Stimulants:
Cocaine and Methamphetamine (and Caffeine)

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Stimulants Overview:

I. Background & History
II. Epidemiology
III. Genetics
IV. Diagnostic factors
V. Pharmacology
VI. Clinical Effects
VII. Pathophysiology/Adverse effects
VIII. Treatment

Caffeine: briefly covered

Not covered: prescription stimulant abuse, MDMA
IA. Cocaine: Background & History

- Traditional use of cocaine
  - Cultural origins
- Modern use
Coca

- *Erythroxylon coca*
- shrub grows in Andes
- used by indigenous people in South America for millenia
- contains 0.5% cocaine
  (Gold & Miller 1997)
Traditional use of coca

- Leaves are harvested
- Chewed with cud inside cheek
- Lime used to change mucosal pH to help absorption
- Effects mild compared to pure cocaine
Modern History of Cocaine

- Cocaine isolated 1860
- Local anesthetic 1884
- Freud: *Uber Coca* 1884
- Harrison Act: 1914
- Epidemics in 1920s, 1970s
- Crack in 1980s-now
IB. Amphetamines: History

• Amphetamine first synthesized in 1887; methamphetamine in 1918

• First available in the U.S. as benzedrine inhaler (OTC) 1932

• Other forms of amphetamines available by Rx in 1939;

• Widespread availability for nonmedical uses continued through the 1960s

• Tighter regulation of manufacture and prescription in 1972
IIA. Cocaine: Epidemiology

Prevalence of Cocaine Use (in >12 y.o.)

- 11.2% of U.S. population report ever using cocaine (NHSDA 2000)
- 1.5% report use within the past year (NHSDA 2000)
- 1.9 million (0.7%) report use within the past month (NSDUH 2008)
- Most common in 18-25 age group (NHSDA 2000)
- 663,000 received treatment for cocaine in past year (NSDUH 2008)
IIA. Epidemiology: Methamphetamine

- Recent increase, after steady decline until 1991 (DAWN data)

- Spread of MA particularly extensive in Western US

- Ethnic differences from cocaine users: fewer African Americans

- Gay men in US metropolitan areas particularly affected

(NIDA 1992; USDHHS/SAMHSA 1995)
Prevalence of Methamphetamine Use
2000 National Household Survey on Drug Abuse

- 4.0% of U.S. population >12 yo report ever using MA
- 0.5% report using MA within the past year
- 0.2% report using within the past month
- Most common in 18-25 yo age group
- 245,000 received treatment for stimulants in past year

NHSDA 2000
Past Year Methamphetamine Use among Persons Aged 12+, by Region: 2002 and 2006

<table>
<thead>
<tr>
<th>Region</th>
<th>2002</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Midwest</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>South</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>West</td>
<td>1.6</td>
<td>1.6</td>
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</table>
Past Month Use of Illicit Drugs in Persons Aged 12 or Older: 2008
(NSDUH 2008; SAMHSA, 9/2/10)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Use in Millions</th>
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<tbody>
<tr>
<td>Marijuana</td>
<td>15.2</td>
</tr>
<tr>
<td>Psychotherapeutics</td>
<td>6.2</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1.0</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>1.1</td>
</tr>
<tr>
<td>Inhalants</td>
<td>0.6</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.2</td>
</tr>
<tr>
<td>Total</td>
<td>20.1</td>
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</tbody>
</table>

Substances for Which Most Recent Treatment Was Received in the Past Year 12 or Older: 2008 (NSDUH 2008, accessed 9/2/10)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Use in Thousands</th>
</tr>
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<tbody>
<tr>
<td>Alcohol</td>
<td>2,662</td>
</tr>
<tr>
<td>Marijuana</td>
<td>947</td>
</tr>
<tr>
<td>Cocaine</td>
<td>663</td>
</tr>
<tr>
<td>Pain Relievers</td>
<td>401</td>
</tr>
<tr>
<td>Heroin</td>
<td>341</td>
</tr>
<tr>
<td>Stimulants</td>
<td>336</td>
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<tr>
<td>Tranquilizers</td>
<td>326</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>287</td>
</tr>
</tbody>
</table>

