Methamphetamine and HIV: Updates and Novel Treatment Approaches

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• Clinical supplies:
  – Medicinova (ibudilast)
  – Pfizer (varenicline)
  – Cephalon (modafinil)
Overview

- Significance of the problem
- What’s new in biological and psychological consequences
  - Neural inflammation
- Review of treatments
  - Evidence based therapies
  - Evidence for tailoring treatments
SIGNIFICANCE OF METHAMPHETAMINE USE

Medical Effects of Methamphetamine
Epidemiology of Methamphetamine Dependence
Methamphetamine – Up Side

- Cheap
- 9-12 h half-life
- Induces euphoria, brightens mood, eliminates fatigue, decreases appetite, focuses attention, facilitates involvement with sex at the “extremes”
Down Sides

• Paranoia
• Skin problems
• Violence
• Sexual dysfunction

• Work and relationship problems
• Neuropsychological problems
• Infectious Disease
Methamphetamine

*Acute Physical Effects*

**Increases**
- Heart rate
- Blood pressure
- Pupil size
- Respiration
- Sensory acuity
- Energy

**Decreases**
- – Appetite
- – Sleep
- – Reaction time
Methamphetamine

Acute Psychological Effects

Increases
- Confidence
- Alertness
- Mood
- Sex drive
- Energy
- Talkativeness

Decreases
- Boredom
- Loneliness
- Timidity
Methamphetamine

Chronic Physical Effects

- Tremor
- Weakness
- Dry mouth
- Weight loss
- Cough
- Sinus infection

- Sweating
- Burned lips; sore nose
- Oily skin/complexion
- Headaches
- Diarrhea
- Anorexia
Addiction

• DSM-V: A spectrum disorder?
• In 2010, 22.1 million (8.7% of adults aged 12 and over met) criteria for substance abuse or dependence not including tobacco dependence (National Survey on Drug Use and Health, 2011).
• Alcohol abuse and dependence represents the majority (17.9 million; 7.0% of adults and 81% of total substance abuse/dependence)
  – remainder splits between drug disorders only and comorbid illicit drug use and alcohol use disorders.
• Less than 10% of those with abuse and 33% of those with dependence receive treatment lifetime (Compton W et al., Archives Gen Psych, 2007)
Worldwide Demand is Strong

Fig. 1. Annual prevalence of illicit drug use among the population aged 15-64, 2008-2010

Source: UNODC.
U.S. Public Substance Abuse Treatment Admissions

Source: Treatment Episode Data Set (TEDS); includes admissions to facilities that receive State alcohol and/or drug agency funds (including Federal Block Grant funds) for alcohol and/or drug treatment services. www.samhsa.gov
Workplace Drug Testing, 2010
Quest Diagnostics

Source: http://ir.questdiagnostics.com/phoenix.zhtml?c=82068&p=irol-newsArticle_print&ID=1603058&highlight=
Local Evidence

• 18% of 60,629 admissions in FY 2009-2010 to publicly funded treatment programs in Los Angeles County were primarily for methamphetamine (SAPC, 2012).
Demand on the Streets

HIV-positive (self-report) = 13.4%
Reback et al., in prep
Meth Use and HIV Transmission in MSM

Meth use correlates with 2-4 fold increases in risk for HIV transmission in:
- Cohort Studies (Plankey et al., 2007)
- New Infections (Drumright et al., 2007; 2009)
- STI settings (Buchacz et al., 2005; Buchbinder et al., 2005)

Attributable fraction of new infections 0.28 (Koblin et al. 2006) to 0.33 (Ostrow et al. 2009)

Carey et al., AIDS & Beh, 2008
AIDS in America: Overlooked Epidemic

Prevalence of HIV among MSM in Los Angeles County is about 19%

Substance use involved in 28% to 33% of incident cases among MSM

What’s New?

