Treatment of Tobacco and Cocaine Use Disorders

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Massachusetts General Hospital
Associate Professor of Psychiatry
Harvard Medical School
My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Advisory Board: Pfizer Inc
Consultant: Pfizer Inc
Public Health Burden of Tobacco Dependence

- Nearly 68 million smokers in the US
- 3 million tobacco-related deaths annually worldwide -- 440,000 in the US
- 19% of Americans currently smoke
- 25% of Americans are former smokers
- 54% of those with SMI smoke
- Numbers of smokers are INCREASING
- 100 million people died in the last century from smoking related causes Anticipated that 1 billion smokers worldwide will die from smoking related causes in this century – WHO
Potential public health impact of improved, integrated addiction treatment in a chronic care model

- **Opioid overdoses** killed more than 29,000 people in 2014, more than any prior year.
- Over 88,000 alcohol related deaths per year and increasing.
- Approx. 18,000 illicit drug overdose deaths
- Over 430,000 tobacco related deaths per year and not decreasing.
Smoking Kills


% survival from age 35

Continuing cigarette smokers since 1951

Never smoked regularly

Age

58%  10 years

81%
Quitting Helps

Effect of stopping smoking at age ~40 on survival from age 40

% survival from age 40

Continuing cigarette smokers

Never smoked regularly

--- stopped age 35–44
Illustration of the effects of a 3-fold difference in annual death rates on mortality at ages 35-79 *

Adapted from the One Million Women Study
Pirie, Peto, et al., Lancet 2013
THE MILLION WOMEN STUDY

Quitting by age 50 cuts mortality in half

All-cause mortality

Relative Risk (95% CI)

1.01 1.05 1.20 1.56

20 30 40 50

Ex-smokers, by age at stopping

Pirie, Lancet, 2013
50 Years after the first Surgeon General’s report of an association between smoking and cancer, adult smoking has declined 55% in the general US population.

Smoking prevalence among adults with SMI in the US today is 53%.

This is higher than in the US general population in 1964.
Smoking-Related Mortality in Those with Psychiatric Disorders

- In those with one or more lifetime hospitalizations for schizophrenia, bipolar disorder, or MDD,

- HALF died from to 1 of 19 diseases identified by CDC as causally linked to tobacco use

Callaghan, 2014
Quitting Reduces

- Death
- MI
- Stroke
- Progression of atherosclerosis
- Bronchitis
- Diabetes Morbidity
- Cancer Risk
- Progression of COPD
META-ANALYSIS CONFIRMS: SMOKING CESSATION IMPROVES PSYCHIATRIC SYMPTOMS, QUALITY OF LIFE

- 26 studies
- Change in psychiatric symptoms was compared between continuing smokers and successful quitters
- **Depression, anxiety, stress and quality of life** improved among those who quit smoking significantly compared to those who continued smoking.
- It did not matter whether one had a pre-existing psychiatric diagnosis or not!!
- Effect sizes comparable to those observed for antidepressant medications!!!
Smoking Cessation Is Associated with Improved Psychiatric Symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>SE</th>
<th>Weight (%)</th>
<th>Weight difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solomon 2006</td>
<td>0.19</td>
<td>25</td>
<td>-0.06 (-0.42 to 0.30)</td>
</tr>
<tr>
<td>Dawkins 2009</td>
<td>0.25</td>
<td>20</td>
<td>-0.19 (-0.68 to 0.30)</td>
</tr>
<tr>
<td>McDermott 2013</td>
<td>0.13</td>
<td>29</td>
<td>-0.74 (-1.00 to -0.48)</td>
</tr>
<tr>
<td>Becroa 2002</td>
<td>0.18</td>
<td>26</td>
<td>-0.37 (-0.72 to -0.02)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>106</td>
<td>-0.37 (-0.70 to -0.03)</td>
</tr>
<tr>
<td>Test for heterogeneity: $\tau^2=0.06$, $\chi^2=10.43$, df=3, $P=0.02$, $I^2=71%$. Test for overall effect: $z=2.16$, $P=0.03$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Depression     |     |            |                            |
| Solomon 2006   | 0.19|            |                            |
| Berlin 2010    | 0.22|            |                            |
| Blalock 2008   | 0.22|            |                            |
| Dawkins 2009   | 0.25|            |                            |
| Kahier 2011    | 0.21|            |                            |
| Vazquez 1999   | 0.17|            |                            |
| Busch 2011     | 0.19|            |                            |
| Kahier 2002    | 0.20|            |                            |
| Munaf 2008     | 0.09|            |                            |
| Kinrunen 2006  | 0.11|            |                            |
| Total          |     | 100        | -0.25 (-0.37 to -0.12)     |
| Test for heterogeneity: $\tau^2=0.01$, $\chi^2=12.83$, df=9, $P=0.17$, $I^2=30\%$. Test for overall effect: $z=3.89$, $P=0.001$ |

