**SUBSTANCE USE DISORDERS AND THE LAW**

***From High to Homicidal***

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1. **OVERVIEW**
2. Risky use of substances and addiction are the largest and most costly preventable health problems in the United States.
3. Substance use disorders account for nearly one third of all hospital inpatient costs and more than 20% of all deaths in the U.S.
4. Between 60-80% of forensic offenders have a substance use disorder.

**II. SUBSTANCE USE AND VIOLENCE**

1. \*Violence and Psychiatric Disorder in the Community-Evidence from the Epidemiologic Catchment Area Surveys *(*Swanson, Holzer, Ganju, Jono 1990)
	* + 1. An epidemiological study in 1990 provided a survey of over 10, 000 persons in the community regarding self-reported violence in the last year.
			2. The data for this study came from three communities surveyed in the National Institute of Mental Health’s Epidemiologic Catchment Area project, the largest community study of psychiatric disorders ever conducted in the United States.
			3. Used the Diagnostic Interview Schedule (DIS)-a structured interview for use by lay trained persons conducted with household residents.
			4. A person was counted as having had violent behavior in the past year if she or he endorsed at least one of the following items and noted that the behavior had occurred during the 12 months preceding the interview.
			5. Did you ever hit or throw things at your wife/husband/partner? Were you ever the one who threw things first, regardless of who started the argument? Did you hit or throw things first on more than one occasion?
			6. Have you ever spanked or hit a child, (yours or anyone else’s) hard enough so that he or she had bruises or had to stay in bed or see a doctor?
			7. Since age 18, have you been in more than one fight that came to swapping blows, other than fights with your husband/wife/partner?
			8. Have you ever used a weapon like a stick, knife, or gun in a fight since you were 18?
			9. Have you ever gotten into physical fights while drinking?
			10. As an overall assessment of the prevalence of violent behavior, **3.7% responded positively to at least one-year period preceding the interview**.
			11. When broken down by diagnoses, the following were shown:

**Violent Behavior in the Last Year**

Diagnosis Percent

No disorder 2

Obsessive-compulsive disorder 11

Panic disorder 12

Major depression 12

Mania or bipolar disorder 11

Schizophrenia 13

Cannabis abuse or dependence 19

Alcohol abuse or dependence 25

Other drug abuse or dependence 35

* + - 1. The higher the number of psychiatric diagnoses, the greater the rate of violence.
			2. The presence of two or more psychiatric diagnoses approximately doubles the risk of violence.
			3. The combination of substance abuse with other major psychopathology is more volatile than either alone. Nearly a third of those with schizophrenia also met the criteria for alcohol or drug abuse and dependence. If schizophrenia was the sole diagnosis, the violence rate was 8.4%.
	1. Violence committed by the mentally ill in the community-\*Rethinking Risk Assessment: the MacArthur Study of Mental Disorder and Violence, (Monahan, Steadman, Silver, & Appelbaum 2001)
		1. In a study of civilly committed psychiatric patients released into the community, most mentally ill individuals were not violent (Monahan, 1997). Although a weak relationship between mental illness and violence was noted, violent conduct was greater only during periods in which the person was experiencing acute psychiatric symptoms.
		2. Contrary to popular belief, a diagnosis of schizophrenia was associated with a lower rate of violence than was a diagnosis of depression or of bipolar disorder. In addition, **Monahan noted that substance abuse was a much greater risk factor for violence than mental illness.** (Monahan, Steadman, Silver & Appelbaum, 2001).
1. **SUBSTANCE USE DISORDERS AND CRIMINAL RESPONSIBILITY**
2. ***Robinson v. California* (1962)**
	1. In this case, the U.S. Supreme Court was asked to review a California statute that made being under the influence of or addicted to narcotics a crime.
	2. Lawrence Robinson was picked up by police officers who observed that he had “tracks” on his arms consistent with intravenous heroin use. Although not under the influence of heroin at the time of his arrest, Robinson was convicted by a jury of being *addicted* to the use of narcotics based on the police officer’s testimony. The prosecution made no claim that the defendant engaged in any other illegal conduct at the time.
	3. On appeal to the U.S. Supreme Court, the issue was whether the California statute was constitutional under the Eighth and Fourteenth Amendments. Justice Stewart pointed out that the California statute allowed the state to find a person guilty of an offense continuously, regardless of whether he had ever actually used narcotics in the state. He relied heavily on the idea that addiction is an illness analogous to mental illness or leprosy, arguing that it would be considered cruel to punish for such illness.
	4. Justice Stewart famously wrote that even “one day in prison for the ‘crime’ of having the common cold” would represent cruel and unusual punishment.
3. ***Powell v. Texas* (1968)**
	1. In this case, the U.S. Supreme Court again considered if substance use should qualify as a mental disease or defect absolving a defendant from criminal blame.
	2. Leroy Powell was well known in Travis County Texas as he had nearly 100 convictions for public intoxication. In December of 1966, he was again arrested for being under the influence of alcohol.
	3. At his trial, a medical expert testified that Powell was in fact a chronic alcoholic and that, while taking his first drink was voluntary, Powell had also acted under a compulsion that was “not completely overpowering” but a “very strong influence.
	4. His defense argued that in light of the *Robinson* ruling, Mr. Powell should not be arrested for having the “disease” of alcoholism. His counsel argues that it was cruel to arrest him since he did not appear in public of his own volition when he was drunk. At his trial, the judge rejected the claim that Mr. Powell was not criminally responsible due to his alcoholism. He was convicted and his case was appealed to the U.S. Supreme Court.
	5. The U.S. Supreme Court distinguished Mr. Powell’s case from their prior holding in *Robinson*. The Court noted that Mr. Powell was not convicted for having the disease of alcoholism but for the disruptive public behavior resulting from his alcohol use. The Court refused to equate alcoholism as a mental disease that would excuse a person from criminal responsibility. In fact, the *Powell* court emphasized, “Nothing could be less fruitful than for this Court to be impelled into defining some sort of insanity test in constitutional terms.”
4. All jurisdictions in the United States exclude voluntary intoxication as the *sole* mental condition permitted to justify an insanity defense (AAPL Guideline 2014). Some jurisdictions allow consideration of substance use disorders as a qualifying mental disorder for insanity in the following three circumstances:
5. *Idiosyncratic intoxication*: when a person has an unexpected and adverse mental reaction to his or her first use of alcohol. Drugs such as cocaine and methamphetamine have well known and long established risks and therefore do not generally qualify for idiosyncratic intoxication.
6. *Involuntary intoxication*: when a person is unaware that he or she has consumed alcohol or a substance and is therefore not responsible for any adverse resulting mental states.
7. *Permanent mental illness or cognitive impairment caused by substance use*: when a person has sustained psychiatric symptoms or cognitive impairment that extends beyond the intoxication period and substance use.
8. In some jurisdictions, these mental states are referred to as “settled insanity” or “settled psychosis” though the definitions of these terms vary widely.
9. *People v. Kelly*, California Supreme Court, 1973

Facts: Valerie Dawn Kelly was charged with assault with a deadly weapon after she repeatedly stabbed her mother with a knife in the mother’s kitchen. Ms. Kelly had used drugs since she was age 15. At 18 years of age, she began taking mescaline and LSD, using those drugs 50 to 100 times in the months leading up to the offense. Experts testified that her repeated use of drugs over a two-month period had resulted in a psychosis that rendered her unable to distinguish right from wrong at the time of the offense. The trial court ruled that her drug use was voluntary and because it was not of a “settled and permanent” nature, she was legally insane. Ms. Kelly appealed this ruling.

