NIDA Blending Meeting
Smoking Cessation Workshop
March 15, Grand Hyatt, New York, NY.

Nicotine Dependence Among Substance Abusing Populations

• The Epidemiology, Neurobiology, and Treatment of Nicotine Dependence
• Interaction of Nicotine and Cigarette Smoking With Substance Abuse
• Practical and Research Experience of Smoking Cessation in Drug Rehabilitation Programs
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General Classes of Drugs

- Sedative/barbs – alcohol, benzodiazepines, GHB?
- Stimulants – cocaine, speed, nicotine
- Opiates – heroin, percodan, dilaudid, vicodin
- Hallucinogens – LSD, mescaline, peyote
- Tranquilizers – ketamine, PCP
- Cannabinoids – pot, hash
- Inhalants - poppers
Substance Use Past Month: NHSDA, 2000

Percent Reporting

- Cigs: 25.8%
- Alc: 46.4%
- MJ: 4.7%
- Cocaine: 0.7%
- Opiates: 0.1%
- LSD/PCP: 0.4%
- Inh: 0.3%
Mortality and its Causes: 2000

![Bar chart showing mortality causes in thousands: AIDS (17), Alcohol (81), MVA (41), Homicide (19), Drugs (14), Suicide (30), Tobacco (430).]

CDC, 2000: http://www.cdc.gov
Important Tobacco and Drug-Related Concepts

• Addiction Potential – correlated with speed drug gets to reward centers in the brain
  – Route of Administration

• Gateway Hypothesis – most heroin users smoke cigarettes, but few cigarette smokers use heroin

• Drug dependence is a chronic, relapsing condition. Multiple treatments usually needed before abstinence is achieved

• Motivation should not be used as titer for treatment
Important Neurobiology Concepts

• Billions of nerve cells in brain that communicate using neurotransmitters
• Neurons have receptors that accept uniquely shaped molecules to “transmit” a message
• Nicotine is shaped much like the neurotransmitter acetylcholine (ACH)
• Substances also act at neurotransmitter sites
• Nicotine and other substances cause psychoactive effects
Nicotine Effects on Brain

- Activity is mediated through responsiveness at nicotinic ACH receptors throughout brain (Plowchalk and deBethizy, 1992)
- Causes desynchronization of EEG (arousal) (Armitage et al., 1968; Remond et al., 1979)
- Serves as a positive reinforcer (Dursun and Kutcher, 1999)
Rewarding Effects of Nicotine

- Rewarding effects mediated via activation of mesolimbic dopamine system (Sing et al., 1982), a common neural substrate for all addictions
- Rewarding (Goldberg et al., 1981) and stimulatory effects (Reid et al., 1998) strongly influenced by environmental factors
- Also serves as potent aversive stimulant at high doses and with non-habituated individuals.
Smoking Cessation Treatments

• Pharmacotherapy

• Behavioral Therapies

• Self-Help
Pharmacotherapy Effectiveness

• **Nicotine Gum:** 16.0% (Viswesvaran & Schmidt, 1992; Tonnesen et al., 1988)

• **Nicotine Patch:** 22.0% (Fiore et al., 1994)

• **Zyban:** 18.4% (Jorenby et al., 1999)
Pharmacotherapy Guidelines

- Clinician familiarity with medications
- Contraindications for the patient
- Patient preference
- Previous experience (pos or neg)
- Patient characteristics (concerns about weight gain; depression history)

Fiore et al., 2000; Clinical Practice Guidelines
Brief Interventions – Five “A”s

• Ask about tobacco use
• Advise to quit
• Assess willingness to quit
• Assist with the quit attempt
• Arrange for follow-up

Fiore et al., 2000; Clinical Practice Guidelines
Behavioral Interventions

- Freedom from Smoking: Psychoeducation, positive reinforcement, anxiety reduction
- Fresh Start: Psychoeducation, positive reinforcement, anxiety reduction
- Mood Management (Hall et al., 1997): Psychoeducation, cognitive behavioral strategies, positive reinforcement
Phenomenology: Smokers Dependent on other Substances

- Smoke a lot; many want to quit
- Social contexts reinforce smoking
- Have many negative health consequences
- Gain from consistent treatment messages
- Reinforcing to quit smoking

Susman, 2000
Dual-Treatment Drawbacks

- Low success rate (Hurt et al., 1993)
- Quitting smoking interferes with outcomes for other substances (?)
- Few negative immediate consequences to smoking (Kalman, 1998)
- Psychological factors support smoking
Substance Abusers who Smoke:

- Began smoking at earlier age (Orleans et al., 1993)
- More addicted to nicotine
- Have more cognitive deficits and psychological problems (Burling et al., 1997)
- Have more medical problems (Susman, in press)
Associations Between Nicotine and Abused Substances