Dependence or Abuse - Past Year 12 or Older: 2008 (NSDUH 2008, SAMHSA accessed 9/20/10)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Use in Thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>4,199</td>
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<tr>
<td>Pain Relievers</td>
<td>1,716</td>
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<tr>
<td>Cocaine</td>
<td>1,411</td>
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<tr>
<td>Tranquilizers</td>
<td>451</td>
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<tr>
<td>Hallucinogens</td>
<td>358</td>
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<tr>
<td>Stimulants</td>
<td>351</td>
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<tr>
<td>Heroin</td>
<td>282</td>
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<tr>
<td>Inhalants</td>
<td>175</td>
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<tr>
<td>Sedatives</td>
<td>128</td>
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</tbody>
</table>

DAWN 2007 Cocaine & Stimulant ED Visits (DAWN 2007, SAMHSA, accessed 9/2/10)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Rates per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>182</td>
</tr>
<tr>
<td>Marijuana</td>
<td>101</td>
</tr>
<tr>
<td>Heroin</td>
<td>62</td>
</tr>
<tr>
<td>Stimulants</td>
<td>28</td>
</tr>
</tbody>
</table>

III A. Genetics of Cocaine Dependence

• Genetic epidemiologic studies support a high degree of heritable vulnerability for cocaine dependence.

• Polymorphisms in genes coding for DA receptors and transporter, opioid receptors, endogenous opioid peptides, cannabinoid receptors, and 5-HT receptors and transporter are all associated with vulnerability.

• CONCLUSION: Despite progress, identification of specific genes and quantification of risk remain to be elucidated.

• Similar conclusions in:
  – Yeforov et al. 2010  Ann NY Acad Sci 1187:184-207
  – Phillips et al. 2008 Neurosci Biobehav Rev 32: 7-7-59

• Pharmacogenetics will be increasingly important in tx
IIIB. Genetics of MA Use Disorders

  - 38 studies
  - 39 genes examined: 18 were found to have a significant genotypic, allelic, and/or haplotypic association with MA use disorder
  - “the genetic epidemiology of MA use disorders is complex and likely polygenic”.

IV. Diagnostic Categories DSM-IV-TR
Cocaine and Amphetamines

• dependence
• abuse
• cocaine- or amphetamine-induced disorders:
  – intoxication
  – withdrawal
  – intoxication delirium
  – psychotic disorders
  – mood disorder
  – anxiety disorder
  – sexual dysfunction
  – sleep disorder
V.A. Cocaine Pharmacology

- Pharmacological action of cocaine
- Pharmacokinetics
- Clinical effects
Major Acute Actions of Cocaine

• Local anesthetic
  – Blocks membrane sodium channels

• Stimulates CNS
  – Blocks presynaptic neurotransmitter reuptake pumps (transporters): dopamine, norepinephrine, serotonin

• Stimulates sympathetic nervous system

• Chronic effects unclear
  (neurotransmitter depletion? receptor upregulation?)

D. Gorelick, NIDA IRP
Cocaine vs Methamphetamine: Effects at the Synapse

Amphetamine
Increases release

Cocaine
Blocks reuptake

D. Gorelick, NIDA IRP, 2002
Mechanism of Cocaine’s Psychoactive Effects

- Binding to dopamine transporter correlates best with behavioral potency in animals → ↑ dopamine levels in nucleus accumbens
- Lesions of mesolimbic dopamine circuit (“reward” circuit) abolish cocaine self-administration
- However, “knockout” mice without dopamine transporter do not show motor stimulation or sleep suppression, but still get reinforcement from cocaine

D. Gorelick, NIDA IRP 2002

- Important roles for nicotinic, cannabinoid, GABAergic, glutamatergic, and opioidergic systems
Cocaine Pharmacokinetics, 1: Metabolism

- Metabolism
  - primarily (95%) by esterases
  - principal metabolite is benzoylecgonine (BE)
- Half-life of cocaine (plasma)
  - generally ranges from 40-90 min
  - acute ~40-60 min; chronic ~ 1.5 h or longer
Cocaine Pharmacokinetics, 2: Excretion

