Psychoactive Substance Use Disorders

Thaddeus Ulzen  MD FRCP(C)FAPA FCGP
Professor & Chair, Department of Psychiatry and Behavioral Medicine,
Associate Dean for Academic Affairs
CCHS/University of Alabama School of Medicine
Assessment

- History of substance use and its effects on psychological, neuro-cognitive, physiological and behavioral functioning.
- General medical and psychiatric history
- Screening of blood, breath and urine for substances used
- Lab investigations
- Consent to contact others
Table 1. DSM-IV-TR Criteria for Substance Abuse

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)

4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for substance dependence for this class of substance.
Table 2. DSM-IV-TR Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1) tolerance, as defined by either of the following:
   a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b) markedly diminished effect with continued use of the same amount of the substance

2) withdrawal, as manifested by either of the following:
   a) the characteristic withdrawal syndrome for the substance
   b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

3) the substance is often taken in larger amounts or over a longer period than was intended

4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

6) important social, occupational, or recreational activities are given up or reduced because of substance use

7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

The diagnosis should specify “With Physiological Dependence” (either item 1 or 2 is present) or “Without Physiological Dependence” (neither item 1 nor 2 is present).
<table>
<thead>
<tr>
<th>Substance</th>
<th>Medical Disorders</th>
</tr>
</thead>
</table>
| Alcohol               | *Gastrointestinal:* esophagitis, Mallory-Weiss tear, gastritis, peptic ulcer disease, fatty liver, alcohol-induced hepatitis, cirrhosis, acute or chronic pancreatitis  
                         | *Cardiovascular:* hypertension, cardiomyopathy, coronary artery disease          
                         | *Neurological:* Wernicke’s encephalopathy, alcohol-related dementia, cerebellar degeneration, peripheral neuropathy, stroke, seizures  
                         | *Hematological:* thrombocytopenia, anemia                                        
                         | *Neoplastic:* cancers of the esophagus, liver, and pancreas                      
                         | *Other:* sexual dysfunction, sleep disorders, vitamin B deficiency, peripheral myopathy |
| Nicotine              | *Cardiovascular:* coronary artery disease, vascular disease                       
                         | *Respiratory:* chronic obstructive pulmonary disease                             
                         | *Neoplastic:* cancers of the mouth, esophagus, and lung                          |
| Cocaine               | *Cardiovascular:* ischemic heart disease, cardiac arrhythmias, cardiomyopathy, aortic dissection, myocardial infarction  
                         | *Respiratory:* spontaneous pneumothorax, pneumomediastinum, bronchitis, pneumonitis and bronchospasm (when smoked)  
                         | *Neurological:* seizures, stroke                                               
                         | *Other:* sinusitis, nasal irritation, septal bleeding and perforation (with intranasal use), HIV and hepatitis (with intravenous use), weight loss and malnutrition |
| Opioids (when used intravenously) | *Gastrointestinal:* acute and chronic viral hepatitis  
                         | *Cardiovascular:* endocarditis                                                  
                         | *Respiratory:* tuberculosis (which may be treatment resistant)                  
                         | *Neurological:* meningitis                                                      
                         | *Other:* cellulitis, abscesses, osteomyelitis, HIV                               |
Variables affecting Treatment

- Age
- Health and medical history
- Extent and severity of the symptoms
- Type and amount of substance(s) used and for how long
- Tolerance for medicines
- Current living situation
- Emotions and thought processes
Context of Somatic Treatments

- Behavioral Therapies and Self – Help Groups
- Inpatient Rx
- Partial Hospitalization
- Intensive Outpatient Programs
- Primary Care Rx
- MHC Rx
- Substance Abuse facilities
Categories of Medication Interventions

- Treatment of intoxication states
- Treatment of withdrawal syndromes
- Agonist maintenance therapies
- Antagonist therapies
- Abstinence promoting and relapse prevention therapies
- Adjunctive treatment of Co-morbid psychiatric disorders
Alcohol
THE CAGE QUESTIONNAIRE

Answer “Yes” or “No” to each of the following questions:

1. Have you ever felt you ought to cut down on your drinking?
2. Have people annoyed you by criticizing your drinking?
3. Have you ever felt bad or guilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye opener)?
MAST

Please circle either Yes or No for each item as it applies to you.