The California Supreme Court has held that a person may be found legally insane because of long term voluntary intoxication when the intoxication causes a mental disorder which remains after the effects of the intoxicant have worn off. While this mental disorder **need *not* be permanent**, it must be of **settled nature.**

1. *People v. Skinner*, California Supreme Court, 1985

Facts: On July 19, 1983, Raymond Skinner was admitted to Oakcrest Hospital on a 5150 involuntary hold and was described as paranoid and agitated. He slept throughout the night and was discharged the next morning. That evening, Raymond checked into the Town House Motel in Santa Rosa, California with his wife of 29 years, Mary Anne. He and his wife then free-based cocaine all night. The next day, the California Highway Patrol saw him driving through a center divider and then stopping his vehicle. He got out of his car and walked between lanes of traffic. When the officer approached him, he yelled out, “Kill me, I want to die…I killed my wife…I want you to kill me.” He told the officers that he had slit his wife’s throat with a broken bottle during the prior night while in the hotel room. His blood contained .03 milligrams per milliliter of cocaine at 2:20 p.m., approximately three hours after the killing. At the time of his arrest, he had signs of cocaine intoxication but was not in a cocaine delirium nor did he have evidence of delusions.

Psychiatric testimony noted at that the time he killed his wife, he was in a cocaine-induced psychosis. In particular, he was laboring under a delusion that his marriage vows bestowed upon him a God-given right to kill his wife if she violated her vows, and that such killing was not wrongful because it was sanctified by the will and desire of God. However, the experts did not provide an opinion as to the duration of the psychosis but agreed that he was legally insane at the time of his act. Two physicians testified that cocaine psychosis could last up to seven days after last use. Mr. Skinner was found guilty of second degree murder. The trial court found that he knew the nature and quality of his actions and the wrongfulness and therefore was not insane. In addition, the court found that his psychosis was due to voluntary ingestion. The court held that even if appellant came within the legal definition of insanity at the time of the killing, his psychosis, brought on by voluntary ingestion of drugs, was not "settled," and therefore did not excuse the act. This ruling was upheld by the court of appeal and then appealed to the California Supreme Court. The California Supreme Court outlined four criteria for determining “settled” insanity:

* + - 1. The illness must be fixed and stable;
			2. **The illness must last for a “reasonable duration.”** In this case, Mr. Skinner’s psychosis was temporary even if it extended beyond the influence of cocaine in the body;
			3. **The illness must not be solely dependent on the ingestion of or the duration of the drug;**
			4. And the person must meet the jurisdiction’s legal definition of insanity.

**IV**. **DSM-5 SUBSTANCE/MEDICATION-INDUCED MENTAL DISORDERS**

* 1. The substance/medication-induced disorders are potentially severe, usually temporary, but sometimes persisting central nervous system (CNS) syndromes that develop in the context of the effects of substances of abuse, medications, or several toxins. These are distinguished from substance use disorders, which involved continued use despite significance substance-related problems.
	2. Key features of a substance-induced mental disorder are:
	3. The disorder represents a clinically significant symptomatic presentation of a relevant mental disorder (i.e. psychosis, depression, etc.).
	4. There is evidence from the history, physical examination, or laboratory findings of both of the following:
		1. The disorder developed during or within 1 month of a substance intoxication or withdrawal or taking a medication; and
		2. The involved substance/medication is capable of producing the mental disorder.
	5. The disorder is not better explained by an independent mental disorder (i.e. one that is not substance-or medication induced). Such evidence of **an independent mental disorder** could include the following:
		1. The disorder preceded the onset of severe intoxication or withdrawal or exposure to the medication; or
		2. The full mental disorder persisted for a substantial prior of time (e.g., at least 1 month) after the cessation of acute withdrawal or severe intoxication or taking the medication. This criterion does not apply to substance-induced neurocognitive disorders or hallucinogen persisting perception disorder, which persist beyond the cessation of acute intoxication or withdrawal.
1. The disorder does not occur exclusively during the course of a delirium.
2. The disorder causes clinically significant distress or impairment in social, occupational, or other areas of functioning.

**ALCOHOL USE DISORDERS: ASSESSMENT AND TREATMENT**

I. **ASSESSMENT**

1. What is a “drink”? **12-14 grams of alcohol,** which equals:
	1. 12 ounces of regular strength beer.
	2. 5 ounces of non-fortified wine.
	3. 1.5 ounces of 80-proof liquor.
2. Unhealthy substance use: any use of alcohol or other drugs that increases the risk for or has been related to health consequences.
3. The National Institute on Alcohol Abuse and Alcoholism (NIAA) defines “risky” drinking as follows:

“At Risk Drinking”

|  |  |  |  |
| --- | --- | --- | --- |
| **Gender** | **Drinks per day** | **Drinks per week** | **Drinks per occasion** |
| Men (<65) | >2 | >14 | >4 |
| Women | >1 | >7 | >3 |

\*Only 2 in 100 individuals who are below these cut offs meet criteria for an alcohol use disorder.

1. **Binge drinking**: NIAA and SAMHSA define binge drinking as a pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dl. This typically occurs after **4 drinks for women and 5 drinks for men on the same occasion** in about 2 hours.
2. **Heavy alcohol use**: SAMHSA defines heavy alcohol use as **binge drinking on 5 or more days in the past month**.

II. **Screening and Brief Intervention** (SBI): a well-established clinical practice supported by evidence from controlled clinical trials. Screening is a clinical activity for patient without known symptoms of the target condition. SBI is not appropriate for patients with known substance use disorders or those seeking treatment for help with symptoms of substance use disorders.

* 1. **Single Screening Questions (SSQ):** brief and have been validated in primary medical care settings. The NIAA and the National Institute on Drug Abuse (NIDA 2014), recommend that the interviewers ask the following SSQ’s.
1. “How many times in the past year have you had five (four for women) or more drinks in a day?” (This question is often asked after first asking, “Do you sometimes drink beer, wine, or other alcoholic beverages.”)
2. “How many times in the past year have you used an illegal drugs or used a prescription medication for non medical reasons?”

These SSQ’s are a positive test when the individual’s response is greater than zero.