• Excretion
  – largely eliminated in urine
  – BE is metabolite in highest concentration

• Detection by urine drug tests
  – BE persists 24-72 hrs, may be as long as 96 hrs
Cocaine Pharmacokinetics, 3: Cocaine and Alcohol forms Cocaethylene

- alcohol-cocaine forms cocaethylene
- metabolite formed in presence of heavy alcohol intake together with cocaine
- formed by transesterification
- similar effects to cocaine, longer half-life, more severe toxicity when present along with cocaine
- greater than additive effects on heart rate and violence potential (Pennings et al. 2002 *Addiction*)
V.B. Pharmacology: Methamphetamine

- Mostly release of monoamines; lesser reuptake inhibition of DA, NE & 5-HT

- Lesser MAOI effects

- Overall, tolerance develops rapidly, but sensitization can also occur (e.g. to psychosis)
Mechanisms of methamphetamine acute actions: enhanced monoaminergic neurotransmission

• Methamphetamine (MA) is an indirect catecholamine and 5-HT agonist
• MA releases newly synthesized (versus stored) DA, NE, & 5-HT (King & Ellinwood 1997)
  – MA enters neuronal membranes through membrane transporters and storage vesicles via vesicle transporters
• May deplete catecholamines and 5-HT
MA Chronic Neurochemical Effects in Animals

- Decreased DA stores
- Decreased DA uptake sites, decreased DA transporters
- Decreased tyrosine hydroxylase & tryptophan hydroxylase activity
Sensitization to Cocaine and other Stimulants

- Sensitization (reverse tolerance) = enhanced response to drug because of prior exposure
  - May especially apply to:
    - craving in response to cues
    - dysphoria, anxiety/panic, psychosis
    - possibly seizures

- Kindling = low intensity, intermittent brain stimulation (electrical, pharmacological) leads to enhanced response to later stimulation

D. Gorelick, NIDA IRP 2002
MA Pharmacokinetics

- Absorption rapid after oral and other routes
- MA ½ life= 11-12 hrs IV or smoked (Karch 1996)
- metabolism: MA → amphetamine by CYP450 2D6; multiple other routes
- drug interactions: CYP450 2D6 blockers such as fluoxetine could potentially prolong MA presence in blood, but no evidence yet
- acidification of urine hastens excretion
- duration of effects: 10-12 hrs (vs 30-50 minutes for cocaine)
Routes of Administration and Forms of Cocaine & MA

- **Intranasal** (nasal insufflation, snorting)
  - powder cocaine HCl, or MA water soluble

- **Injection**
  - powder cocaine HCl or MA
  - quickest effects, in seconds

- **Pulmonary** (smoked)
  - Rapidity of effect rivals IV, in 6-8 seconds
  - crack = free base cocaine, alkaloidal cocaine, has lower melting point and can be smoked
  - “ice” = pure crystal meth – not free base
Forms of Cocaine Use

- **Powdered Cocaine HCl**
  for Intranasal or Injection use

- **Making freebase cocaine**

- **Crack cocaine**
Kinetics of Smoked Cocaine

Cocaine: Blood levels after Smoked vs Snuffed

After cocaine base
smoked (1 mg/kg)
two inhalations

After cocaine hcl
snuffed (2 mg/kg)
Average of 20 subjects

ng/ml of plasma

minutes after dose

R.T. Jones, 1983
VI. Cocaine & MA Clinical Effects
Medical Use of Stimulants

• COCAINE:
  – Topical, local anesthetic

• OTHER STIMULANTS:
  – Attention deficit (hyperactivity) disorder
  – Narcolepsy
  – Appetite suppression for weight loss
  – Decongestion
  – Bronchodilation (ephrine)
  – Depression (esp. geriatric, medically ill)
  – Reduce fatigue, drowsiness
Federal Schedule of Controlled Substances, Schedule II Stimulants

• Examples:
  – cocaine, amphetamine, methamphetamine, methylphenidate, phenmetrazine