1. Do you feel you are a normal drinker?
2. Have you ever awakened the morning after some drinking the night before and found that you could not remember a part of the evening before?
3. Does your wife, husband, parent, or other near relative ever worry or complain about your drinking?
4. Can you stop drinking without a struggle after one or two drinks?
5. Do you ever feel guilty about your drinking?
6. Do friends or relatives think you are a normal drinker?
7. Are you able to stop drinking when you want to?
8. Have you ever attended a meeting of Alcoholics Anonymous (AA)?
9. Have you ever gotten into physical fights when drinking?
10. Has drinking ever created problems between you and your wife, husband, parent, or other near relative?
11. Has your wife, husband, a parent, or other near relative ever gone to anyone for help about your drinking?
12. Have you ever lost friends or girlfriends/boyfriends because of your drinking?
13. Have you ever gotten into trouble at work because of drinking?
14. Have you ever lost a job because of drinking?
15. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?
16. Do you drink before noon fairly often?
17. Have you ever been told you have liver trouble? Cirrhosis?
18. After heavy drinking, have you ever had delirium tremens (DTs) or severe shaking, or heard voices, or seen things that weren't really there?
19. Have you ever gone to anyone for help about your drinking?
20. Have you ever been in a hospital because of drinking?
21. Have you ever been a patient in a psychiatric hospital or on a psychiatric ward of a general hospital where drinking was part of the problem that resulted in hospitalization?
22. Have you ever been seen at a psychiatric or mental health clinic, or gone to a doctor, social worker, or clergyman for help with any emotional problem where drinking was part of the problem?
23. Have you ever been arrested for drunken driving while intoxicated or driving under the influence of alcoholic beverages?
24. Have you ever been arrested, even for a few hours, because of other drunken behavior?
New tools for addictions pharmacotherapy

- **Pharmacogenetics**
  - Naltrexone and alcohol – OPRM1 gene
  - Disulfiram and stimulants – DBH gene

- **Partial agonists**
  - Buprenorphine - opiates
  - Varenicline - nicotine

- **Vaccines**
  - Cocaine
  - Nicotine
Pharmacogenetics

Alcohol and Naltrexone
(opiate receptor)
Cocaine and Disulfiram (dopamine beta hydroxylase)
Heavy Drinking

- 14 drinks/week for men
- 7 drinks/week for women
- Binge – 6-20 drinks at a “session”.

- OPRM1 gene (alcohol and naltrexone)
- DBH gene (disulfiram and stimulants)

Drink = 1.5 oz of liquor, 12 oz of beer and 5 oz of wine
Naltrexone responsive Sub-groups

- More complex and severely dependent patients may be better for naltrexone
- Strong family history of alcoholism
- Related to beta endorphin [BE]
  - Mu opiate neurotransmitter
  - High alcoholism risk with LOW BE levels
- Genetic responsivity: mu opiate receptor polymorphism
Biological underpinnings of alcoholism and addiction

- Opioid receptors, alterations in the release and regulation of stress response mediators, and genetic polymorphisms that contribute to substance abuse via A118G micro-opioid receptors (MOR).

- dopamine
- GABA
- glutamate
- Opiates
Neurobiological adaptation

- "fun or pleasure"

- "compulsive drinking" – involving internal craving, social pressure, alcohol or drug cues and stress
Medical Therapy - Alcohol

- Alcohol
- Increase in brain endorphin and enkephalin activity
- Pleasure
Antagonist therapies

- Naltrexone
- Good oral availability long half-life.
- Prevents opiate mediated euphoria and cravings from alcohol
- Must be given to opioid – free patients.
- Dose – 50mg
- Some hepatotoxicity reported
- Works best when combined with a relapse prevention approach such as CBT or coping skills
Naltrexone responsive sub-groups

- More complex and severely dependent patients
- Strong family history of alcoholism
- Related to LOW beta endorphin (BE) levels
- Mu opiate receptor polymorphism
Baseline β-Endorphin Levels in Low- and High-risk, and Abstinent Alcoholic Patients
Naltrexone in Alcoholism (Oslin 2003)
Mu-opiate receptor polymorphism

- Naltrexone vs placebo in 141 alcoholics
- Asn40Asp variant in 24-36% of Europeans
- Associated with alcoholism in Swedes accounting for 11% of inheritance (Kreek 2004)
- Functional polymorphism – 3 fold increase in beta endorphin binding to mu receptor
- Pharmacogenetics confirmed in COMBINE: national multisite study of over 1000 subjects
Endophenotype

Endorphin Dependent Alcoholism

- Alcohol → Endogenous Opioids
- Euphoria/Stimulation from beta endorphin [BE]
- Family History with genetic polymorphism
- Sensitive µ Receptors & low beta endorphin
- Specific therapy with Naltrexone to raise BE
- Alcohol stimulation and Craving from BE surge blocked by Naltrexone
Abstinence promotion/Relapse prevention