1. The **AUDIT** (Alcohol Use Disorder Identification Test) is a 10-item screening tool available from the World Health Organization. Scores range from 0-40. In primary care settings, a score of 4-7, provides the optimal sensitivity and reasonable specificity for unhealthy use. A score of 20 or higher suggest a severe alcohol use disorder.
2. The **AUDIT-C** is a short screening version of the AUDIT with three alcohol consumption questions when screening in the United States:

1. “How often do you have a drink containing alcohol?

 Never: 0

 Monthly or less: 1

 Two to four times a month: 2

Two to three times a week: 3

Four or more times a week: 4

2. “How many drinks containing alcohol do you have on a typical day when you are drinking?

 None: 0

 1 or 2: 0

 3 or 4: 1

 5 or 6: 2

 7 to 9: 3

 10 or more: 4

3. “How often do you have five (four for women) or more drinks on occasion?

 Never: 0

 Less than monthly 1

 Monthly 2

 Weekly 3

 Daily or almost daily 4

A score of **4 or more for men and 3** or more for women is considered positive. A score of **7-10 or greater suggests a severe alcohol use disorder**.

III. **EPIDEMIOLOGY**

1. DSM-5 and alcohol use disorders: Using the National Epidemiologic Survey, face to face interviews were conducted with 36,309 non institutionalized US civilian adults. Results indicated (Grant et al 2015):
	1. 12 month prevalence of an AUD was **13.9%.**
	2. Lifetime prevalence of an AUD was **29.1%.**
	3. Prevalence was highest for: men, white or Native American, previously married or never married, lower socioeconomic status, and younger (age 18-29).
	4. Alcohol use disorders go largely untreated.
	5. Comorbid disorders in individuals with DSM-5 Alcohol Use Disorder:

Odds Ratio of having another disorder with a diagnosis of any alcohol use disorder.

|  |  |  |
| --- | --- | --- |
| **DISORDER** | **12-month** | **Lifetime** |
| Drug Use Disorder | 3.3  | 4.1 |
| Nicotine Use Disorder | 2.5 | 3.2 |
| Major Depressive Disorder | 1.2 | 2.0 |
| Bipolar 1 | 1.4 | 2.0 |
| Any Anxiety Disorder | 1.1 | 1.3 |
| PTSD | 1.0 | 1.1 |
| Antisocial Personality Disorder | 1.6 | 1.9 |
| Borderline Personality Disorder | 1.6 | 2.0 |

1. In the ECA study examining lifetime prevalence, 46% of those with bipolar disorder have an AUD, 34% of those with schizophrenia have an AUD, and 17% of those with depression having an AUD.
2. In their review of two national data sets involving nearly 80,000 individuals, Grant et al. (2017) compared twelve-month alcohol use, high-risk drinking, and *DSM-IV* AUD in US Adults. Findings include:
	1. Between 2001-2002 and 2012-2013, 12-month alcohol use, high-risk drinking, and *DSM-IV* AUD increased by 11.2%, 29.9%, and 49.4%, respectively. This indicates that in the past 10 years, **there has been a dramatic increase** in over 18 year olds’ alcohol use, high-risk drinking, and Alcohol Use Disorders.
	2. Increases in all of these outcomes were greatest among women, older adults, racial/ethnic minorities, and individuals with lower educational level and family income.

IV. **EVIDENCE-BASED PSYCHOSOCIAL-BEHAVIORAL TREATMENTS**

A. **Cognitive-Behavioral** Therapies:

* 1. CBT has strong empirical support across a range of substance use disorders as well as psychiatric syndromes that frequently co-occur with substance use disorders.
	2. Effects of CBT appear to be comparatively durable, with several studies reporting continuing improvement after patients leave treatment, known as the “sleeper effect.”
	3. Technology-based models of providing CBT, such as CBT4CBTR, are showing great promise.

B. **Motivational Interviewing** (Miller and Rollnick, 2002, 2013 Guilford Press)

1. “A collaborative, person-centered form of *guiding* to elicit and strengthen motivation to change.”
2. <https://www.youtube.com/watch?v=9ACi-D5DI6A> Website that has video titled “How to Change People Who Don’t Want to Change” and demonstrates basic principles of motivation interviewing.
3. “The Effective Physician: Motivational Interviewing Demonstration” is a video that allows you to see MI techniques put into practice. <https://www.youtbue.com/watch?v=URiKA7CKtfc>
4. MI is NOT:
* Psychotherapy
* Stages of change model
* Decisional balance (pros and cons)
* For every patient in every situation
* Brief Intervention
* Easy to attain competence
1. Four processes of MI are:
* Engaging-the relational foundation (using “OARS” and demonstrating that you are listening)
* Focusing-guiding client to a target behavior that is important for them. Agreeing on what to talk about. Shared decision making.
* Evoking-drawing out client’s reasons for change-requires evoking Change Talk while suppressing Sustain Talk
* Planning-translating motivation into change

6. Motivational Enhancement Therapy (MET): a four-session treatment used in outpatient and after care settings in the large multisite alcohol treatment trial called Project MATCH.

* Effects of ME/MET can vary considerably. When compared with weaker comparison condition (e.g. waitlist control), MI/MET demonstrates stronger effects. However, when compared with other treatments, MI/MET approaches demonstrate small or equivalent effects.
* In the short term (<3 months), MI/MET approaches demonstrate stronger effects that are moderate to large in size. However, at longer term follow-up, small or nonsignificant differences are observed. It seems that these approaches may hasten the change that is naturally occurring.
* Three studies have demonstrated adverse effects of MI for participants who were more highly motivated and needed more action-oriented therapies.

B. **Alcoholic Anonymous (AA)**

* 1. AA is the most popular self-help program for alcohol-related problems.
	2. AA is considered a fellowship of “mutual association of persons on equal and friendly terms; a mutual sharing, as of experience, activity, or interest.”

* 1. Since AA’s founding in 1935, there are now more than 2 million members in more than 100,000 groups in at least 150 countries.

C. **Twelve-Step Facilitation (TSF)**

1. TSF if not Alcoholics Anonymous (AA) and is not endorsed by AA.
2. TSF is an evidence-based practice with a large research base and and therapy manual.
3. TSF is a method for helping the patient both get to and productively use 12-step meetings, as well as a method for the clinician to learn and use key concepts about 12-step meeting as part of overall therapy.