| Mixed anxiety and depression |     |            |                            |
| Blalock 2008    | 0.44|            |                            |
| Kahier 2009    | 0.29|            |                            |
| Steinberg 2011 | 0.14|            |                            |
| Mino 2000      | 0.26|            |                            |
| Chassian 2002  | 0.13|            |                            |
| Total          |     | 100        | -0.31 (-0.47 to -0.14)     |
| Test for heterogeneity: $\tau^2=0.00$, $\chi^2=1.94$, df=4, $P=0.75$, $I^2=8\%$. Test for overall effect: $z=3.61$, $P=0.001$ |

| Stress         |     |            |                            |
| Manning 2005   | 0.17|            |                            |
| Hajek 2010     | 0.09|            |                            |
| Chassian 2002  | 0.13|            |                            |
| Total          |     | 100        | -0.27 (-0.40 to -0.13)     |
| Test for heterogeneity: $\tau^2=0.00$, $\chi^2=0.77$, df=2, $P=0.68$, $I^2=8\%$. Test for overall effect: $z=3.80$, $P=0.001$ |

Taylor et al., BMJ, 2014

Evins, MGH CAM
Addiction to Nicotine: Mechanism and Therapeutic Targets

• Acetylcholine stimulates nicotinic cholinergic receptors on dopaminergic and glutamatergic neurons in hippocampus prefrontal cortical areas as well as nucleus accumbens and other reward areas

• Nicotine stimulates a4b2, a7 and other nAChRs in brain

• Therapies target Nicotinic Receptors: NRT, Varenicline, Cytisine

• Or downstream targets such as dopaminergic targets: Bupropion, agents specific for subtypes of dopaminergic receptors under development

• **Exception:** Nicotine stimulation upregulates receptor expression, especially high-affinity a4b2 receptors
Cessation Works:
Pharmacotherapy + Behavioral Therapy Doubles to Triples Abstinence Rates

Cahill et al., JAMA 2014

<table>
<thead>
<tr>
<th>Comparison (Intervention vs Control)</th>
<th>No. of Studies</th>
<th>Total No. of Individuals</th>
<th>Intervention n/N (%)</th>
<th>Control n/N (%)</th>
<th>Odds Ratio (95% Credible Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRT vs placebo</td>
<td>119</td>
<td>51225</td>
<td>4704/27258 (17.3)</td>
<td>2464/23967 (10.3)</td>
<td>1.84 (1.71-1.99)</td>
</tr>
<tr>
<td>Buproplon vs placebo</td>
<td>36</td>
<td>11440</td>
<td>1214/6409 (18.9)</td>
<td>535/5031 (10.6)</td>
<td>1.82 (1.60-2.06)</td>
</tr>
<tr>
<td>Varenicline vs placebo</td>
<td>15</td>
<td>6293</td>
<td>964/3496 (27.6)</td>
<td>332/2797 (11.9)</td>
<td>2.88 (2.40-3.47)</td>
</tr>
<tr>
<td>Buproplon vs NRT</td>
<td>8</td>
<td>2581</td>
<td>191/954 (20.0)</td>
<td>375/1627 (23.0)</td>
<td>0.99 (0.86-1.13)</td>
</tr>
<tr>
<td>Varenicline vs NRT</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>1.57 (1.29-1.91)</td>
</tr>
<tr>
<td>Varenicline vs buproplon</td>
<td>3</td>
<td>1622</td>
<td>174/823 (21.1)</td>
<td>111/799 (13.9)</td>
<td>1.59 (1.29-1.96)</td>
</tr>
</tbody>
</table>
Cessation Works: Pharmacotherapy + Behavioral Therapy Doubles to Triples Abstinence Rates

First Line Tx:  
1a. Varenicline, Dual NRT,  
1b. Bupropion, Single NRT  
1c. Varenicline + NRT (single study)  
   Cahill et al., *JAMA*, 2014  
   Anthenelli et al., *Lancet* 2016

Varenicline & Dual NRT *superior to* bupropion & single NRT  
   Cahill et al., *JAMA*, 2014

Varenicline + NRT more effective than placebo + varenicline  
   Koegelenberg et al., *JAMA*, 2014
Addiction Treatment Works: Expect and Treat Relapses

For tobacco dependence: average of 5 attempts at abstinence before long-term abstinence achieved.