- Alcohol use disorders –
- Disulfiram - Ingesting alcohol after disulfiram results in the inhibition of alcohol dehydrogenase and accumulation of acetaldehyde along with unpleasant symptoms of heat, flushing, nausea and vomiting. * Slowly eliminated from body so can be active up to 14 days after last dose.
- Naltrexone – causes inhibition of centrally mediated cravings via mu receptors
- Acamprosate – Amino acid derivative of taurine which resembles GABA and reduces glutamergic excitation during early recovery
Medical Therapy – COMBINE study 2006

- Naltrexone (Re Via) – best results with counseling

- Injectable Naltrexone (Vivitrol)

- Acamprosate (Campral)- no better than placebo alone

- COMBINE study showed that taking “pills” active or placebo improved outcome in alcoholics when combined with counseling.

- Medical management consisted of visits, 15 minutes each over 16 weeks, education about effects of alcohol on health, support for compliance, and referral to AA as needed
Psychiatric Co-morbidity

- 32% of individuals with alcohol use disorder have a psychiatric disorder.
- 22% of individuals with a psychiatric disorder have an alcohol use disorder.
- 33% of patients with Schizophrenia have AUD
- 22% of patients with Mood Disorders have AUD
- 18% of patients with Anxiety Disorders have AUD
Project MATCH - 1997

- Cognitive Behavioral Coping Skills Therapy
- Motivational Enhancement Therapy
- Twelve-Step Facilitation Therapy

“Psychiatric severity “ was the only discriminating factor in whether a treatment approach was less useful
Intoxication States
Intoxication states

- Acute Opioid overdose – Naloxone is a mu, kappa and sigma antagonist.
- For CNS depression – 0.05 -0.4mg IV;
- For Respiratory depression – 2.0mg IV.
- Doses may be repeated every 2-3 minutes till results are noted.

Maximum dose – 10mg
Intoxication states - Benzodiazepines

- Benzodiazepine overdose is characterized by confusion, loss of coordination, stupor and respiratory depression.
- Flumazenil is a central benzodiazepine antagonist given in IV doses of 2mg at a time.
Withdrawal syndromes
Treatment of withdrawal syndrome

- Opioid – Methadone, buprenorphine
- Benzodiazepines – alcohol and sedative withdrawal; other medications used adjunctively in alcohol withdrawal include Carbamazepine – 600 - 800mg/day; beta-blockers [Inderal and atenelol] and clonidine 0.5-1.0mg bid -tid
- Numerous benzodiazepine protocols are present: Diazepam -10mg q 2-4 hr, Chlordiazepoxide – 50mg q 2-4 hr, lorazepam 1mg q2h
Withdrawal syndromes

- Thiamine
- Antipsychotic agents – usually Haloperidol, geodon or risperidal for delusions and hallucinations
- ? Intravenous alcohol
- Do not use anticonvulsants without benzodiazepines in alcohol withdrawal.

- Nicotine dependence - NRTs
Agonist Maintenance Therapies

- Methadone – mu receptor agonist
- Buprenorphine – long acting partial opioid agonist
- L- alpha- acetyl methadol (LAAM) – mu receptor agonist [not available in US – cardiac problems]
THC withdrawal

- Withdrawal symptoms occur after sudden cessation of heavy chronic use.
- Though bupropion, depakote, naltrexone and nefazadone have been used no evidence is present to support the use of any of these agents.
Cocaine withdrawal

- Acute withdrawal – associated with a “crash” – fatigue, dysphoria, suicidality which progresses to insomnia over a period of weeks.
- Agents tried: Dopamine agonists - Amantadine; bromocriptine – no consistent results.
- Disulfiram promotes cocaine abstinence by inhibiting dopamine beta hydroxylase aided conversion of DA to NE
- Also tried are beta – blockers with mixed results.
Disulfiram and DBH
Pharmacogenetics for Cocaine
Pharmacotherapy
Hypodopaminergic State In Drug Addiction

Reward Circuits

Non Drug Abuser

Addicted Subject
Dopamine Agonist Therapy
Reverse Craving and Attenuate Priming

- Reverse stimulant induced dopamine deficiency – receptors down, transporters up
- D2 agonists not effective – bromocriptine
- Indirect agonists promising
- Disulfiram: inhibit dopamine beta hydroxylase conversion of dopamine to norepinephrine
Disulfiram increases dopamine (DA) by inhibiting its conversion to norepinephrine (NE)

**NE neuron**
- Low DβH reduces DA to NE conversion
- Higher Dopamine (lower NE) for release

**DA and NE-responsive Neuron**
- Alpha 2 and DA1 receptors
Disulfiram Effects on Acute Cocaine (2mg/kg I.N.)
Yellow (cocaine alone), Red (disulfiram + cocaine)