D. **Contingency Management (CM)**:

1. CM interventions bring positive consequences for drug abstinence.
2. Higgins and colleagues (1994) developed the first CM intervention designed to promote and sustain abstinence from stimulant drugs using negative urine tests as the objective marker of recent abstinence. Reinforcers were vouchers awarded for each stimulant-negative urine result obtained during three-times-per-week urine testing. The number of points awarded increased under an escalating schedule for each consecutive negative urine and reset to their original low if a missing or positive urine was obtained. The voucher intervention was combined with an intensive cognitive-behavioral counseling intervention. 75% of those who were offered intensive counseling combined with the voucher incentive completed 24 weeks of treatment compared to 40% who received intensive counseling alone.
3. Fishbowl method uses different prize levels for reinforcement and has been found efficacious for stimulant abusers.
4. Brief window of alcohol detection in breathalyzer would suggest that CM interventions would not be useful. However, a study of patients at a VA clinic, nevertheless showed that patients in a CM group more successfully completed treatment compared to a control group (84% vs. 22%) and had a significant reduction in return to drinking and also drank less when they did return to drinking.
5. Future methods incorporating better biomarkers of alcohol use may improve utility of CM in this group. For example, Secure Continuous Remote Alcohol Monitoring (SCRAM) bracelets that detect alcohol consumption from sweat on the skin can detect EtG, a longer lasting biological marker.
6. CM can also be used to improve medication adherence, such as use of naltrexone.

D**. Network Therapy (NT)**:

1. Integrated approach that draws on the support of a group of family and peers who are introduced into individual therapy sessions.
2. Networks generally consist of three or four members. Establishment of a network is undertaken with active collaboration between patient and therapist.
3. The therapist’s relationship to the network is one of a task-oriented team leader rather than of a family therapist oriented toward structuring relationships.
4. The network is established to implement a straightforward task, that of aiding the therapist to sustain the patient’s abstinence.
5. Network members ARE NOT led to expect symptom relief or self-realization for themselves.
6. In the network format, a cognitive framework can be provided for each session by starting out with the patients recounting events related to cue exposure or substance use since the last meeting. Network members are then expected to comment on this report to ensure that all are engaged in a mutual task with correct, shared information.
7. Often uses administration of disulfiram under the observation of a network member and attendance at AA meetings.
8. NT is included in the APA (1995) practice guideline for the treatment of substance use disorders as an approach to facilitating adherence to a treatment plan.

V. **PROJECT “MATCH”**

* 1. **Project MATCH** began in 1989 in the United States and was sponsored by the [National Institute on Alcohol Abuse and Alcoholism](https://en.wikipedia.org/wiki/National_Institute_on_Alcohol_Abuse_and_Alcoholism) (NIAAA).
	2. The project was an 8-year, multi site, $27-million investigation that studied which types of alcoholics respond best to which forms of treatment. MATCH studied whether treatment should be uniform or assigned to patients based on specific needs and characteristics.
	3. Three types of treatment were provided: Motivational Enhancement Therapy; Cognitive Behavioral Therapy, and Twelve Step Facilitation.
	4. The authors concluded that there were no specific patient characteristics associated with enrollment/success in any one particular program and that all three were equally effective.
	5. Critics noted that there were no control groups, so the results are virtually meaningless as many individuals decrease drinking on their own.

VI. **MEDICATIONS FOR USE IN ALCOHOL REHABILITATION**

Note: Medications to decrease risk of relapse or alcohol consumption are grossly underutilized in the treatment of individuals with alcohol use disorders.

1. **Disulfiram (Antabuse)-**
2. The **only alcohol-sensitizing medication** approved in the United States. Approved by the FDA.
3. Works by inhibiting aldehyde dehydrogenase, which catalyzes the oxidation of acetaldehyde to acetic acid.
4. DER reaction-results from elevated acetaldehyde concentration.
* Symptoms include warmness and flushing of the skin, increased heart rate, palpitations, decreased blood pressure, nausea, vomiting, shortness of breath, sweating, dizziness, blurred vision, and confusion.
* Most DERs are self-limited, lasting about 30 minutes.
* Severe reactions are usually associated with high doses (over 500 mg/day).
1. Not strong evidence in regard to its efficacy of relapse prevention. When compliance is ensured, may limit the severity of relapse when it occurs.
2. Does not reduce craving.
3. In one large study, patients who received disulfiram at 250 mg/day had fewer drinking days than those taking lower doses or placebo.
4. Because disulfiram binds irreversibly to aldehyde dehydrogenase, the potential exists for a DER to occur two weeks from the last ingestion of disulfuram.
5. Patients should be monitored regularly for visual changes and neurologic symptoms.
6. Liver enzymes should be monitored monthly during the first 3 months of treatment and quarterly thereafter to identify hepatotoxic effects. Disulfuram should be avoided in patients with liver disease.
7. Daily dose in the US is limited to **250 to 500 mg a day**.
8. Should not be used as approach to treatment moderation (i.e. abstinence only due to side effect risks).
9. Requires monitoring that client took the medication.

1. **Naltrexone(Revia)**:
	1. An opioid antagonist: targets **reduced alcohol reinforcement** and **cue-induced craving**.
	2. Approved for the use of opioid dependence in 1984 and for alcohol use disorder in 1994.
	3. Results in less craving and fewer drinking days than placebo.
	4. Helps limit the progression from initial sampling of alcohol to heavy drinking.
	5. A clear advantage compared to placebo on the following drinking outcomes: number of drinking days; time to relapse; percentage of drinking days; number of drinks per drinking days, total consumption of alcohol during treatment.
	6. Combination with gabapentin has demonstrated a longer interval to heavy drinking with fewer heavy drinking days.
	7. Poor compliance with oral naltrexone has led to interest in long-acting injectable form administered monthly.
	8. **FDA has approved long-acting naltrexone (Vivitrol)** for monthly administration at a dosage of 380 mg/day. Approved for patients who are abstinent from alcohol and who are also receiving psychosocial treatment.
	9. There is a black box warning for hepatotoxicity, though this side effect is rare. Before beginning, make sure out of acute alcohol withdrawal and test liver enzymes. Ongoing monitoring required only if symptoms warrant it and naltrexone may decrease liver enzyme concentrations.
	10. Dosing: initially dosed at **25 mg/day** and can be increased by 25 mg every 3-7 days to a maximum dosage of 150 mg. There is no clear evidence, however, that higher dosage is more efficacious than FDA approved dosage of 50 mg/day.
	11. Side effects may include transient flu-like symptoms.
2. **Acamprosate (Campral)**
	1. Amino acid derivative that increases GABA neurotransmission and also has complex effects on excitatory amino acid neurotransmitter. Although acamprosate’s mechanism of action has not been clearly established, it may work by reducing symptoms of postacute (protracted) withdrawal, such as insomnia, anxiety, and restlessness.

Acamprosate is thought to be a brain glutamate receptor stabilizer that promotes abstinence by alleviating the physical and psychological discomfort (sweating, anxiety, and sleep disturbances) experienced by many alcohol-dependent individuals once they stop drinking.