Treatments double to triple abstinence rates and are Underutilized!

With Sustained Treatment Efforts, Addictive Disorders for which Treatments are Available are Good Prognosis Disorders.
Repeat Cessation Attempts Are Effective

Varenicline, 12-week trial, was associated with significantly higher quit rates than placebo in those who had failed one or more prior varenicline trials.

Consider Maintenance Treatment: Point Prevalence Abstinence During One Year Maintenance Treatment


247 enrolled, 203 started open treatment, 87 (43%) attained abstinence at week 12 and were randomized to 40 weeks maintenance therapy

Evins, Cather, et al., *JAMA*. 2014
Maintenance Tx Normalizes the Relapse Curve for Smokers with Schizophrenia and Bipolar Disorder

Evins, et al., *Schiz Res.*, 2017

Proportion of participants abstinent

Study week

- SBD varenicline
- non-SBD varenicline
- non-SBD placebo
- SBD placebo
Smoking Cessation Tx Recommended but Underutilized, Particularly in Psychosis

- 2010 PORT guidelines for tx of schizophrenia recommend physician advice to quit and medication with bupropion with or without NRT for all smokers with schizophrenia.
- Smoking rates are not declining in those with psychosis
- Psychiatrists rarely offer counseling to quit smoking. In one study, only 12.4% of smoking patients were advised to quit.
- Smokers with SMI are even less likely to receive a medication to help them to quit.
- Varenicline especially underutilized in smokers with psychosis

_Treatment is effective in the long run and is under-prescribed_

Buchanan et al., 2010; Himloch and Daumit, 2003; Thorndike et al., 2001; Huang et al., 2014; Cook 2014
EAGLES Trial

- Compare risk of clinically significant neuropsychiatric AEs & efficacy of varenicline, bupropion, NRT patch, placebo
- >8000 Smokers aged 18 to 75 years; ≥10 cigs/day
- > 4000 smokers, no lifetime psychiatric diagnosis
- > 4000 smokers, 1+ clinically stable, lifetime diagnoses

<table>
<thead>
<tr>
<th>Mood Disorders</th>
<th>Major depressive disorder (MDD), bipolar I, bipolar II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety Disorders</td>
<td>Panic disorder with or without agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, generalized anxiety disorder</td>
</tr>
<tr>
<td>Psychotic Disorders</td>
<td>Schizophrenia, schizoaffective disorder</td>
</tr>
</tbody>
</table>

Clinical Characteristics of the EAGLES Psychiatric Cohort

• Included:
  – Stable but symptomatic
  – Half on psychotropic medication at baseline (>95% with psychotic disorder)
  – Half with major depressive disorder had recurrent depression
  – One third had a second psychiatric diagnosis / comorbidity
  – One fourth had a prior substance use disorder
  – One eighth had made a prior suicide attempt

  – Excluded those with active self-injurious behaviors, imminent suicide risk, or active SUD
Primary Endpoint: Composite Neuropsychiatric Adverse Event

**Primary Safety Endpoint:** Percent of subjects reporting worsening or new onset of one or more of the following during treatment and up to 30 days after last dose:

<table>
<thead>
<tr>
<th>≥1 “severe” AE of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Feeling abnormal</td>
</tr>
<tr>
<td>Hostility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>And/or ≥1 “moderate” or “severe” AE of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Homicidal ideation</td>
</tr>
<tr>
<td>Psychosis</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Mania</td>
</tr>
<tr>
<td>Suicidal ideation</td>
</tr>
<tr>
<td>Feeling abnormal</td>
</tr>
<tr>
<td>Delusions</td>
</tr>
<tr>
<td>Panic</td>
</tr>
<tr>
<td>Suicidal behavior</td>
</tr>
<tr>
<td>Hostility</td>
</tr>
<tr>
<td>Hallucinations</td>
</tr>
<tr>
<td>Paranoia</td>
</tr>
<tr>
<td>Completed suicide</td>
</tr>
</tbody>
</table>