• Schedule II Criteria:
  – High potential for abuse
  – Accepted medical use with severe restrictions
  – Abuse may lead to severe psychological or physical dependence
Cocaine & MA: Subjective and Behavioral Effects

• Onset
  – Intranasal effects within minutes (5-15)
  – Smoked effects within seconds

• Acute Effects
  – Euphoria, hyperactivity (motoric & verbal), hypersexuality initially
  – Insomnia, anorexia.
  – Persecutory delusions (paranoia) and hallucinosis (aud, vis, & tactile), agitation
  – Confusion rare except in very high doses when delirium can occur
  – Stereotyped movements may occur (teeth grinding, skin picking)

• Chronic use produces tolerance to euphoria, positive effects decrease, agitation & anxiety increase
Cocaine & MA Effects: Physiological

• Sympathomimetic effects
  – Elevated
    • BP
    • HR
    • Temp

• At high doses:
  – Hyperthermia
  – Rigidity
  – Seizures
Stimulants: Withdrawal

• “Crash” after discontinuation of prolonged high dose use
  – first described for cocaine (Gawin & Ellinwood 1988)
  – depression, fatigue, may have suicidal ideation
  – improves over several days -weeks
  – withdrawal symptoms not uniformly reported
  – Intense craving and anhedonia are common

• DSM-IV-TR for both Cocaine & Amphetamine WD:
  dysphoric mood consisting of:
  1. Fatigue
  2. Vivid, unpleasant dreams
  3. Insomnia or hypersomnia
  4. Increased appetite
  5. Psychomotor retardation or agitation
Changes in Mood with Cocaine Abstinence
Weddington et al, Arch Gen Psych 1990

Fig 1.—Mean (± SEM) scores of mood over time using the Profile of Mood States and the Beck Depression Inventory. Day 1 is the day of admission. Solid squares represent cocaine-addicted subjects; open squares, control subjects. Addicted subjects demonstrated significantly elevated scores of mood disturbances and rates of mood change over time for all scores other than “Vigor” (see Table 2).
MA Clinical presentation

• Patterns of use
  – frequency: often weekend binge pattern -- binges 12-24 hrs to 2-3 days; accompanied by rapid tolerance
  – amount varies enormously from 10 mg to 1 gram or more/day
  – route of administration: intranasal, oral, IV, rectal, smoked
  – “ICE”-- purified form of d-isomer, often in large crystals, not the “free base” form, which is liquid at room temp & has very limited use (SAMSHA, 1997)
  – binges followed by crash, with depression, fatigue, hypersomnolence, craving
Methamphetamine Effects in Humans

- At low doses:
  - wakefulness
  - increased physical activity
  - anorexia
  - increased respiration
  - hyperthermia
  - euphoria
  - hypersexuality

- At higher doses:
  - anxiety
  - irritability
  - insomnia
  - confusion
  - tremor
  - seizures
  - delusions
  - hallucinations
  - aggressiveness

(adapted from NIDA Infofax 016, 1998)
VII. Stimulants: Pathophysiology & Adverse Effects of Abuse

For both Cocaine and Methamphetamine:

• **Medical**
  • CNS
  • Cardiovascular
  • Pulmonary

• **Public Health**
  • HIV
  • Hepatitis B & C
  • STDs
  • TB

• **Psychiatric**
  • Psychosis
  • Mood & anxiety disorders
Medical Complications of Cocaine

• Complications reflect primarily:
  – excessive CNS stimulation
  – vasoconstriction

• Cardiac
  – Myocardial ischemia/infarct
  – Arrhythmias
  – Myocarditis

• Central Nervous System
  – Hyperpyrexia
  – Seizures
  – Cerebral infarct
  – Cerebral hemorrhage

Benowitz 1993; Boghdadi & Henning 1997
FIG. 3 Pathophysiology of medical complications of cocaine abuse (except for reproductive complications).
Medical Complications: Association with Routes of Stimulant Administration

• Intranasal use
  – erosion of nasal mucosa & perforated septum (especially cocaine)
  – Hepatitis C (HCV)
• Injection Use
  – HIV
  – HCV
  – endocarditis
  – soft tissue infections: abscesses & cellulitis
• Smoking
  – pulmonary edema, pneumonitis, pneumothorax
MA Psychiatric Morbidity
(Baberg 1996)