* 1. In 1994, FDA approved at a dosage of 1,998 mg/day in patients who are abstinent for alcohol and receiving psychosocial treatment.
	2. The most common side effects experienced by people taking acamprosate are diarrhea, insomnia, anxiety, muscle weakness, nausea, itchiness, and dizziness. Uncommon, but serious, side effects include depression and suicidal thoughts. Most side effects are usually mild and transient, lessening or disappearing within the first few weeks of treatment.
	3. NOT metabolized by the liver so that **renal function is the rate limiting factor** in the drug’s elimination. Renal functioning is warranted prior to initiation of the drug, particularly in individuals who have a history or are otherwise at risk of renal disease. Patients with severe renal impairment (creatinine clearance <30 mL/min) should not use acamprosate. Those with moderate renal impairment (creatinine clearance 30–50 mL/min) may be able to take the medication with dosage adjustments and careful monitoring.
	4. Patients with liver damage usually cannot use either naltrexone or disulfiram. However, because acamprosate is not metabolized in the liver, patients with liver damage can safely take the medication.
	5. Acamprosate has not been found to be associated with any significant drug (including alcohol) interactions and does not affect the action of coadministered disulfiram, diazepam, nordiazepam, imipramine, desipramine, selective serotonin reuptake inhibitors, naltrexone, or naltrexol. No adjustment of dosage is recommended in patients taking these other medications.
	6. The manufacturer of acamprosate recommends that acamprosate therapy be continued for 1 year (the effectiveness and safety of the medication have not been evaluated for periods of use longer than a year).
1. Non FDA approved medications
	1. Anticonvulsants (carbamazepine, divalproex, topirimate).
	2. Baclofen, a GABA B receptor agonist. Patients treated with Baclofen have been shown to be more likely to remain abstinent over a 1-month treatment period, as well as showing a greater number of cumulative abstinence days. Some evidence of misuse of this medication.
	3. Recent study indicated that there is no benefit to the use of any antidepressant in patients with alcohol use disorder without comorbid depression.

VII. **The “COMBINE” STUDY**

1. In the May 3, 2006, issue of the Journal of the American Medical Association, Anton and colleagues reported results from the largest known controlled pharmacotherapy clinical trial for treating alcohol dependence, i.e., the COMBINE study, which was supported by the National Institute on Alcohol Abuse and Alcoholism.
2. This study evaluated the efficacy of specific pharmacotherapies, behavioral or psychosocial interventions, and their combinations for the treatment of alcohol dependence. The COMBINE study evaluated treatment response to novel medication and psychosocial treatment combinations for 1,383 alcohol-dependent, treatment-seeking patients from 11 US sites.
3. In the COMBINE study, alcohol-dependent patients were randomly assigned for four months to placebo pills and/or one or two medications given in combination as 3g/day of acamprosate and/or 100mg/day of naltrexone, both of which are currently approved by the FDA for treating alcohol dependence.
4. In the COMBINE study, all medication or placebo pills prescribed were given in the context of a maximum of nine manual-guided counseling visits across four months, delivered by medical practitioners, i.e., medical management (MM).Other than the first MM visit, which was approximately 45 minutes in length, the eight follow-up MM visits were approximately 20 minutes each. The medical clinicians who delivered MM used an easy-to-follow manualto provide their patients with education about their disease and potential treatments, to give patients advice for reducing drinking, to inquire about any medication side-effects, and to emphasize the importance of routinely taking medications as prescribed. Following this systematic approach reflected in the MM manual, clinicians would spend part of the time with the patient at each visit reviewing pill-taking practices, and, when indicated, the clinician would discuss with the patient ways to improve pill adherence.
5. In addition, one-half of the patients taking medication also received manual-guided, specialty alcohol therapy, i.e., combined behavioral intervention (CBI),for up to approximately twenty 50-minute sessions (the median number of CBI sessions actually attended by patients in the 4-month trial was 10). CBI was specially developed by a subgroup of COMBINE investigators to include a strategic “meld” of prior proven behavioral treatments, e.g., motivational enhancement therapyand cognitive behavioral therapy.By providing specialty therapy to only half of the patients taking medications, this study was designed to assess the advantages of combining specialty treatment with pharmacotherapy.
6. The results of the COMBINE study are as follows:
	1. Many of the patients benefited by participating in the study because all nine groups had a substantial reduction in days of drinking, i.e., more abstinent days over the four months of treatment, compared to pretreatment drinking levels. However, not all patient groups reported similar outcome rates. That is, the patient groups who demonstrated the best (statistical) drinking outcomes after 16 weeks of outpatient treatment had received naltrexone with MM counseling alone (no specialty CBI) or had received specialty therapy, CBI, with just the placebo pills and MM counseling. There was no advantage found in the COMBINE study for adding acamprosate either to MM or to specialty alcohol treatment.
	2. The group that received specialty treatment (CBI) without pills, i.e., no placebo pills or active medication, demonstrated the poorest outcomes—a reminder of the powerful “placebo” effects that are anticipated in controlled clinical trials and why double-blinded, placebo-controlled designs are important in evaluating true medication effects.
	3. The results of the COMBINE study demonstrated that a pharmacotherapy, like naltrexone, when given with medical counseling that emphasizes taking medications as prescribed, can yield clinically significant outcomes (reduced drinking/increased abstinence) that are either as compelling, and under some conditions, more compelling than those observed with specialty behavioral therapy.
	4. This study also noted that a patient's decision to stop taking medications during alcohol treatment appears to take place during a weeks-long process of disengagement from treatment. Patients who discontinue medications early in treatment or without medical consultation appear to drink more frequently and more heavily.

**VIGNETTE: “I won’t drink this time if released!”**

A treatment team is considering the release of a NGRI acquittee, whose primary diagnosis is Alcohol Use Disorder, severe. Over a 12 year period, he has had three trials out on CONREP and each time, after about four months, he has relapsed into drinking alcohol. He has been back in the hospital this last time for four years. During his instant offense, he was intoxicated with alcohol and he also has the diagnosis of Bipolar Disorder. He is adamant that he “won’t drink this time if released” and articulates his relapse prevention plan with great skill.

Do you think he is a good candidate for pharmacotherapy for his alcohol addiction?

If so, what specific medications might be recommended?

**CANNABIS USE DISORDERS**

**I. DRUG “SCHEDULES”**

1. **Schedule I**: drugs with no currently accepted medical use and a high potential for abuse. Some examples of Schedule I drugs are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote.
2. **Schedule II**: drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous. Some examples of Schedule II drugs are: Combination products with less than 15 milligrams of hydrocodone per dosage unit (Vicodin), cocaine, methamphetamine, methadone, hydromorphone (Dilaudid), meperidine (Demerol), oxycodone (OxyContin), fentanyl, Dexedrine, Adderall, and Ritalin.
3. **Schedule III:** Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs but more than Schedule IV. Some examples of Schedule III drugs are: Products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, testosterone.
4. **Schedule IV**: defined as drugs with a low potential for abuse and low risk of dependence. Some examples of Schedule IV drugs are: Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol.
5. **Schedule V:** defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes. Some examples of Schedule V drugs are: cough preparations with less than 200 milligrams of codeine or per 100 milliliters (Robitussin AC), Lomotil, Motofen, Lyrica, Parepectolin.