AE, adverse event; NPS, neuropsychiatric

Designed in collaboration with FDA and EMA to be broad and capture an array of events

**Severity assessment**
Moderate = interferes to some extent with subject’s usual function
Severe = interferes significantly with subject’s usual function
EAGLES Allows Comparison of Neuropsychiatric Safety and Efficacy in Those without Psychiatric Illness

CARs Week 9-12

- Varenicline (N=2037)
- Bupropion (N=2034)
- NRT (N=2038)
- Placebo (N=2035)

Primary NPS Composite Safety Endpoint

- Varenicline (N=2037)
- Bupropion (N=2034)
- NRT (N=2038)
- Placebo (N=2035)

No Difference in Primary Composite Safety Endpoint by Treatment for Those with Primary Psychotic, Anxiety and Mood Disorders

Continuous Abstinence Rates by Treatment and Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Psychotic Disorders</th>
<th>Anxiety Disorders</th>
<th>Mood Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=390</td>
<td>Varenicline (n=95)</td>
<td>Bupropion (n=98)</td>
<td>Placebo (n=98)</td>
</tr>
<tr>
<td></td>
<td>Bupropion (n=98)</td>
<td>Nicotine patch (n=99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo (n=98)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Smoking Cessation Rates, %**

- **Primary comparisons**
  - Varenicline vs placebo
    - Weeks 9-12: 7.58 (2.46-23.33) p=0.0004
    - Weeks 9-24: 4.99 (1.58-15.78) p=0.0062
  - Bupropion vs placebo
    - Weeks 9-12: 3.22 (0.97-10.64) p=0.0551
    - Weeks 9-24: 2.90 (0.86-9.73) p=0.0847

**Secondary comparisons**

- Nicotine patch vs placebo
  - Weeks 9-12: 3.61 (1.12-11.63) p=0.0317
  - Weeks 9-24: 2.66 (0.79-8.89) p=0.0113
- Varenicline vs nicotine patch
  - Weeks 9-12: 2.10 (0.97-4.56) p=0.0607
  - Weeks 9-24: 1.88 (0.79-4.47) p=0.1542
- Bupropion vs nicotine patch
  - Weeks 9-12: 0.89 (0.37-2.14) p=0.799
  - Weeks 9-24: 1.09 (0.42-2.81) p=0.8545
- Varenicline vs bupropion
  - Weeks 9-12: 2.35 (1.05-5.29) p=0.0382
  - Weeks 9-24: 1.72 (0.72-4.10) p=0.2212
EAGLES Allows Comparison of Neuropsychiatric Safety and Efficacy in Those with Psychiatric Illness

Primary NPS Composite Safety Endpoints by Treatment for Those with Primary Psychotic, Anxiety and Mood Disorders

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Psychotic Disorder</th>
<th>Anxiety Disorder</th>
<th>Mood Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>6.3</td>
<td>5.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Bupropion</td>
<td>6.3</td>
<td>8.0</td>
<td>6.4</td>
</tr>
<tr>
<td>NRT</td>
<td>5.1</td>
<td>4.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.3</td>
<td>5.7</td>
<td>4.6</td>
</tr>
</tbody>
</table>

CARs Week 9-12 by Treatment and Psychiatric Diagnosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Psychotic Disorder</th>
<th>Anxiety Disorder</th>
<th>Mood Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>23.2</td>
<td>27.0</td>
<td>30.4</td>
</tr>
<tr>
<td>Bupropion</td>
<td>11.2</td>
<td>13.9</td>
<td>21.7</td>
</tr>
<tr>
<td>NRT</td>
<td>13.1</td>
<td>21.9</td>
<td>21.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.1</td>
<td>8.0</td>
<td>13.2</td>
</tr>
</tbody>
</table>

Adapted from Evins, et al., Society for Research on Nicotine and Tobacco 2016; Chicago
a. One additional participant (NRT group/mood subcohort) who reported suicide ideation was identified after clinical database lock and was not included in the analysis
EAGLES is a Confirmatory Trial for Efficacy