MEDICAL CONSEQUENCES
Partial Recovery of Brain Dopamine Transporters in Methamphetamine (METH) Abuser After Protracted Abstinence

Effects of Drugs on Dopamine Release

**METHAMPHETAMINE**

- Accumbens
- % of Basal Release
- Time After Methamphetamine
- DA
- DOPAC
- HVA

**COCOAINE**

- Accumbens
- % of Basal Release
- Time After Cocaine
- DA
- DOPAC
- HVA

**NICOTINE**

- Accumbens
- Caudate
- % of Basal Release
- Time After Nicotine
- DA
- DOPAC

**ETHANOL**

- Accumbens
- % of Basal Release
- Time After Ethanol
- Dose (g/kg ip)
- 0.25
- 0.5
- 1
- 2.5

*Source: Shoblock and Sullivan; Di Chiara and Imperato*
PET and fMRI: Controls (n=18) vs MA Abusers (n=17)

Erosion of Cognitive Resource

A Role for Glia?

• Methamphetamine:
  – Releases monoamine neurotransmitters
  – Blocks re-uptake

• Behavioral effects of methamphetamine:
  – Altered levels of cyclic adenosine 3′,5′-monophosphosphate (cAMP) in D1 and D2 receptors
  – Activated glial cells (astrocytes and microglia) increase pro-inflammatory cytokine production and immune response

Preclinical Evidence

Glial Modulator; PDE-I

• MODULATE GLIAL ACTIVATION
  – PDE4-I (rolipram) ↓ opiate and cocaine CPP (Thompson 2004), MA- and opiate induced hyperlocomotion (Iyo, 1995; Mori 2000), MA behavioral sensitization (Iyo 1996)
  – Minocycline – ↓ MA-induced glial activation, ↓ locomotion, ↓ striatal DAT levels, ↓ impairments of recognition memory and behavioral sensitization (Mizoguchi 2008)
  – Propentofylline (MXNTH) ↓ CPP from MA and opiates

• ANTI-INFLAMMATORY EFFECTS
  – ↓ GDNF ↑ effects of MA-induced neurotoxicity; ↑ GDNF ↓ neurotoxicity (Boger et al., 2007)
  – Mice lines with ↓ GDNF expression potentiates MA expression, behavioral effects; GDNF reverses these (Yan et al., 2008)
Prevents Stress-Induced Relapse

Ibudilast Blunts MA-Induced Locomotor Activity

Chronic MA-induced locomotor activity dose dependently reduced by ibudilast; no effect on chronic exposure to saline
- Reduced MA-sensitization

Acute MA-induced locomotor activity showed similar pattern of results – ibudilast reduced behavior under meth, not saline

Snider et al., European J Pharm 679 (2012) 75–80
Methamphetamine Use in HIV: ART Adherence

- Use of drugs, especially stimulant drugs, reduces ART adherence
- 3-day reported adherence rates:
  - On stimulants: 51%
  - Off stimulants: 72%
- Main effects of meth observed on behavioral organization

Hinkin et al., 2007, *AIDS & Behav* 11:185–194;
Methamphetamine and HIV Disease Outcomes

- Meth $\uparrow$ TNF-$\alpha$ in infected mice splenocytes
- Cocaine $\uparrow$ TNF-$\alpha$ and HIV replication in PBMCs in humans
- Careful analysis suggested ARV in meth users $\rightarrow$ high VLs, likely from incomplete adherence

Ellis et al., 2003, *JID*: 188:1820-26
## Drug Use and HIV Serostatus in the MACS

<table>
<thead>
<tr>
<th>Exposure Variables</th>
<th>HIV – Coefficient (95% CI)</th>
<th>HIV + Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2003 Cohort vs pre-2001 cohort</td>
<td>**</td>
<td>1.38 (1.24, 1.55) *</td>
</tr>
<tr>
<td>Cumulative medication adherence (10 ART-years)</td>
<td>N/A</td>
<td>4.07 (3.52, 4.71)*</td>
</tr>
<tr>
<td>Cumulative cigarette smoking (10 pack-years)</td>
<td>1.10 (1.02, 1.18)*</td>
<td>**</td>
</tr>
<tr>
<td>Cumulative meth use (10 use-years)</td>
<td>**</td>
<td>0.93 (0.88, 0.98)*</td>
</tr>
<tr>
<td>Cumulative cocaine use (10 use-years)</td>
<td>**</td>
<td>0.93 (0.89, 0.96)*</td>
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Evidence Based Approaches

• SBIRT – especially for smoking, alcohol
• A palette of medications are approved for use:
  – Smoking (NRT, bupropion, varenicline)
  – Opioids (methadone, Suboxone, naltrexone)
  – Alcohol (naltrexone, acamprosate, disulfiram)
  – Signals for bupropion, naltrexone for methamphetamine
• Different behavioral therapy models have efficacy:
  – Cognitive Behavioral Therapy
  – Contingency Management
  – Motivational Interviewing
  – Community Reinforcement Approach
• Lack of diversity in efficacious treatments
Evidence-Based Treatment Targets