**II CANNABIS OVERVIEW:**

1. Cannabis is a **Schedule I drug**.
2. Cannabis and cannabinoids act on two specific receptors: CB1 and CB2.
3. Marijuana is the common name for the plant “*cannabis sativa*” and “*cannabis idica*”, the flowers and leaves of which contain the psychoactive chemical Delta-9-tetrahydrocannabinol (**Delta-9-THC**). TCH is primarily an agonist at CB1, which is what yield the “high.”
4. Another psychoactive ingredient is **cannabidiol,** which is mostly devoid of psychoactive activity but has anti-inflammatory and analgesic effects. Cannabidiol is primarily an antagonist at CB1, thereby decreasing the experience of being “high.”
5. Skunk is a term often used interchangeably with cannabis, but skunk cannabis is a much more potent form of the drug. It has around two to three more times of the main active ingredient - tetrahydrocannabinol, or THC.
6. **Sinsemilla** – Female cannabis plants which have not been pollinated. May grow from cutting or from seed. TCH concentrations range from 7% to 14%.
7. A total of 38,681samples of cannabis preparations were received and analyzed between January 1, 1995 and December 31, 2014. The data showed that, while the number of marijuana samples seized over the last four years has declined, the number of sinsemilla samples has increased. Overall, the potency of illicit cannabis plant material has consistently risen over time since 1995 from approximately **4% in 1995** to approximately **12% in 2014.** On the other hand, the CBD content has fallen on average from approximately 0.28% in 2001 to <0.15% in 2014, resulting in a change in the ratio of THC to CBD from 14 times in 1995 to approximately 80 times in 2014.
8. Different cannabis preparations are found in the illicit market. These include **cannabis** (marijuana, sinsemilla, and ditchweed), **hashish** (the resinous parts of the plants mixed with some plant particles and shaped into different forms depending on the preparation method) and **hash oil** (concentrated extract of cannabis plant material or hashish as an oil or semisolid preparation).

**III. SYNTHETIC CANNABINOIDS “SPICE”**

1. A diverse group of agents that are agonists or partial agonists at CB1 receptors.
2. Synthetics are sprayed on herbal plants and disingenuously marketed as “natural, legal, and herbal” marijuana.
3. Sold under names link Spice, K2, Moon Rocks, and Genie.
4. Not detected in standard urine drug screens.
5. Reported side effects include aggression, paranoia, anxiety, agitation, visual hallucinations, somnolence, tachycardia, systolic hypertension, increased blood glucose, panic attacks, and renal impairment.
6. **HU-210** is a [synthetic cannabinoid](https://en.wikipedia.org/wiki/Synthetic_cannabinoid) that was first [synthesized](https://en.wikipedia.org/wiki/Chemical_synthesis) in 1988. HU-210 is 100 to 800 times more potent than natural [THC](https://en.wikipedia.org/wiki/Tetrahydrocannabinol) from [cannabis](https://en.wikipedia.org/wiki/Cannabis_%28drug%29) and has an extended duration of action.. The abbreviation "HU" stands for Hebrew University.

**IV**. **METHODS OF USE**

1. Inhalation of vaporized cannabinoid leaves (“smoke”). This is typically done via small pipes, bongs, blunts or a vaporizer. Smoked marijuana reaches the brain in minutes and the effects last 1-3 hours. Smoking delivers a large amount of TCH into the bloodstream.
2. Ingestion, with psychoactive effect if the leaves are heated or dehydrated and mixed with butter or mild in foods and teas. Less commonly, cannabinoids are extracted with high-proof spirits and are drunk as a tincture. Eating or drinking marijuana takes ½ to 1 hour to have an effect. Effects last up to 4 hours. This method delivers significantly less TCH into the bloodstream.
3. Medical indications:

Glaucoma

Los of appetite

Nausea

Chronic pain

Muscle spasticity

Dronabinol (Marinol): synthetic Delta 9-THC: **Schedule III**. Approved by the FDA to treat emesis refractory to conventional antiemetics.

Nabilone (Cesamet): a structural analogue of THC but produces minimal euphoria. Schedule III. Approved by the FDA to treat emesis refractory to conventional antiemetics.

**V. EPIDEMIOLOGY**

1. Recreational marijuana is legal in nine states and medical marijuana is legal in 29 states.
2. According to the National Institute on Drug Abuse (NIDA), marijuana is the most commonly used illicit drug used in the United States.
3. In 2015, more than 11 million young adults ages 18 to 25 used marijuana in the past year.According to the [Monitoring the Future](https://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future) survey, rates of marijuana use among middle and high school students have dropped or leveled off in the past few years after several years of increase. However, the number of young people who believe regular marijuana use is risky is decreasing.

**VI**. **CANNABIS USE AND RISK TO DEVELOP A CANNABIS USE DISORDER (CUD)**

1. **9%** of people who use marijuana will become “addicted” (compare to heroin- 23% and tobacco-32%). This risk increases to 17% in people who start using in their teens. The risk increases to 25-50% in people who are daily users.
2. Approximately 20% of lifetime users of cannabis will meet criteria for a diagnosis of DSM-5 CUD. 23% of these will meet criteria for a “severe” CUD and half of this group are not functioning in any role (Hasin et al 2016).

**VII. CANNABIS USE DISORDERS**

1. **Cannabis intoxication:** conjunctival injection, increased appetite, dry mouth, and tachycardia, and slowed reaction time. Many users experience a pleasurable high. However, some may also experience anxiety, paranoia, a distorted sense of time, associative thinking (“random” thinking), and short-term memory loss.
2. **Cannabis withdrawal:**
3. DSM-5: Three or more symptoms of the following:
* Irritability, anger, or aggression.
* Nervousness or anxiety
* Sleep difficulty (insomnia, disturbing dreams) (Sleep difficulties may last more than 30 days).
* Decreased appetite or weight loss
* Restlessness
* Depressed mood
* At least one physical symptom causing discomfort: abdominal pain; shakiness/tremors; sweating; fever; chills; or headache.
1. Cannabis withdrawal syndrome is most intense during the first week of abstinence, but can persist as long as a month after use. Up to one third of regular users in the general population report cannabis withdrawal. Among adults and adolescents enrolled in treatment or heavy cannabis users, **50% to 95%** report cannabis withdrawal. There is no specific indication for treatment of cannabis withdrawal.
2. **Cannabis psychosis**:
	1. Acute psychotic episodes tend to occur when a high dose of cannabis is consumed in food and drink rather than smoked.
	2. Cannabis use has a detrimental effect on functioning in patients with schizophrenia.
	3. Starzer et al (2017) noted that 47.4% of person who experienced a cannabis induced psychosis converted to having schizophrenia or bipolar disorder. Young age was associated with a higher risk of converting to schizophrenia. Self-harm after a substance-induced psychosis was significantly linked to both schizophrenia and bipolar disorder.
3. **Cannabinoid Hyperemesis Syndrome : Intense Nausea and Vomiting.** Regular, long-term marijuana use can lead to some people to develop. This causes users to experience regular cycles of severe nausea, vomiting, and dehydration, sometimes requiring emergency medical attention.