Craving for cocaine

Nervousness from cocaine
Disulfiram increases Cocaine-Free Urines in over 600 Outpatients (7 Studies - P<0.001)
Other dependence
Partial Agonists

- **Buprenorphine** for Opiates (vs. methadone)
  - Reduced overdose & abuse potential
  - Fewer withdrawal symptoms
  - Office based practice – lower stigma
  - Higher cost, but greater availability

- **Varenicline** for Nicotine (vs. NRT)
  - Increased efficacy (not vs. combo agonist)
  - Lower toxicity- ? Behavioral complications ?
  - Higher cost & more difficult availability
Opiate dependence and abuse

- Opioid agonists
- Methadone > 40-60mg/day & LAAM (off market – Cardiac arrhythmias)
- Available only through SAMHSA programs
- Treatment goals include an adequate dosage to suppress withdrawal and reduce cravings; stop illicit use and engage patients in comprehensive treatment.
Opioid dependence and abuse

- **Buprenorphine** – mixed (mu) agonist and (Kappa) antagonist
- Sublingual 8 -32mg/day
- Safer in overdose than methadone
- **Naltrexone** - opioid antagonist
  - given only after body is free of opiates.
- Has no abuse potential
- 100mg /100mg/150mg - MWF
Use of Illicit Drugs: The opiate surprise

- 2.9 million used an illicit drug for the first time within the past 12 months; this averages to nearly 8,000 initiates per day.

- Most initiates (56%) younger than 18 and female.

- Most recent initiates abused pain relievers (2.2 million) and marijuana (2.1 million)

Results from the 2005 National Survey on Drug Use and Health: National Findings, Office of Applied Studies, Substance Abuse Mental Health Services Administration, September 7, 2006, http://www.oas.samhsa.gov/nsduh/2k5nsduh/2k5Results.pdf
Opiate Pharmacotherapy: Buprenorphine (Suboxone®)

- Partial opioid agonist
  - Lower overdose potential & abuse liability
  - Less severe withdrawal than methadone when stopped
- Comparable to methadone in treatment retention & reduced heroin abuse
- Can be given in the doctors office
  - Increased availability and reduced stigma
SUBOXONE Helps Patients Reduce Opioid Use and Cravings @ wk 4

- Opiate-free urines

  - 4-week, multicenter, randomized, placebo-controlled trial of once-daily buprenorphine (16 mg) plus naloxone (4 mg) versus placebo


- Drug Craving

  - No other medications are approved for office-based use under the Drug Addiction Treatment Act (DATA) 2000
Maintenance Treatment Using Buprenorphine

- Numerous outpatient clinical trials comparing efficacy of daily buprenorphine with placebo, and with methadone
- These studies conclude that:
  - Buprenorphine is more effective than placebo
  - Buprenorphine is as effective as moderate doses of methadone (eg, 60 mg per day)
Buprenorphine Versus Methadone: Treatment Retention

Study Week

Percent Retained

- 73% Hi Meth
- 58% Bup
- 20% Lo Meth
Buprenorphine Versus Methadone: Opioid Urine Results

All Subjects

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Mean % Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19% Lo Meth</td>
</tr>
<tr>
<td>2</td>
<td>40% Bup</td>
</tr>
<tr>
<td>3</td>
<td>39% Hi Meth</td>
</tr>
<tr>
<td>4</td>
<td>19% Lo Meth</td>
</tr>
</tbody>
</table>

Study Week Range: 1 to 17
Levels: 0 to 100

Legend:
- 40% Bup
- 39% Hi Meth
- 19% Lo Meth
Tobacco
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer (Points assigned to response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How soon after you wake up do you smoke your first cigarette?</td>
<td>Within 30 min (1) After 30 min (0)</td>
</tr>
<tr>
<td>2. Do you find it hard to refrain from smoking in places where it is forbidden (e.g., church, library, airplanes)?</td>
<td>Yes (1) No (0)</td>
</tr>
<tr>
<td>3. Which cigarette would you hate most to give up?</td>
<td>The first one in the morning (1)</td>
</tr>
<tr>
<td></td>
<td>Any other (0)</td>
</tr>
<tr>
<td>4. How many cigarettes a day do you smoke?</td>
<td>15 or less (0) 16-25 (1) 26 or more (2)</td>
</tr>
<tr>
<td>5. Do you smoke more frequently during the first hours after awakening than the rest of the day?</td>
<td>Yes (1) No (0)</td>
</tr>
<tr>
<td>6. Do you smoke if you are so ill that you are in bed most of the day?</td>
<td>Yes (1) No (0)</td>
</tr>
<tr>
<td>7. What is the tar content of your brand?</td>
<td>Low (0) Medium (1) High (2)</td>
</tr>
<tr>
<td>8. Do you inhale?</td>
<td>Never (0) Sometimes (1) Always (2)</td>
</tr>
</tbody>
</table>

*Total point score of 1 to 6 indicates low to moderate nicotine dependence; score of 7 to 11 indicates high dependence.