- Cocaine and nicotine high: synergism and substitute for each other reported in cocaine users (Sees, 1993)
- Crack cocaine and tobacco smokers exposed to cocaine cue: enhanced cocaine craving
  - Nicotine patch enhanced cocaine craving
  - Nicotine blocker, mecamylamine, reduced cocaine craving (Reid et al., 1998, 1999)
- In animals: Mecamylamine inhibited alcohol drinking (Ericson et al, 1998), Nicotine enhanced cocaine self-administration (Horger et al., 1992).
Smoking and Stimulants

• Among healthy smokers, rate of cigarette smoking increased following an injection of cocaine (Nemeth-Coslett et al., 1986) or amphetamine (Low et al., 1984)

• Among cocaine dependent smokers, urine cotinine was higher on days when urine samples also indicated recent cocaine use (Roll et al., 1997)
Smoking and Alcohol

- Strong association between alcohol use and smoking in general population (Craig & Van Natta, 1977)
- Strong predictor of relapse in self-quitters is alcohol use (Ockene, 2000)
- Among alcoholics in treatment, about half are interested in smoking cessation (Joseph, 1993)
- No data that smoking cessation degrades outcomes for substance treatment
Smoking and Methadone

- Methadone dose increases associated with increased smoking; Methadone dose decreases associated with decreased smoking (Schmitz et al., 1994)

- Methadone self-administration (up to 10 ml) highest for nicotine 4mg gum, moderate for 2mg gum, lowest for placebo (Spiga et al., 1998)
Smoking Cessation in Methadone Maintenance

• Prevalence of smoking in methadone maintained between 85%-98%
• Clinical trial of relapse prevention, contingency management (alone and in combination) for optimizing outcomes using nicotine replacement therapy

Acknowledgements: NIDA 1 R01 DA 09992 and GlaxoSmithKline
Method

- 175 Subjects received NRT and randomly assigned to 1 of 4 conditions for 12 weeks
  - 8 weeks at 21 mg
  - 2 weeks at 14 mg
  - 2 weeks at 7 mg
- Relapse prevention – weekly group
- Contingency management - $447 max
Method (Cont’d)

• Urine and breath collection on Mondays, Wednesdays, Fridays; Follow-up assessments at 6- and 12-months

• Carbon monoxide criteria indicating smoking abstinence was 8 ppm
Results

• 73.1% completed 12 weeks of treatment
• Subjects receiving CM showed higher rates of smoking abstinence during the trial than those not assigned to CM (p=.0003); no similar effect for RP
• No significant differences in smoking abstinence at 6- and 12-month follow-ups
Percentage of Smokers vs. Non-Smokers after 12 Weeks of Treatment

- Smokers: 78%
- Non-Smokers: 22%
Effect of Contingency Management on CO During Treatment

*H(3)=14.49, p=.002
Confirmed Non-Smokers by Condition

% Non-Smokers

- Patch
- RP
- CM
- RP+CM

Condition

- 12 weeks
- 6 months
- 12 months
Results

• Subjects provided more opiate and cocaine-free urine samples during weeks when they met criteria for smoking abstinence than during weeks when they did not meet these criteria
Conclusions

• Contingency management optimized smoking cessation outcomes using NRT during treatment for opiate dependence
  – Effects not maintained
• Strong associations between reductions in cigarette smoking and reductions in illicit drug use during treatment
Prospective Study of Illicit Drug Use and Smoking

- Seven consecutive days of urine samples, analyzed for metabolites of nicotine, heroin, and cocaine
- Concurrent collection of expired carbon monoxide
- Detailed smoking history

Frosch et al., 2001
## Participant Demographics

<table>
<thead>
<tr>
<th></th>
<th>Heavy Smokers (n=11)</th>
<th>Chippers (n=11)</th>
<th>Non-Smokers (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>40.18 (4.83)</td>
<td>43.36 (8.14)</td>
<td>46.00 (12.49)</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td>72.7</td>
<td>72.7</td>
<td>55.6</td>
</tr>
<tr>
<td><strong>% Hispanic</strong></td>
<td>81.8</td>
<td>63.6</td>
<td>33.3</td>
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</table>
Carbon Monoxide Levels by Smoking Status