- Efficacy conclusions replicate and extend findings from smaller trials and meta-analyses in those with and without mental illness
- The efficacy data are clear
  Varenicline > bupropion and nicotine patch > placebo
- Agreement with overall, growing body of evidence, raising confidence in the findings
Quantified NPS Risk Across Treatment and Cohort

• Greater risk of NPS AE’s in Psych group versus Non-Psych group, independent of treatment
  – ~2% NPS AE rate in smokers without mental illness
  – ~5-7% NPS AE rate in smokers with mental illness

• NPS AE rates in smokers during a cessation attempt are not different by treatment, including placebo

• No pattern of NPS AE’s
  – No pattern in the most worrisome NPS AE’s
  – No psychiatric subgroup appears to be at increased risk

Neuropsychiatric Adverse Event Rate During Smoking Cessation is Independent of Treatment

- NPS AEs are seen in trials regardless of treatment
- Clinicians who prescribe a treatment and observe a NPS AE likely attribute this AE to the treatment.
- This happened in our large maintenance treatment trial of varenicline, in trials of bupropion, and in clinical practice.

Why Might There be Significant NPS AEs Among Smokers, Independent of Treatment (and Abstinence)?

• Smoking is an addiction; like all drug addictions, there are:
  – Well documented brain changes
  – Increased neuropsychiatric events, e.g. suicide
  – Suicide risk reduced in smokers who quit
• People with psychiatric illness are more likely to smoke
• Attempts to quit smoking are not risk free, with or without pharmacologic support and independent of abstinence
  – Well replicated in smokers with history of depression

EAGLES is a Landmark Study of Clinical and Public Health Importance

• The EAGLES trial is the first:
  – To compare safety and efficacy of all 3 FDA approved smoking cessation therapies in large samples of patients with and without a history of psychiatric disorder
  – To allow for comparison of safety and efficacy of smoking cessation aids in smokers with different mental illnesses
Varenicline Safety in 17 Randomized Controlled Trials:

Pooled Analysis of ALL Psychiatric Adverse Effects in 17 RCT’s of Varenicline

Varenicline increased incidence of nausea but not psychiatric adverse events while increasing abstinence rates by 124% vs placebo and 22% vs. bupropion

Having a psychiatric illness increased the risk for psychiatric adverse events in smokers trying to quit and did so equally in those assigned to varenicline and placebo

In a large observational study in 35,800 outpatients trying to quit smoking, there were fewer psychiatric adverse events in those prescribed varenicline than those prescribed NRT

Results replicated now in multiple studies in different practice populations: DoD, VA, UK NHS

Gibbons and Mann 2013; Tonstad et al., 2010; Kotz et al., 2015
FDA to Remove, Update Boxed Warnings on Mental Health Side Effects of Chantix, Zyban

“EU lifts suicide warning on Pfizer's smoking-cessation pill” –Associated Pressed

“FDA Approves Removal Of Boxed Warning Regarding Serious Neuropsychiatric Events From CHANTIX® (varenicline) Labeling” -Nasdaq

“FDA drops black box warning on Pfizer's anti-smoking drug” –Fox News

“FDA Removes Warnings on Smoking-Cessation Medication” –Pharmacy Times

“FDA Drops Stringent Warning on Smoking-Cessation Drug Chantix” –The Wall Street Journal
Implication of EAGLES: Offer Treatment to Smokers, Including Those with Stable Mental Illness

• Confirms NPS safety and efficacy of smoking cessation treatments for smokers with mental illness, a group that is:
  – More likely to smoke, to smoke heavily, and be dependent
  – Less likely to quit without a cessation aid
  – More likely to relapse after discontinuation of cessation aids
  – Likely to benefit from maintenance treatment
  – Less likely to receive advice to quit from a medical provider
  – Less likely to receive cessation aid

• Smokers with mental illness are less likely to receive a pharmacotherapeutic cessation aid from a medical provider
  – This contributes to the 25 year mortality gap in those with mental illness,
    secondary to diseases causally related to tobacco smoking
  – 28 year mortality gap for those with schizophrenia
Risk/Benefit Considerations

- Clinicians **overestimate** the risk of NPS AEs with varenicline and bupropion, particularly in those with psychotic illnesses.
- And **underestimate** the benefit of varenicline and bupropion on improving quit rates.
- It is imperative we find ways to increase use of the most effective smoking cessation treatment for our patients who try time and again to quit smoking.