- **SBIRT** – early detection and intervention
  - 5 A’s
  - AUDIT, CAGE
  - NIDA ASSIST
- **Pharmacological Targets**
  - Substitution (agonists)
  - Relieve withdrawal symptoms (craving)
  - Block relapse (antagonists)
  - Mixed approaches (partial agonists)
- **Behavior Therapy Targets**
  - Instilling of abstinence
  - Prevention of relapse
  - Improve mood and cognition
  - Reduce craving
- None of these targets imply *cure*
Screening, Brief Intervention, Referral to Treatment

LOW INTENSITY INTERVENTIONS
“Knock it Off!” Works...

Remits Needs Intervention

Babor et al., 2005
Telephone Quit Lines

- Telephone quit lines are funded by the 1998 Master Settlement Agreement
- Connects smokers with trained counselors
  - Individual smoking history, customized cessation plan including pharmacotherapy follow-up telephone calls
- 1 800-NOBUTTS provides vouchers for medications for Medical recipients
- Telephone quit lines are convenient, serve diverse and multilingual populations, and anonymity
- 70%-85% of smokers would prefer to use a quit line to a clinician.
- Only 4.5% of smokers in California could identify quit lines as a way to help them quit
- Odds of cessation are 1.56, which compares to NRT which are 1.74

Schroeder, *JAMA, July 2005.*
### Brief Intervention – 5 A’s

<table>
<thead>
<tr>
<th>Ask</th>
<th>Implement an officewide system that ensures that, for every meth using MSM at every clinic visit, meth use status is queried and documented</th>
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<tbody>
<tr>
<td>Advise</td>
<td>In a clear, strong, and personalized manner, urge every patient to quit</td>
</tr>
<tr>
<td>Assess</td>
<td>Ask every meth using MSM if he is willing to make a quit attempt now (next 30 days)</td>
</tr>
<tr>
<td>Assist</td>
<td>Help the patient plan, provide practical counseling, recommend meds, be supportive</td>
</tr>
<tr>
<td>Arrange</td>
<td>Provide for follow-up support, phone calls</td>
</tr>
</tbody>
</table>

Adapted from Fiore et al., 2008, Clinical Practice Guidelines for Smoking Cessation
Evidence for SBIRT

Madras et al., *Drug Alc Dep*, 99:280-295
MOTIVATIONAL INTERVIEWING
Motivational Interviewing: Basic Assumptions

- People change thinking and behavior along a series of stages
- Individuals may enter treatment at different “stages of change”
- The natural change process can be changed using MI techniques
- MI engages individuals in longer term treatment and promotes specific behavior changes
- Confrontation of “denial” is counterproductive and may be harmful
MI: Meta Analysis

• Cochrane Review: Mean reduction of substance use compared to non-treatment control = 0.79 SD (Smedslund et al., 2011, *Cochrane Review*, CD008063)

• MI4MSM – 13 studies (9 on sexual risk reduction, 3 on sex risk and AOD, 1 on HIV testing): no difference between MI and control conditions across all outcomes excepting drinks per drinking day (Berg et al. 2011, *AIDS Ed & Prev*, 23:533-549)
CONTINGENCY MANAGEMENT
Contingency Management

• Providing vouchers of increasing value or chances to draw from a lottery for consecutive biological samples documenting substance abstinence

• Evidence of efficacy for use with opioids, nicotine, cocaine, methamphetamine

• Effective as treatment, but has variable effects implemented with non-treatment seekers
  – Strona et al., 2006
  – Menza et al., 2011; Corsi et al., 2012
Contingency Management

- Significantly longer retention
- Significantly more “clean urine”
- Significantly longer stretches of consecutive clean urine samples

Shoptaw Reback, 2005 Drug Alc Dep. 78:125-134
Contingency Management

FIGURE 1. Mean Effect Sizes Across Substance Use Disorders Under Treatment

FIGURE 2. Mean Effect Sizes Across Treatment Types

Cognitive Behavioral Therapy: Key Concepts

- Encourage and reinforce behavior change
- Recognize and avoid high risk settings
- Behavioral planning (scheduling)
- Skills for coping with conditioned “triggers”
- Understand and deal with craving
- Abstinence violation effect – “getting back on the wagon”
- Understanding basic psychopharmacology principles
- Self-efficacy
CBT Meta Analysis

