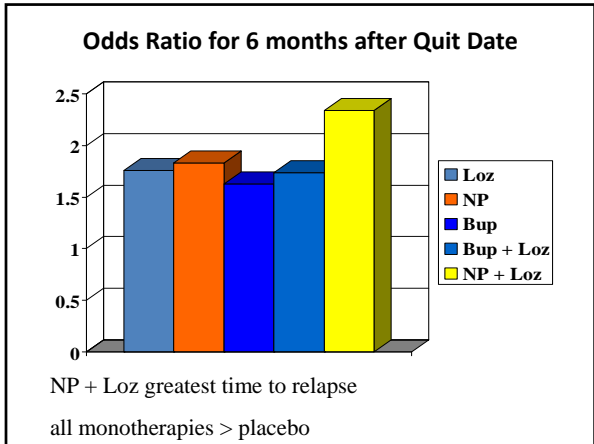
Well tolerated

Kornitzer 1995

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

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

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

First-line Treatments (FDA Approved)

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

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

Slemmer 2000

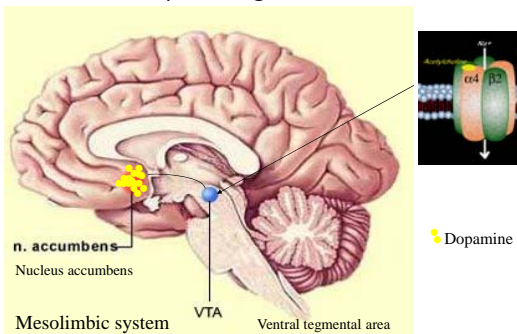
Bupropion SR

- Similar efficacy to NRT
- Effect independent of depression
- Works in different genders or races
- Works in those who failed prior NRT
- Works in those who failed prior bupropion (ie. Retreatment is effective)
- Less weight gain with 300mg than placebo

Varenicline Summary

- $\alpha 4\beta 2$ partial Nicotinic agonist
- No drug-drug interactions
- Excreted by kidney (urine)
- Only precaution in severe kidney disease

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



Varenicline

Partial Agonist

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

“Antagonist”

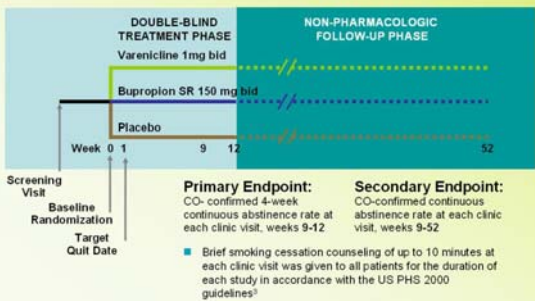
- Blocks nicotine binding $\alpha 4\beta 2$

Most Common Varenicline Side Effects

- Nausea
- Insomnia
- Abnormal dreams
- Constipation
- Flatulence
- Vomiting

Dosed twice a day
with food to reduce
nausea

Design of Chantix™ (varenicline) Phase 3 Primary Efficacy Studies



1. Gonzalez D et al. JAMA. 2006;296:47-55. 2. Jorenby DE et al. JAMA. 2006;296:56-63.
3. Fiore MC et al. U.S. DHHS. U.S. Public Health Service. 2000.

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

Review of Studies for Neuropsychiatric Adverse Events

- 17 Pfizer-sponsored studies (N=8027)
 - 1004 with psychiatric
- DOD (N=35,800) VAR vs NRT
 - No ↑ in hospitalizations for AE
 - Prior to FDA warning; gen pop sample
- Depression, aggression/agitation, suicidal events and nausea

Gibbons et al., AJP, 2013

Review of Studies for Neuropsychiatric Adverse Events

- VAR **not** significantly associated with suicidal thoughts or behavior (OR=0.57)
- VAR **not** significantly associated with depression (OR=1.01)
- VAR **not** significantly associated with aggression/ agitation (OR=1.27)

- Rates of NP AE 2.28% VAR vs 3.16% for NP

Gibbons et al., AJP, 2013

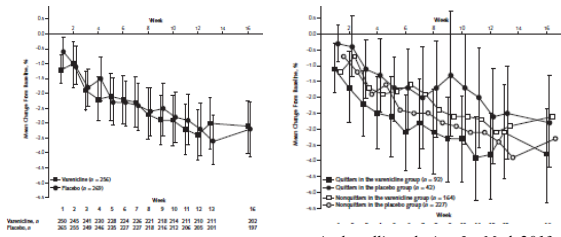
Varenicline- Major Depression

- 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

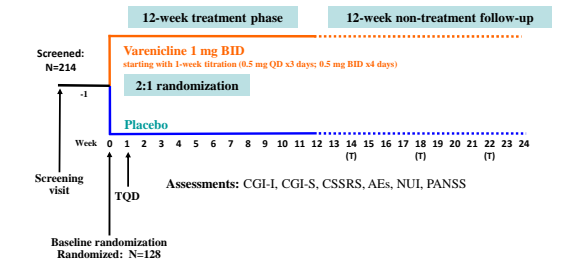
No difference in AEs (abnormal dreams, anxiety, agitation, restlessness, SI)



