Treatment of Tobacco and Cocaine Use Disorders

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Advisory Board: Reckitt Benckizer
Substance Use Disorders in Prior Year: Ages ≥ 12 Years 2002-2005
Not Including Nicotine

SAMHSA, 2006, NSDUH; CDC 2009.
Tobacco Dependence is Even More Prevalent with a Large Public Health Burden

- 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
Addiction Treatment: 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
Abnormal Activity in Two Circuits:

1) Reward System –
Over-activated by drugs and drug cues

2) Prefrontal Cortex –
Reduced inhibitory control over behavior

Baler & Volkow, 2006; Koob & Volkow 2009
Pharmacology of SUD Treatment
Example: Nicotine

• 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

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

• Glutamatergic agents under development

• Exception: Nicotine stimulation upregulates receptor expression, especially high-affinity a4b2 receptors
Treatment for Nicotine Dependence

- Pharmacotherapy + Behavioral Tx **Doubles to Triples** Quit Rates over placebo and are Universally Recommended

- Pharmacotherapy
  - **First line:** 1a. varenicline, dual NRT (short- + long-acting NRT)
    - 1b. Bupropion, single NRT
  - Second line: nortriptyline

- Behavioral Treatment
  - Brief advice, individ/group tx, set a quit date, use “quit lines”
  - Web, phone, in person, printed materials

- Multiple quit attempts are usual and should be expected.
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
- 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  www.mghcme.org
Quitting Reduces

• Death
• MI
• Stroke
• Progression of atherosclerosis
• Bronchitis
• Diabetes Morbidity
• Cancer Risk
• Progression of COPD
Smoking Kills


% survival from age 35

Continuing cigarette smokers since 1951

Never smoked regularly

81%

58%

10 years

4

26

97

94

91

81

59

24

26

4

2

0

100

80

60

40

20

0

40

50

60

70

80

90

100

Age

Fig. 2

19-APR-2004 14:55:00

www.mghcme.org
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

Fig. 3b
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)

- Ex-smokers, by age at stopping

Current smokers

Never smokers

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.
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
Cessation Works:
Pharmacotherapy + Behavioral Therapy Doubles to Triples Abstinence Rates

Cahill et al., JAMA 2014
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)

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
Effective Treatments: Underutilized!

- Treatment guidelines recommend physician advice to quit at every visit, and physician recommendation for cessation plan for all smokers.
- But physicians document smoking status at 70% of visits; counsel to quit at 30% of visits; prescribe medications at <1% of visits.
- No improvement since 1990.
- Psychiatrists rarely offer counseling to quit smoking. In one study, only 12.4% of smoking patients were advised to quit.

Treatment is effective in the long run and is underprescribed!

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.

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!!!

*Taylor et al. BMJ 2014*
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
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
Lower Rates of Depression and Self-harm With Bupropion And Varenicline Compared with NRT

<table>
<thead>
<tr>
<th></th>
<th>Patient-years</th>
<th>Number of events</th>
<th>Incidence of event per 1000 patient-years</th>
<th>Hazard ratio</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Crude</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NRT</td>
<td>50558</td>
<td>8274</td>
<td>163.7</td>
<td>1</td>
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<tr>
<td>Bupropion</td>
<td>3162</td>
<td>357</td>
<td>112.9</td>
<td>0.69 (0.62–0.77)</td>
</tr>
<tr>
<td>Varenicline</td>
<td>24965</td>
<td>2395</td>
<td>95.9</td>
<td>0.59 (0.56–0.61)</td>
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<tr>
<td>Self-harm</td>
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<td></td>
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</tr>
<tr>
<td>NRT</td>
<td>52832</td>
<td>540</td>
<td>10.2</td>
<td>1</td>
</tr>
<tr>
<td>Bupropion</td>
<td>3259</td>
<td>20</td>
<td>6.1</td>
<td>0.60 (0.38–0.94)</td>
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<tr>
<td>Varenicline</td>
<td>25570</td>
<td>119</td>
<td>4.7</td>
<td>0.46 (0.37–0.56)</td>
</tr>
</tbody>
</table>

Kotz et al., 2015
Varenicline and Suicidal Behavior: Cohort Study in a General Practice Research Database

- 63,265 smokers treated with NRT,
- 10,973 treated with varenicline, and
- 6,422 treated with bupropion
- 2 year follow up

- Compared with NRT, the hazard ratio was
  - 1.12 (95% CI 0.67 - 1.88) for self harm with varenicline and
  - 1.17 (0.59 - 2.32) for self harm with bupropion

- No evidence varenicline associated with increased risk:
  - Depression (n=2244) (HR: 0.88 (0.77 -1.00) or
  - Suicidal thoughts (n=37) (HR: 1.43 (0.53 - 3.85)

Gunnell et al., BMJ 2009
Due to case reports of impulsive, violent, suicidal behavior, in 2008 FDA ordered additional safety studies of varenicline.

Since then FDA has ordered additional safety studies on 132 approved drugs.

Pfizer and GSK have conducted a study of >8000 smokers with and without Axis I and Axis II psychiatric illnesses: Major depressive disorder, bipolar disorder, anxiety disorders, schizophrenia, borderline personality disorder. Results will be presented this year.

Ledford, Nature 2010
Varenicline Safety

• Meta analysis of 18 RCT’s: 5072 assigned to varenicline and 3449 to placebo, included trials in schizophrenia and MDD

• NO evidence for increased rates of neuropsychiatric adverse events relative to placebo

• Meta analysis of 5 RCT’s that included the C-SSRS
• 1130 assigned to varenicline, 777 to placebo, included trials in schizophrenia and MDD
• NO evidence for increased rates of suicide related adverse events relative to placebo

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm394880.htm
More on Neuropsychiatric Adverse Events Attributable to Varenicline

- Case reports and pharmcovigilance reports of psychiatric adverse events with varenicline
- Neither prospective observational trials nor RCT’s have demonstrated an association between varenicline and psychiatric adverse events in smokers in the general population of ‘real world smokers’ or in smokers with depressive disorders or schizophrenia
- Psychiatric Adverse Event Rate among smokers with psychiatric illness trying to quit is High but NOT different between varenicline and placebo
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
- Studies underway to determine incidence and causal relationship between varenicline and behavioral symptoms
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
Bupropion SR

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

Nicotine Replacement Therapy (NRT)

- First-line
- 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.
May improve abstinence rates, especially for smokers who have relapsed after treatment with single agent:

- 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
  – 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
Tobacco Abstinence: Effects on Metabolism

- 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
### Smoking Prevalence in Psychiatric Patients

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Overall (Outpatients)</td>
<td>50%</td>
</tr>
<tr>
<td>Major depressive Disorder</td>
<td>50% to 70%</td>
</tr>
<tr>
<td>Bipolar I Disorder</td>
<td>70%</td>
</tr>
<tr>
<td>Other Substance Use Disorders</td>
<td>80%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>70% to 90%</td>
</tr>
</tbody>
</table>
Smoking Cessation and Risk of MDE Relapse

- History of single and multiple MDE are associated with MDE on smoking cessation
- Smokers with a history of MDE who quit smoking may be at higher risk of recurrence of MDE for at least 6 months after quitting smoking than those who continue smoking
- Other studies report reduced anxiety and depressive symptoms after smoking cessation
- Recommend prophylaxis with antidepressant for those with history MDE, especially recurrent, upon abstinence

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
Treating Cocaine Withdrawal

• 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
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
Treating Cocaine Dependence

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
Massachusetts General Hospital Department of Psychiatry

*Presents*

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