- CBT produces as small, but significant improvement over comparison conditions (McGill & Ray, 2009)
  - 58% of patients treated with CBT showed improvement over comparisons

McGill, Ray 2009  *J. Stud. Alcohol Drugs* 70: 516-527
Behavioral Therapy for AMP Vs Minimal Intervention

Behavioral Therapy for AMP
Vs High-Intensity Intervention

PHARMACOTHERAPY
No Broadly Effective Medication

<table>
<thead>
<tr>
<th>MEDICATION (DOSE)</th>
<th>PRIMARY OUTCOME</th>
<th>REFERENCE</th>
</tr>
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<tbody>
<tr>
<td>Imipramine (10 mg/ 150 mg)</td>
<td>Negative</td>
<td>Galloway, et al., 1996</td>
</tr>
<tr>
<td>Fluoxetine (40 mg)</td>
<td>Negative</td>
<td>Batki et al, 2000</td>
</tr>
<tr>
<td>Baclofen (20 mg tid)</td>
<td>Negative</td>
<td>Heinzerling et al, 2006</td>
</tr>
<tr>
<td>Gabapentin (800 mg tid)</td>
<td>Negative</td>
<td>Heinzerling et al, 2006</td>
</tr>
<tr>
<td><strong>Sertraline (50 mg b.i.d.)</strong></td>
<td>Negative</td>
<td>Shoptaw et al, 2006</td>
</tr>
<tr>
<td><strong>Aripiprazole (15 mg/day)</strong></td>
<td>Placebo&gt;Aripiprazole clean urines</td>
<td>Tiihonen et al., 2007</td>
</tr>
<tr>
<td>Odansetron (.25, 1, 4mg bid)</td>
<td>Negative</td>
<td>Johnson et al, 2008</td>
</tr>
<tr>
<td>Mirtazepine (30 mg/day)</td>
<td>No difference from Placebo</td>
<td>Cruickshank et al, 2008</td>
</tr>
<tr>
<td>MEDICATION (DOSE)</td>
<td>PRIMARY OUTCOME</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Methylphenidate (54 g/day)</td>
<td>Methylphen&gt;Placebo clean urines</td>
<td>Tiihonen et al., 2007</td>
</tr>
<tr>
<td>Bupropion (150 mg b.i.d.)</td>
<td>Bupropion &gt; placebo in light users</td>
<td>Elkashef et al., 2008</td>
</tr>
<tr>
<td>Naltrexone (50 mg/day)</td>
<td>Naltrexone&gt;Placebo; 2 wks abstinen</td>
<td>Jayaram-Lindstrom, 2008</td>
</tr>
<tr>
<td>Bupropion (150 mg b.i.d.)</td>
<td>Bupropion &gt; placebo in light users</td>
<td>Shoptaw, Heinzerling 2008</td>
</tr>
<tr>
<td>Modafinil (200 mg/day)</td>
<td>Trend for modafinil in subjects compliant with meds</td>
<td>Shearer et al, 2009</td>
</tr>
<tr>
<td>Slow release d-amphetamine (up to 110mg/day)</td>
<td>D-amphetamine &gt; placebo</td>
<td>Longo et al., 2009</td>
</tr>
<tr>
<td>Modafinil (400 mg/day)</td>
<td>Trend for modafinil on retention in heavy users</td>
<td>Heinzerling, Shoptaw et al, 2010</td>
</tr>
<tr>
<td>Mirtazapine (30mg/day)</td>
<td>Mirtazapine&lt;Placebo positive urines 0.57 (95%CI 0.35-0.93)</td>
<td>Colfax et al., 2011</td>
</tr>
</tbody>
</table>
Summary

• Demand for methamphetamine continues to be very high in Los Angeles
  – Substantial proportion of MSM report recent use
  – Still a major driver for treatment in Los Angeles

• Multiple ways methamphetamine interferes with brain function and to HIV care
  – Adherence to ARVs buffers negative effects of MA

• SBIRT and low intensity interventions require little investment, but can have large pay-off