Daily Expired CO Values

<table>
<thead>
<tr>
<th>Day 1**</th>
<th>Day 2*</th>
<th>Day 3**</th>
<th>Day 4*</th>
<th>Day 5*</th>
<th>Day 6**</th>
<th>Day 7**</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.00</td>
<td>7.46</td>
<td>9.55</td>
<td>9.00</td>
<td>8.00</td>
<td>9.09</td>
<td>8.80</td>
</tr>
<tr>
<td>2.89</td>
<td>2.89</td>
<td>2.78</td>
<td>3.00</td>
<td>2.67</td>
<td>2.78</td>
<td>2.56</td>
</tr>
<tr>
<td>*<em>p&lt;.001, <em>p&lt;.01</em></em></td>
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<td>*<em>p&lt;.001, <em>p&lt;.01</em></em></td>
</tr>
</tbody>
</table>
Daily Urine Cotinine Concentrations Adjusted for Creatinine

Day 1** Day 2** Day 3* Day 4 Day 5* Day 6 Day 7*

Heavy Smokers
Chippers
Non-smokers

**p<.05, *p<.10
Cocaine and Opiate TES by Group

Cocaine TES*
- Heavy Smokers: 3.00
- Chippers: 5.09
- Non-smokers: 7.00

Opiate TES*
- Heavy Smokers: 1.18
- Chippers: 2.00
- Non-smokers: 6.11

*p<.01
Daily Methadone Dose by Group

- **Heavy Smokers**: 67.87 mg/day
- **Chippers**: 48.84 mg/day
- **Non-smokers**: 51.11 mg/day
## Relationship of Methadone Dose, Smoking Status, and Opiate TES

<table>
<thead>
<tr>
<th>Variable Entered</th>
<th>$\Delta R^2$</th>
<th>$\Delta F$</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone Dose</td>
<td>.12</td>
<td>4.03 (df = 1,29)</td>
<td>n.s.</td>
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<tr>
<td>Smoking Status</td>
<td>.36</td>
<td>9.49 (df = 2,27)</td>
<td>p&lt;.01</td>
</tr>
<tr>
<td>Final Model: F(3,27) = 8.46, p&lt;.001</td>
<td></td>
<td></td>
<td></td>
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### Relationship of Methadone Dose, Smoking Status, and Cocaine TES

<table>
<thead>
<tr>
<th>Variable Entered</th>
<th>$\Delta R^2$</th>
<th>$\Delta F$ (df)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone Dose</td>
<td>.04</td>
<td>1.22 (1,29)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>.22</td>
<td>4.06 (2,27)</td>
<td>$p &lt; .05$</td>
</tr>
</tbody>
</table>

**Final Model:** $F(3,27) = 3.20$, $p < .05$
Conclusions

• Tobacco “chipping” extends to methadone maintained tobacco smokers
• Ordered relationship between nicotine, cocaine, and heroin use
• Association appears to be stronger than the relationship between methadone dose and illicit drug use
Smoking Cessation Treatment at Inpatient and Residential Drug Rehabilitation Programs: Research over the Past Decade

- Types of Smoking Cessation Programs

- Smoking Abstinence Quit Rates

- Effects on Drug and Alcohol Use

- Retention in Drug Rehabilitation
Burling and colleagues, 1991

- Individual counseling with a 10 day intensive program with nicotine fading (n=19) vs standard care (n=20), at 4 month VA residential alcohol and drug rehabilitation program (treatment started after minimum of 30 days in the program).

- Smoking abstinence - Intervention Group End of Treatment: 40%, 12 and 26 week postdischarge: 0%

- Primary substance abstinence - Both Groups 12 week postdischarge: 47% (smoking cess) vs 40% (control) 26 week postdischarge: 47% (smoking cess) vs 35% (control)

- Rehabilitation retention, 30 days post enrollment: 95% (smoking cess) vs 45% (control)*
Joseph and colleagues, 1993

• 3 group lectures and hand-out material with no nicotine replacement (n=154) vs standard care (n=160), at 21-day residential rehabilitation program.

• Smoking abstinence - Intervention Group
  Quit smoking for at least 1 week: 19% (* vs 3%)
  10-16 mo. post-discharge: 10% (smoke cess) vs 3% (control)

• Self reported drug & alcohol improvement
  10-16 mo. post-discharge: 55% (smoke cess) vs 62% (control)

• Rehabilitation retention, 1 week post enrollment:
  91% (smoking cess) vs 91% (control)*
Hurt and colleagues, 1994

- 10 group counseling sessions with optional nicotine gum (n=51) vs standard care (n=50), at Mayo Clinic inpatient drug and alcohol rehabilitation program (postdischarge phone/mailings).

- **Smoking abstinence**
  - End of Treatment: 22% (smoke cess) vs 10% (control)
  - 52 week postdischarge: 12% (smoke cess) vs 0% (control)*

- **Drug & Alcohol abstinence - Both Groups**
  - 52 week postdischarge: 67% (smoking cess.) vs 66% (control)

- **Rehabilitation retention, length of stay:**
  - 24 days (smoking cess) vs 28 days (control)
Bobo and colleagues, 1998

- Individual smoking cessation counseling (n=240: 6 sites) vs. standard care (n=246: 6 sites) prior to discharge from residential alcohol and drug rehabilitation programs and at 8, 12 and 16 week post discharge via telephone.