**VIII. CANNABIS USE AND VIOLENCE**

* 1. In the longitudinal Dunedin study, marijuana dependent individuals were 3.8 times more likely to report violence than controls (Arsenault et al. 2000). This result was true even after controlling for confounding variable such as other psychiatric disorders or other substance misuses (including alcohol use disorder).
	2. In their research of 1, 236 recently discharged patients who were part of the MacArthur Risk Assessment study, Dugre et al. (2017) prospectively examined risk factors associated with violence in 10 week intervals over a year period. Research results noted that the continuity of cannabis use across more than one time wave was associated with increased risks of future violent behavior. Patients who reported having used cannabis at each follow-up periods were 2.44 time more likely to display violent behavior.

**IX. CANNABIS USE AND LATER LIFE OUTCOMES STUDY**

1. New Zealand researchers Fergusson and Boden (2008) studied the relationship of increasing use of cannabis between the ages of 14-21 and later life outcomes over the course of a 25-year longitudinal study. The analysis was based on the 1003 study participants for whom information was available for outcomes at ages 21-25. A wide range of potentially confounding factors were controlled for.

1. Study findings noted that increasing cannabis use in later adolescence and early adulthood is associated with a range of adverse outcomes in later life. In all cases, there was a marked dose-response relationship between cannabis consumption and less positive outcomes. In particular, high levels of cannabis use are related to:
	1. Poorer educational outcomes;
	2. Lower income at age 25.
	3. Greater welfare dependence and unemployment
	4. Lower relationship quality
	5. Decreased life satisfaction
2. Outcomes for those who used cannabis less than 100 times did not differ markedly from those who did not use cannabis at all.

**X. HEAVY CANNABIS USERS AND COGNITIVE FUNCTIONING (Solowig et al 2002)**

1. Solowij et al. (2002) examined the effects of duration of cannabis use on specific areas of cognitive functioning among users seeking treatment for cannabis dependence.
2. Compared daily long-term users (23.9 years of use), to daily shorter-term users (10.2 years of use), to individuals with no use.
3. Findings:
	1. Long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention.
	2. Long-term heavy cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.
	3. There was no difference between shorter-term users and control.

**XI. PERSISTENT CANNABIS USE IN ADOLESCENCE AND NEUROPSYCHOLOGICAL DECLINE**

1. More recent reports indicate that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages and more adolescents are using cannabis on a daily basis.
2. Meir et al (2012) tested the association between persistent cannabis use and neuropsychological decline to determine whether decline is concentrated among adolescent onset cannabis users.
3. The subjects were 1,037 individuals who were followed prospectively from birth until age 38.
4. Neuropsychological testing was conducted at age 13, prior to initiation of cannabis use and again at age 38 years of age, after a pattern of persistent cannabis use had developed.
5. Findings were as follows:
6. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education.
7. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline.
8. Cessation of cannabis use did n0T fully restore neuropsychological functioning among adolescent-onset cannabis users.
9. Impairment was apparent to third-party informants.

**XII. ADOLESCENT COGNITIVE BRAIN DEVELOPMENT (ABCD) STUDY**

1. The ABCD study is the largest long-term study of brain development and child health in the United States.
2. Approximately 10,000 children ages 9-10 will be recruited and followed into early adulthood. Integrating structural and functional brain imaging with genetics, neuropsychological, behavioral, and other health assessments, the ABCD Study will increase our understanding of the many factors that can enhance or disrupt a young person’s life trajectory.

**XIII. PSYCHOTHERAPUTIC APPROACHES OF CANNABIS USE DISORDER**

1. The most commonly used therapies are:
	1. 12-step facilitation (TSF)
	2. Motivational interviewing
	3. Cognitive-behavioral therapy (CBT)
	4. Contingency management
2. Although CM has been shown to be superior to other psychotherapeutic approaches, at later follow-ups, the combined treatment of either CBT + CM or MET-CBT + CM has demonstrated the highest percentages of individuals as abstinent (Kadden et al., 2007; Stanger et al. 2009).
3. There is growing evidence for the use of brief interventions in both adults and adolescents.

**XIV. PHARMACOTHERAPY OF CANNABIS USE DISORDER**

1. There is no FDA approved medication for the treatment of cannabis use disorder.
2. Of the few RCTs evaluating pharmacological treatments for marijuana dependence, most studies include a behavioral intervention.
3. Promising preliminary findings with N-acetylcysteine (NAC) and gabapentin have recently emerged, but these medications require further study.
4. The following medications have not shown a significant effect in reducing marijuana use: Buspirone; Agonist therapy (dronabinol); Nefazodone; Divalproex sodium.
5. Clinicians should treat any comorbid psychiatric symptoms, with an understanding that mood, sleep, and anxiety symptoms may worsen during the cannabis withdrawal period.
6. Dronabinol may relive symptoms of marijuana withdrawal in patients who are reducing use.

**STIMULANT USE DISORDERS**

I. **STIMULANT OVERVIEW**

1. Generally taken for pleasurable “high,” consisting of increased energy, sense of grandiosity, and pleasure.
2. DSM-5 Stimulant Intoxication criteria have been criticized for being non specific. For example, high or low blood pressure; psychomotor agitation or retardation. Likewise, stimulant withdrawal criteria are also vague includes: insomnia or hypersomnia; and psychomotor agitation or retardation.
3. Symptoms of stimulant intoxication: may present with rambling speech, headache, transient ideas of reference, and tinnitus. There may be paranoid ideation, auditory hallucinations in a clear sensorium, and tactile hallucinations.
4. Symptoms of stimulant withdrawal: Physiological changes during withdrawal are opposite those of intoxication.
5. DSM-5 also notes the following disorders associated with stimulant use in Intoxication (I) and/or Withdrawal (W) in addition to substance use disorders, substance intoxication, and substance withdrawal:

 1. Psychotic disorders (I)

 2. Bipolar disorders (I/W)

 3. Depressive disorders (I/W)

 4. Anxiety (I/W)

 5. Obsessive-compulsive and related disorders (I/W)

 6. Sleep disorders (I/W)

 7. Sexual dysfunctions (I)

 8. Delirium (I)

1. Stimulant psychosis vs. schizophrenia/schizoaffective psychosis:
	1. Psychiatric effects: Anxiety, irritability, **panic attacks**, hypervigilance, paranoia, grandiosity,, impaired judgement. **Tactile hallucinations** are especially typical of stimulant psychosis. Cocaine-induced psychosis may differ from acute schizophrenic psychosis in having less thought disorder and bizarre delusions and fewer negative symptoms.
	2. Behavioral effects include restlessness, agitation, **tremor, dyskinesia, and repetitive behaviors** such as picking at the skin or foraging for drug.
	3. Physiologic effects: tachycardia, pupil dilation, diaphoresis, and nausea.
	4. Chronic cocaine or amphetamine use is associated with cognitive impairment that may persist for several months.