Huang et al., BMC Public Health 2014
Give Brief Physician Advice to Quit

- Advise all your patients who smoke to quit
- Review health risks of tobacco use
- Educate about effective available treatments, choose and prescribe a pharmacotherapy
- Emphasize past successes, even if small, and encourage repeat attempts
- Set a quit date
- Refer for peer group support and or Quit Line
- Refer for or perform behavioral relapse prevention – CBT
- Brief advice to quit smoking has a significant impact on abstinence rates at 6 months
  - Brief advice alone decreases fatal coronary artery disease, lung cancer, and total mortality

Lancaster and Stead, 2005a
Varenicline (Chantix)

- Selective, partial a4 b2 and full a7 NACHR agonist
- FDA approved 2006 as an aid for smoking cessation
- Reduces nicotine withdrawal symptoms
  - Stimulates NACHRs
- Reduces nicotine-induced dopamine release and reward
  - Blocks binding of nicotine at NACHRs
- Superior efficacy vs placebo (and bupropion and NRT)
- Well tolerated from a psychiatric standpoint in all controlled studies to date as well as all large epidemiologic studies.
Varenicline: Safety

Case Reports: Irritability, Impulsive Behavior, Depressed Mood, Suicidal Behavior

**NOT** seen in controlled trials to date in smokers with or without co-morbid psychiatric illness

Boxed warnings removed by FDA and EMA following EAGLES Trial
Varenicline (Chantix)

- Dosing: 0.5 and 1.0 mg tabs
  - 0.5 mg/d x 3 d
  - 0.5 mg bid x 4 d
  - 1.0 mg bid x 11 weeks
  - Additional 12 weeks Tx recommended in those who achieve abstinence
  - 12-month safety data published: well tolerated

- Renal excretion

- No significant drug-drug interactions or effect on cytochrome enzymes

- Nausea-common, headache, insomnia/dreams
Bupropion SR

- Antidepressant acting via dopaminergic & noradrenergic mechanism; also a competitive NACHeR inhibitor
- First-line (1b) treatment
- Doubles odds of long-term abstinence
- Independent of depressive symptoms
- 40-44% abstinence at end of treatment
- Approx 50% relapse at 12 months

Varenicline and Bupropion Improved Health Related Quality of Life

• Treatment with Varenicline (n=696) and Bupropion (n=671) Significantly Improved Self Rated Quality of Life Over Placebo (n=685) at 12, 24, and 52 Weeks

• Significant positive association between smoking cessation and self rating of vitality, self-control, anxiety, and overall mental health profile

• Replication of several studies demonstrating reduced self report of anxiety after smoking cessation...

Hays et al., 2010
Nicotine Replacement Therapy (NRT)

- First-line (Dual NRT 1a, single NRT 1b)
- Doubles odds of abstinence over placebo
- Helpful with or without counseling
- All forms appear equally effective overall
- In heavy smokers, there is a dose-response curve with gum favoring higher dose (4 mg)
- Dose: 20-30 mg/day; may be a benefit to increased doses of NRT and to combinations of NRT forms
  - Long acting: transdermal patch
  - Short acting: gum, inhaler, nasal spray
  - Proper use of gum is critical
  - Combination use is most common

Silagy et al, 2005.
Combination Pharmacotherapy for Nicotine Dependence

May improve abstinence rates

For smokers who have relapsed after treatment with single agent, consider maintenance treatment or combination treatment:

• NRT: long acting (patch) + short acting (gum, inhaler or nasal spray) + CBT
• Bupropion 150 mg bid + NRT + CBT
• Varenicline + NRT
Behavioral Interventions

- Current guidelines recommend behavioral tx + pharmacotherapy
  - Motivational enhancement
  - Relapse prevention
  - Partner support
- Guidelines are based on several large meta-analyses of controlled trials
- Telephone counseling provides a modest benefit in quit rates vs minimal intervention
  - www.trytostop.org or 1-800-TRY-TO-STOP
- Physical exercise can decrease cravings and attenuate weight gain

USPHS, 2000; Stead et al, 2003
Withdrawal Syndrome: Nicotine

- Peaks in 4 days
- Lasts for several weeks
- Can be severe, not life threatening
  - Anxiety
  - Awakening during sleep
  - Depression
  - Difficulty concentrating
  - Impatience
  - Irritability/anger
  - Restlessness
  - Decreased heart rate
  - Weight gain
Smoking speeds hepatic metabolism of many medications.