• psychosis
  – acute--classically paranoid, persecutory delusions, ideas of reference, heightened awareness of environment
  – chronic--can persist after acute episode or recur with little or no further MA use
    • pathophysiology uncertain

• mood disorders
  – mania during intoxication
  – depression during withdrawal
MA Medical Morbidity

- Chronic use: similar to cocaine
  - But more dental pathology ("meth mouth")

- High dose acute intoxication similar to cocaine
  - ventricular irritability
  - hypertension
  - MI
  - hyperthermia (hyperpyrexia)
  - rhabdomyolysis
  - seizures
  - stroke
Methamphetamine Neurotoxicity

• **History**
  - PCA-related 5HT depletion 1st shown in early 60s
  - more recently shown with MDMA, etc

• **5-HT depletion**
  - rapid decrease in 5HT synthesis
  - persistent in animals > 110 da

• **DA depletion**
  - decreased brain DA concentration & decreased DA uptake sites
Amphetamine Psychosis

- **History**
  - 1st reported 1938

- **Characteristics**
  - Clear consciousness
    - Occasionally confused
  - Relatively little formal thought disorder
  - Persecutory delusions
    - Occasionally nonparanoid & disorganized
  - Hallucinations – all modalities
  - Persistent psychosis of long duration is possible

- **Sensitization**
  - Psychosis of increased duration
  - Induced by lower doses – increased vulnerability
  - Spontaneous psychosis

- Persistent sx of psychosis may be more likely in MA than cocaine abuse
  (Mahoney et al, 2008)
Cocaine and Pregnancy

- Irregular placental blood flow
- Placental abruption
- Premature rupture of membrane (PROM)
- Premature labor and delivery

- In a recent meta-analysis, the only adverse event significantly associated with cocaine was PROM (Addis et al. 2001 Reprod Toxicol)
Putative Effects of Cocaine on Birth and Fetal Development

• Frequently attributed effects:
  – Prematurity
  – Low birth weight
  – Decreased head circumference
  – Lower developmental test scores
  – Delayed language skills

• Less frequently attributed effects
  – Transient EEG abnormalities
  – Cerebral infarct
  – Seizures
  – Small brain hemorrhages
Meta-analysis of Effects of Cocaine on Early Childhood Development

• Conclusion of 2001 JAMA review:
  – among children aged 6 or younger
  – there is no convincing evidence that prenatal cocaine exposure is associated with developmental toxic effects that are different in severity, scope, or kind from the sequelae of multiple other risk factors.
  – many findings once thought to be specific effects of in utero cocaine exposure are correlated with other factors, including prenatal exposure to tobacco, marijuana, or alcohol, and the quality of the child’s environment.
  – “Further replication is needed of preliminary neurological findings.”

(Frank et al. 2001 JAMA)
Developmental Effects, 2

- Studies through 6 years have shown no long-term direct effects of prenatal cocaine exposure (PCE) on children's physical growth, developmental test scores, or language outcomes. Little is known about the effects of PCE among school-aged children aged 6 years and older.

- **RESULTS:** Associations between PCE and growth, cognitive ability, academic achievement, and language functioning were small and attenuated by environmental variables. PCE had significant negative associations with sustained attention and behavioral self-regulation, even with covariate control.

- **CONCLUSIONS:** Consistent with findings among preschool-aged children, environmental variables play a key role in moderating and explaining the effects of PCE on school-aged children's functioning. After controlling for these effects, PCE-related impairments are reliably reported in sustained attention and behavioral self-regulation among school-aged children.
VIII. Treatment of Stimulant Use Disorders

• Overview:
  – Pharmacologic
  – Non-pharmacologic

• Key variables to help determine what level of care is needed
  – severity of use
  – stage of the use (intoxication vs. abstinence)
  – readiness for change (motivation)
  – level of social support
  – other psychiatric and medical comorbidity
Psychosocial Treatments