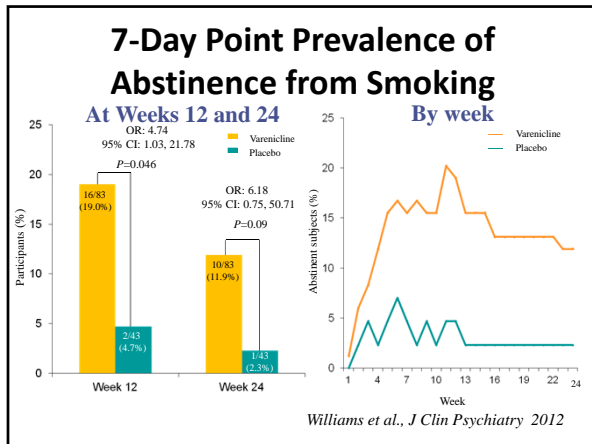
Anthenelli et al., Ann Int Med, 2013

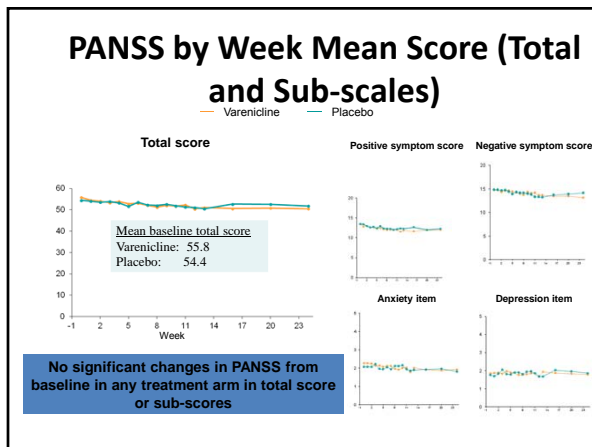
Safety and Efficacy of Varenicline for Smoking Cessation in Patients with Schizophrenia and Schizoaffective Disorder

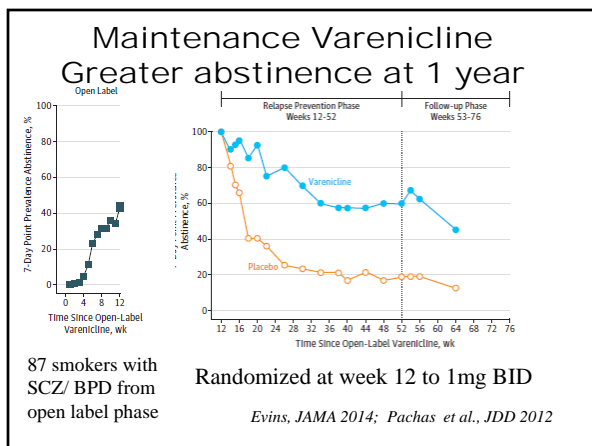
Randomized, placebo-controlled, double-blind, multicenter study

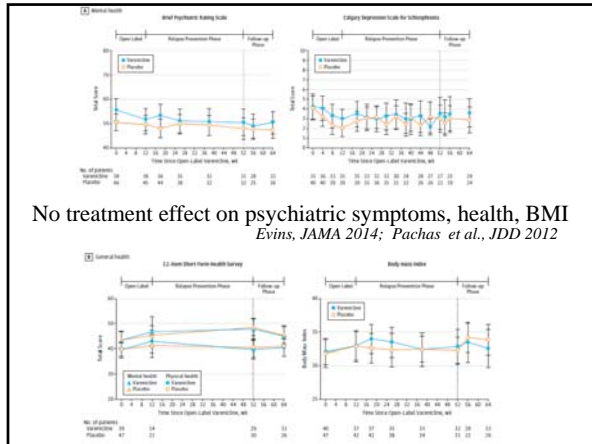


AEs, adverse events; BID, twice daily; CGI-I, Clinical Global Impression Improvement; CGI-S, Clinical Global Impression Severity of Illness scale; CSSRS, Columbia-Suicide Severity Rating Scale; NUI, nicotine use inventory; PANSS, Positive and Negative Symptom Scale; QD, once daily; T, telephone visit;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









- ### Bupropion Adverse Effects
- French dataset: 700,000 patients
 - 1682 cases of adverse reactions were reported
 - ~ 1/3 of these involved SAR
 - Allergic reactions (31.2%), including angioedema and serum sickness-like reactions.
 - Serious neurological reactions were frequent (22.5%), mostly comprising seizures; almost half of these patients had history seizures or other risk factors.
 - Serious neuropsychiatric adverse events reported (17.3%), suicide attempts/suicides were a cause for concern, although risk factors (history of depression, suicide attempts, etc.) were described for 66% of patients experiencing these events.
- Beyens et al., 2008*

- ### Black Box Warnings
- Antidepressants- suicidal ideation in children
 - Lithium - toxicity
 - Divalproex (Depakote) – hepatic failure
 - Carbamazepine (Tegretol)- aplastic anemia
 - Lamotrigine (Lamictal) – Toxic epidermal necrolysis
 - Bupropion (Wellbutrin)- serious allergy, seizure
 - Methylphenidate (Ritalin/ Concerta)
 - Clozapine (Clozaril) agranulocytosis
 - Antipsychotics– mortality elderly dementia-psychosis
- <http://blackboxrx.com/index.php>

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**



Conclusions

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 treatments