- Smoking Abstinence
  - 4 wk post discharge: 3% (smoking cessation) vs 2% (control)
  - 26 wk post discharge: 8% (smoking cessation) vs 4% (control)

- Drug Abstinence
  - 4 wk post discharge: 19% (smoking cessation) vs 21% (control)
  - 26 wk post discharge: 34% (smoking cessation) vs 35% (control)

- Alcohol Abstinence
  - 4 wk post discharge: 74% (smoking cessation) vs 72% (control)
Burling and colleagues, 2001

• Individual counseling with nicotine patch following a nicotine fade (n=50) vs standard care (n=50), VA residential alcohol and drug rehabilitation program (treatment after minimum of 30 days in program).

• Smoking abstinence
  4 wk post-quit: 40% (smoke cess) vs 2% (control)
  12 & 26 wk post-quit: 18% (smoke cess) vs 11% (control)

• Drug & alcohol abstinence
  4 week post-quit: 77% (smoke cess) vs 61% (control)
  12 week post-quit: 67% (smoke cess) vs 63% (control)
  26 week post-quit: 67% (smoke cess) vs 67% control)

• Smoking cessation retention, full 9 wk Tx: 45%
Summary of Previous Research

• Stopping smoking during drug or alcohol rehabilitation: no negative impact on treatment of drug and alcohol dependence

• Moderate success in quitting smoking is obtained, better with nicotine replacement therapy

• Evidence for improved rehabilitation retention, and reduced alcohol drinking
Smoking Cessation Study: NIDA-CTN-0009

- Protocol Development
  - Concept Submission and Protocol Development by Committee
  - Team of Scientists, Clinic Directors, NIDA
- Communications
- Design Factors
  - Clinic and Clients: Feasibility and Interest
  - Medications
  - Counseling Platform
  - Site Logistics and Staffing needs
Smoking Cessation Study: Study Intervention

• Smoking Cessation State-of-the-Art
  – Counseling: Mood Management and Cognitive Behavioral Treatment to Prevent Smoking Relapse
  
  – Medication: NicoDerm CQ
Smoking Cessation Study: Pharmacotherapy

• Study Design Issue: Selection of nicotine patch therapy
  • Drug availability: GlaxoSmithKline - NicoDerm CQ
  • OTC medication: Good safety profile, no need for MD oversight, “real world” availability.
  • Efficacy: Equal with Zyban in standard smoking cessation efficacy trials. Most effective when combined with counseling
  • Program Integration: Already offered in some drug rehabilitation settings (MMTP, alcoholism TX)
Smoking Cessation Study: Counseling Program

- **Counseling Platform:**
  - Mood Management and Cognitive Behavioral Smoking Cessation Program (Hall, Muñoz, Norman, at UCSF).
  - Group Counseling: 2 pre-quit week, 2 post-quit week, weekly for treatment weeks 2-6
  - Staggered Start: Smoking Cessation Treatment Initiated every 4th week
  - CTP smoking cessation counselors must be non-smokers
  - Counselor supervision and monthly QA ratings
Smoking Cessation Study: Design Elements

- **Study Design Issue: Control Subjects**
  - Ethics: Desire of clinics to offer smoking cessation to all study participants
  - Retention: Adequate outcome data from non-treatment, control group
  - **Solution:** Deferred smoking cessation for control group (eligibility = expected level of study compliance)

- **Study Design Issue: Open label medication**
  - Ethics: No placebo group = all study participants receive full treatment intervention.
Smoking Cessation Study: Protocol Development

- **Study Design:** 9 wk treatment trial (1 wk + 8 wk)
  - All subjects continue standard outpatient substance abuse rehabilitation
  - Smoking cessation treatment vs control group:
    - Group 1: Smoking Cessation Counseling and NicoDerm patch
    - Group 2: No Smoking Cessation Treatment (26 wk deferred)
  - One study protocol applied in two settings: Drug Free Outpatient or MMTP/LAAM Clinics (72 patients/clinic)
  - Smoking prevalence, Client interest, Drug Use and Smoking Assessments, Drug Rehabilitation Retention
  - Assessment Schedule: 1 x wk, Follow-up at 13 wk and 26 wk post-quit date
Smoking Cessation Study: Timeline and Longterm Goals

• Protocol Development: 2 yr
• Protocol Implementation: 12 sites across the country
  – Study Initiation: June, 2002
  – Enrollment Completion: August, 2003
  – Study Completion: February, 2004
• Legacy: Participating clinics establish smoking cessation counseling programs. Assistance with medication procurement.