- Community Reinforcement
- Community Reinforcement plus Vouchers
- Contingency Management (Voucher based reinforcement)
- Cognitive/Behavioral Therapy (CBT)-Relapse Prevention, e.g. the Matrix Model
- 12-Step facilitation
- Acupuncture
  
  (CSAT 1999; Knapp et al 2007)

- PLUS: Voucher-based reinforcement therapy (Contingent cash-value vouchers)
Community Reinforcement Approach (CRA)

- CRA is an individualized treatment designed to promote lifestyle change in key areas needed for recovery (CSAT 1999)
  1. Marital therapy if spouse is not a user
  2. Vocational assistance
  3. New social networks and recreational activities that promote recovery
  4. Self-help participation
  5. Relapse prevention skills training (refusal skills, mood regulation, time management, etc.)
  6. Disulfiram and compliance support

- Limited evidence for efficacy in cocaine dep (Roozen et al, 2004)

Community Reinforcement Approach (CRA) Plus Voucher Incentives

- Voucher-based incentives for cocaine-free urine tests added to CRA
- Use of Incentives improved CRA outcomes further (Higgins et al, 1994)
  * 75% vs 40% completed 24 weeks of tx
  * 12 vs 6 weeks continuous cocaine abstinence
Psychosocial Treatments for Cocaine Dependence:
NIDA Collaborative Cocaine Treatment Study

• Method
  – Large (n=487), controlled study over a 6-month period:
    • Group Drug Counseling (GDC)
    • Individual Drug Counseling (IDC) (12-Step Facilitation) + GDC
    • Cognitive Behavioral psychotherapy (CBT) + GDC
    • Supportive Expressive psychotherapy (SET) + GDC

• Results
  – IDC + GDC provided greatest improvement on ASI and days of cocaine use over past month
  – Psychotherapy was not superior to GDC for those with severe psychiatric illness
  – CBT not superior for treatment of ASP

NIDA Collaborative Cocaine Treatment Study
Voucher Based Incentives

• Multiple positive studies: some examples
  – In cocaine dependence:
    • Vouchers alone: Higgins et al, 1994 & 2000; etc.
    • Vouchers + medication
      – Levodopa/Carbidopa or placebo with or w/o voucher-based reinforcement therapy (VBRT) [Schmitz et al (2008) Drug Alcohol Dependence]: Levodopa/carbidopa more effective than placebo, but only when combined with VBRT
  – In methadone pts w cocaine dep:
    • Vouchers alone: Silverman et al, 1999; Petry et al 2007; etc.
    • Vouchers + medication
      – Desipramine/Pla, +/- vouchers [Kosten et al, 2003]
      – Bupropion/Pla, +/- vouchers [Poling et al 2006]
Review of Psychosocial Treatments for Cocaine, 1.

- 27 randomized controlled studies; 3663 subjects
- Cocaine was the psychostimulant used by participants in all but one that studied amphetamine.
- Comparisons were made of psychosocial treatments but most of them did not show statistically significant differences between interventions,
- Evidence currently available does not have data supporting a single psychosocial treatment approach.

• Overall, cognitive behavioral interventions reduced dropouts from treatment and use of cocaine when compared with drug counseling.

• Behavioral interventions also performed better than clinical management (psychotherapy sessions attended), usual care (lower rates of cocaine users at 1 and 3 months), information and referral (non-attendance).

• A multimodal intensive intervention was more effective than non-intensive delivery.

• Cognitive behavioral treatments with contingency management (voucher-based incentives) also showed benefits.

• Many of the results come from single studies, which limits their generalizability.

• Simple reduction in the amount of drug used or retention in treatment is not a measure of meaningful changes in lifestyle.