Psychiatric Co-morbidity in Clinical populations

- Prevalence of lifetime mental disorder is 81%
- Prevalence of lifetime mood disorder is 62%
- Prevalence of lifetime anxiety disorder is 51%

Universal Screening for psychiatric disorders in SA patients is therefore strongly recommended. Treatment guidelines for the treatment of co-morbid psychiatric disorders should be followed.
Abstinence promotion and relapse prevention

- Nicotine dependence –
- Buproprion – mechanism unknown but thought to be related to blockade of DA and NE reuptake and antagonism of high affinity nicotinic acetylcholine receptors
- Varenicline (Chantix) 0.5-2mg/day – selective $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist. Varenicline blocks the ability of nicotine to activate $\alpha_4\beta_2$ receptors, preventing nicotine-induced stimulation of the mesolimbic dopaminergic system and thereby reducing the reinforcement and reward effects of cigarette smoking.
Conclusions: Addictions pharmacotherapy

- **Pharmacogenetics**
  - Naltrexone and alcohol – OPRM1 gene
  - Disulfiram and stimulants – DBH gene

- **Partial agonists**
  - Buprenorphine – opiates, office based RX
  - Varenicline – nicotine, vs. patch+lozenge

- **Vaccines**
  - Cocaine – multi-site RCT starting
  - Nicotine – four commercial products
Psychosocial Treatments

- Motivational Enhancement Therapy (MET) has the best empirical support for alcohol use disorders.
- Cognitive behavioral Therapy (CBT), Behavioral Self Control Training (BSCT), Community Reinforcement Approach (CRA), Behavioral Couples Therapy (BCT), Social Skills Training (SST) are all comparable in effectiveness.
- Therapist’s effect ranges from 10 - 50%.
- The use of Manual based treatments reduces this variability.
- Treatment of co-morbid psychiatric disorders is necessary.
Multi-systemic approaches

- Primary Care Rx
- Specialized Programs
- Criminal Justice Systems
- Educational Programs
- Social welfare interventions
Alabama

- Alcohol – 12+ past 30 days
- THC
- Cocaine
- Pain relievers
- Other illicit
- Tobacco

- 40% (binge 19%)
- 5%
- 2%
- 5%
- 4%
- 34%
Ghana

- N = 2500
- Alcohol – 25.3%
- Tobacco – 8.7%
- Cannabis – 1.7%
- Tranquillizers, sedative hypnotics – 0.6%
- heroin (0.3%),
- amphetamines (0.2%)
- Opiates (0.1%)

Immunotherapy and Vaccines for Cocaine Dependence
Drugs of abuse easily enter the brain.
Antibodies can reduce brain concentrations of drug.

Capillary Blood Flow

Antibody holds drug in bloodstream.
Cocaine Vaccine: What is it?

- Active immunisation
- Hapten: Cocaine derivative
- Carrier protein: Cholera toxin B (rCTB)
- Aluminium hydroxide adjuvant
Cocaine bound to Cholera toxin
Effects of cocaine vaccine in animals

- Vaccine generated antibodies can bind modest amounts of injected cocaine
- NO animal toxicity. Even at several times a clinically relevant dose
- Vaccine decreased cocaine self administration (SA) in rodents
Good Drug Effect

High AB

Low AB

Smoked Cocaine Dose (mg)

Ratings (mm)

max = 100

Week 3

Week 13

0 25 50

79% 49%

0 25 50

23% 13%

Week 13

Week 3
Self-reported Cocaine Use

High AB

Low AB

Dollars/5 days

Week 3

Week 13
Cocaine urines fall as Antibody levels rise

Weeks 1, 4, 8, 12, 16, 20; p<0.0001 (Z= -4.0)
Cocaine Vaccine (Kosten et al 2006)

(Reduction in cocaine use from baseline (0-12 weeks))

% patients

Vaccine
Placebo

25% reduction
50% reduction

0 5 10 15 20 25 30 35 40

% patients

20
15
10
5
0

Vaccine
Placebo

25% reduction
50% reduction
THANK YOU