Serum concentrations of medications that are stable in smokers may rise following abstinence.

CYP 1A1, 1A2, and 2E1:
- Abstinence associated with 30-42% reduction in 1A2 activity over the first 1-3 days of abstinence.
- Therapeutic drug monitoring and 10% dose reduction has been recommended.

Take care when prescribing bupropion to those on clozapine because of additive seizure risk.

Seppala NH, et al., 1999.
Summary – Nicotine Dependence

• Give physician advice to quit smoking
• Develop a “quit day” plan, teach coping skills, build in self-rewards, and provide written cues to reinforce abstinence
• Treat with combined behavioral treatment and pharmacotherapy
• Long-term NRT or non nicotine treatment may be warranted, both to sustain abstinence and to improve symptoms
Cocaine Dependence

- Major epidemic since 1980
- Availability of cheap, high-potency drug
- New forms: freebase/crack
- 30 million in US have used cocaine
- <20% become regular users
- 17% risk of dependence (NCS)
- Increasing incidence of lacing with Levamisole
  - Up to 80% of samples
  - 3-13% risk of agranulocytosis with sustained exposure
Pharmacology of Cocaine Dependence

- Dopamine stimulation of neurons in nucleus accumbens normally limited by dopamine reuptake
- Cocaine blocks dopamine reuptake
- Assoc. with excessive dopamine stimulation in reward system of brain - “HIGH”
- Also assoc. with depletion of dopamine in the nerve terminals of the dopaminergic neurons involved - “LOW”
- Compensatory down-regulation of post-synaptic dopamine receptors
  - Protracted syndrome of refractoriness to reward
Cocaine Use Patterns

• Binge symptoms:
  – Intense euphoria
  – Increased anxiety, dysphoria, tremor, hyperactivity
  – Long-lasting craving
  – Paranoid ideations, delusions
  – Panic attacks, depression, mania

• Withdrawal:
  – Onset: <24 hrs, peak: 2-4 days
  – Duration: 7-10 days
  – Protracted depression, craving: 1-3 months
Treating Cocaine Intoxication

- Acute cocaine intoxication:
  - Onset: seconds
  - Duration: 30-60 min
  - Dysphoria: within hours
  - Recovery: < 48 hrs
  - OD requires life support, airway

- Cocaine delusional disorder
  - Diazepam for agitation
  - Antipsychotics for delusions

- Hospitalize if suicidal or delusional
• Pharmacotherapy not required in mild withdrawal states

• For severe cocaine withdrawal:
  • Amantadine – indirect dopamine agonist, increases dopamine levels
  • Propranolol – B-adrenergic blocker reduces anxiety / severe adrenergic symptoms - 1 mg IV q min, up to 8 min

• Seizures: IV diazepam
Treating Cocaine Dependence

Relapse prevention: Pharmacotherapy

- **Disulfiram** effective in 3 trials
  - Inhibits DA-beta hydroxylase
  - Reduced craving & relapse
- **Baclofen** – GABA-B agonist: 20 mg tid
- **Topiramate** increases GABA & inhibits glutamate:
  25 mg po qd, slowly increase to 200 mg qd (Kampman, 2004)
- **Modafinil** enhances glutamate levels: 200-400 mg po qd

- However, Overall:
  - Disulfiram: evidence not supportive
  - Topiramate, other anticonvulsants: evidence not supportive
  - Anticonvulsants: evidence not supportive
  - Antipsychotics: evidence not supportive
Relapse prevention: Psychotherapy

- Contingency Management
- Manual-guided CBT
- 12-step facilitation
- Individual plus group therapy
- Behavioral reinforcement:
  - Urine testing with contingencies
  - Restrict access to money & friends
- High-intensity support to disrupt binge cycles
As with any substance use disorder, treat anxiety and depressive symptoms in those suspected of having an independent mood or anxiety disorder, especially if these symptoms appear to be interfering with attainment of abstinence.

Co-morbid depression:

- SSRIs – effective if depressed
- “May” also reduce cocaine use
- Avoid TCAs, may be associated with cardiac arrhythmia when combined with cocaine

Co-morbid bipolar disorder: No adequate med trials

- Consider combination therapy if rapid cycling