Treatment of Acute Cocaine Intoxication

• Psychosis
  – Usually resolves spontaneously
  – First line-treatment should be a benzodiazepine, preferably lorazepam (CSAT 1999)
  – Antipsychotics are an effective backup if benzodiazepines alone are inadequate
    • Warning -- typical antipsychotics will lower seizure threshold and increase risks of rigidity/hyperthermia
    • inadequate data on use of atypicals in emergencies

• Hypertension, tachycardia, hyperthermia, seizures
  – Supportive treatment
  – Sedation with benzodiazepines
  – Lower body temp
  – Treat seizures: diazepam, phenobarbital or phenytoin (CSAT 1999)
Pharmacotherapy for Cocaine Withdrawal

• Numerous medications have been tried
• Dopaminergic agonists among most frequently tested
  – e.g. Amantadine (200-400 mg/day) and Bromocriptine (BCT) (dose range: 0.625-7.5 mg/day)
  – Results of clinical trials are inconsistent, perhaps a bit more evidence for amantadine
  – Some overdose lethality risk with amantadine
  – Adverse effects with BCT make use inadvisable
  – There may be a subset of patients who benefit; but characteristics of such patients not yet identified
• Conclusion: **no medications proven effective to reduce cocaine withdrawal sx**
  
  (de Lima et al. 2002 *Addiction*)
Cocaine Pharmacotherapy for Abstinence Initiation, Use Reduction, or Relapse Prevention

- Many medications tried
- Most common categories: antidepressants, dopaminergic agents, anticonvulsants
- Aim to reduce abstinence symptoms or craving
- Or aim to block/reduce subjective effects of cocaine
- Promising recent RCT studies
  - modafinil, topiramate, disulfiram, cocaine vaccine, SR methamphetamine, baclofen
- **Conclusion**: No medication has yet shown reproducible efficacy in the treatment of cocaine dependence
Medications for Cocaine Tx: Recent Meta-analyses, 1.

**Dopamine agonists**
- 17 studies, 1224 participants
- Amantadine, bromocriptine, and pergolide were evaluated.
- Main outcomes: urine cocaine metabolites and retention
- No significant differences between interventions.
- Current evidence does not support clinical use of dopamine agonists in cocaine dep.

**Anticonvulsants**
- 15 studies (1066 participants)
- Anticonvulsants studied: carbamazepine, gabapentin, lamotrigine, phenytoin, tiagabine, topiramate, valproate.
- No significant differences for any efficacy measures.
- No current evidence supporting clinical use of anticonvulsants in cocaine dep.

Alvarez et al (2009) J Subst Abuse Treatment: similar findings; only topiramate > placebo
Medications for Cocaine Tx: Recent Meta-analyses, 2.

**Antipsychotics**

  - 7 small studies included (293 participants)
  - Antipsychotics: risperidone, olanzapine, haloperidol.
  - No significant differences for any efficacy measures comparing any antipsychotic with placebo. Risperidone superior to placebo in diminishing dropouts.
  - No current evidence supporting clinical use of antipsychotics in cocaine dep.

**Disulfiram**

  - Disulfiram vs placebo: 7 studies, 492 participants,
  - Disulfiram vs naltrexone: 3 studies, 131 participants,
  - Disulfiram vs no pharmacological treatment: 1 study, 90 participants
  - “There is low evidence, at the present, supporting the clinical use of disulfiram for the treatment of cocaine dependence.”
Conclusions
Pharmacotherapy of Cocaine Withdrawal, Abstinence, or Relapse Prevention in 2010

• No medication has been consistently shown to be useful

• Promising agents:
  – stimulants, modafinil, topiramate, buprenorphine, others
  – most recent
    • vigabatrin (Brodie et al. 2009 Am J Psychiat)
    • vaccine (Martell et al. 2009 Arch Gen Psychiat)

• None are FDA-approved

• Available pharmacotherapies are much less robust in effects than psychotherapeutic and psychosocial interventions
Acupuncture


- 7 studies with a total of 1433 people.
- Most of the studies compared acupuncture with ‘sham’ acupuncture: needles inserted into random places in the ear but not into the specific points required for treatment.
- The authors conclude that there is no evidence that any form of auricular acupuncture is effective for treating cocaine dependence.

Largest study:
- Multicenter trial (Margolin et al, JAMA 2001)
- Randomized, controlled with sham acupuncture
- n=620
- Results: no differences between treatment conditions
MA Treatment
Treatment of MA Psychosis

Cochrane Review

• antipsychotic medications demonstrate efficacy in providing short-term relief when a heavy user of amphetamines experiences psychosis
• equivalent efficacy between atypical anti-psychotics and conventional antipsychotics, mostly haloperidol with older drugs causing more severe side effects).
• there is no evidence to guide decisions regarding long-term clinical care using these medications for preventing relapse to psychosis.
Management of Amphetamine Intoxication

• Confirm diagnosis by urine toxicology screen
• If ingestion is oral, use gastric lavage and activated charcoal; avoid ipecac emesis due to risk of seizure, arrhythmia, or hypertensive crisis
• For seizures use diazepam acutely
• For psychosis/agitation use diazepam, back up with antipsychotic if needed
• Hyperthermia: external cooling

(Source: McCance-Katz, AAAP 1999)
Tx of MA Withdrawal


- “No medication is effective for treatment of amphetamine withdrawal. “

- “The benefits of mirtazapine as a withdrawal agent unclear based on findings from two randomised controlled trials:
  - one report showed improvements in amphetamine withdrawal symptoms over placebo;
  - a second report showed no differences in withdrawal symptoms compared to placebo. “

- “Further potential treatment studies should examine medications that increase central nervous system activity involving dopamine, norepinephrine and/or serotonin neurotransmitters, including mirtazapine.”
Pharmacotherapy for Methamphetamine Dependence, 1.

- Few clinical trials have tested pharmacotherapies for methamphetamine dependence

- Controlled trials
  - **Negative**: imipramine, sertraline, fluoxetine, amlodipine, and flumazenil/gabapentin/hydroxyzine (“Prometa”)
  - **Promising**: most recent controlled trials with positive findings:
    - Bupropion (Elkashef et al. 2008 *Neuropsychopharm*; Shoptaw et al. 2008 *Drug Alc Dep*)
    - Modafinil (Shearer et al. 2009 *Addiction*)
    - Methylphenidate (Tiihonen 2007 *Am J Psychiat*)
    - SR d-amphetamine (Longo et al. 2009 *Addiction*)

- **Summary of pharmacotherapies for MA**
  - No pharmacological treatments have been shown to be effective in repeated, large-scale controlled trials
  - No treatments FDA-approved
Pharmacotherapy for Methamphetamine Dependence, 2.

- Summary of pharmacotherapies for MA
  - **No pharmacological treatments** have been shown to be effective in repeated, large-scale controlled trials
  - No treatments FDA-approved
  - Most recent reviews:
Methamphetamine: Psychosocial Therapies

• Matrix Model (Shoptaw, Rawson, et al)
  – DHHS Publication No. (SMA) 06-4152; Printed 2006
  – 16 weeks, several sessions per week
  – Psychoeducation, Relapse prevention, family education, group support

• Possible utility of contingency management

• Self-help groups, e.g. Crystal Meth Anonymous (CMA)
Caffeine, 1

• Xanthine alkaloid
• Sources:
  – Coffee
    • 1 cup = 80-175 mg
  – Tea
  – Yerba Mate
  – Guarana
Caffeine, 2: Dependence & Abuse

  - Presently, due to a paucity of clinical evidence on caffeine dependence or abuse, no such diagnosis is included in DSM-IV

  - Caffeine activates a few regions mainly involved in the control of vigilance, anxiety, and cardiovascular regulation, but does not affect areas involved in reinforcing and reward.
Caffeine, 3: Energy Drinks

  – increasing reports of caffeine intoxication from energy drinks,
  – In children and adolescents who are not habitual caffeine users, vulnerability to caffeine intoxication may be markedly increased due to absence of tolerance.
  – Genetic factors may contribute to vulnerability to caffeine-related disorders including caffeine intoxication, dependence, and withdrawal.
  – combined use of caffeine and alcohol is increasing sharply, and studies suggest that such combined use may increase the rate of alcohol-related injury.
  – Several studies suggest that energy drinks may serve as a gateway to other forms of drug dependence.
Summary

• Cocaine and Methamphetamine
  – Lower prevalence of use than alcohol, nicotine, cannabis
  – High cardiovascular and CNS morbidity, including psychosis
  – Treatment remains largely psychosocial