**II**. **COCAINE OVERVIEW**

1. Cocaine is a Schedule II drug.
2. Cocaine is the **second most widely used illegal drug** in the United States, after marijuana.
3. **One in six persons** who use cocaine for nonmedical purposes will become cocaine dependent.
4. Based on data from the combined 2014–2015 National Surveys on Drug Use and Health, 1.7 million young adults aged 18 to 25 in the United States used cocaine in the past year (4.98 percent of the young adult population). This equates to about 1 out of every 20 young adults across the nation using cocaine in the past year.
5. Cocaine is the illicit drug associated most often with visits to the emergency room department.

**III.** **COCAINE FORMULATIONS AND METHODS OF USE**

1. Cocaine is a tropane ester found in leaves of the coca bush.
2. Cocaine is available for illicit use in two forms:
	1. Base: has a low melting point (98 degrees Celsius), which vaporizes and allows it to be smoked.
	2. Salt: has a high melting point, so it is destroyed by heating. Cocaine salt is water soluble making it easy to dissolve by injection.
3. Cocaine is used clinically in the United States as a local or topical anesthetic (by blocking membrane sodium channels).
4. Cocaine acts by binding to the extracellular face of transporters and inhibiting the reuptake of previously released monoamine neurotransmitters.
5. Half-life of cocaine generally last from 40-90 minutes.
6. Methods of use:
	1. Smoking: rapidly absorbed by the lungs reaching the brain in 6 to 8 seconds. Free base “crack” cocaine is smoked.
	2. Intravenous: produces peak brain uptake in 4 to 7 minutes.
	3. Intranasal and oral: slower absorption and onset of effect, up to 30 to 45 minutes, with a longer peak effect and a gradual decline from peak. Cocaine intranasal powder is referenced as “snorting” or “insufflated.”
7. In humans, 95% of cocaine is metabolized to benzoylecgonine (BE) and ecgonine methyl ester. Cocaine is largely eliminated in the urine with BE persisting for 24-72 hours, potentially up to 96 hours.
8. When an individual uses alcohol and cocaine at the same time, **cocaethylene** develops in the liver as a result of the metabolic processing of both alcohol and cocaine. The addition of cocaethylene to the alcohol and cocaine already in the system can produce effects that are much more powerful than the effects that alcohol or cocaine alone produce.

Increased toxic effects: [Cocaethylene is significantly more toxic](https://www.ncbi.nlm.nih.gov/pubmed/9243342) than cocaine. Laboratory studies suggest that it may have a toxicity level 30 percent higher than cocaine. Once the liver begins producing it, the chemical keeps being released in the system and remains in the body up to three times longer than cocaine, resulting in increased potential for toxic effects. Cocaethylene toxicity may be associated with a number of sudden deaths and cardiovascular events that occur in cocaine users.

**IV.** **COCAINE TREATMENT (ALSO APPLIES TO MOST STIMULANTS)**

**A.** Intoxication

* 1. Polydrug use is common among cocaine users. Intoxication symptoms often resemble mania. With increased doses and duration, cocaine an also produce a state of mental confusion and excitement known as cocaine delirium.
	2. Individuals may also experience a cocaine induced psychosis.
	3. Initial approach for treating cocaine (and stimulant) intoxication/psychosis is: ART

A-Acceptance of the patient’s immediate needs

R-Reassurance that the condition is due to drug and likely wil disspiate within a few hours.

T-Talk down, to provide reality orientation

* 1. Avoid physical restraints as they can increase risk of hyperthermia and rhabdomyolsis.
	2. The use of B-adrenergic antagonists for the acute treatment of cocaine-associated chest pain should be avoided. **Propranolol and esmolol are contraindicated for treated cardiovascular problems**.
	3. Benzodiazepines are the treatment of choice for cocaine intoxication.
	4. If antipsychotics are required, high-potency agents (first generation) are preferred due to minimal anticholingergic side effects.
	5. Antipsychotics should be used cautiously because they may worsen the hyperthermia and may lead to fatality in some cases.
	6. **Levamisole** adds bulk and weight to powdered [cocaine](https://en.wikipedia.org/wiki/Cocaine) (whereas other adulterants produce smaller "rocks" of cocaine) and makes the drug appear purer. Levamisole suppresses the production of [white blood cells](https://en.wikipedia.org/wiki/White_blood_cell), resulting in [neutropenia](https://en.wikipedia.org/wiki/Neutropenia) and [agranulocytosis](https://en.wikipedia.org/wiki/Agranulocytosis). With the increasing use of levamisole as an [adulterant](https://en.wikipedia.org/wiki/Adulterant), a number of these complications have been reported among cocaine users. Levamisole has also been linked to a risk of [vasculitis](https://en.wikipedia.org/wiki/Vasculitis), and two cases of vasculitic skin necrosis have been reported in users of cocaine adulterated with levamisole.Levamisole-tainted cocaine was linked to several high-profile deaths. [Toxicology](https://en.wikipedia.org/wiki/Toxicology) reports showed levamisole, along with cocaine, was present in [DJ AM](https://en.wikipedia.org/wiki/DJ_AM)'s body at the time of his death.Andrew Koppel, son of newsman [Ted Koppel](https://en.wikipedia.org/wiki/Ted_Koppel), was also found with levamisole in his body after his death was ruled a drug overdose.
1. Pharmacotherapy:
2. Currently, there are no approved treatments for cocaine addiction by the FDA.
3. Gender specific treatments: Oral progesterone treatment in women has shown to help to attenuate the effects of cocaine in women and a study of oral progesterone in reducing cocaine use in women is underway.
4. Cocaine vaccine (TA-CD): A cocaine vaccine was created by combining [norcocaine](https://en.wikipedia.org/wiki/Norcocaine) with inactivated [cholera](https://en.wikipedia.org/wiki/Cholera) toxin. Phase III Clinical Trials showed no significant difference between users given placebo and users given TA-CD.
5. Behavioral treatments: the most important component of cocaine addiction treatment involves behavioral therapies. Specific therapies with demonstrated efficacy include TSF, CBT and contingency management (CM). In regard to therapy, there is a higher dropout rate observed in cocaine users compared to individuals with other addictions.

**V. AMPHETAMINES OVERVIEW**

* 1. Amphetamines and other stimulants may be obtained by prescription for the treatment of obesity, ADHD, and narcolepsy. Consequently, prescribed stimulants can be diverted into an illegal market.
	2. Stimulants typically produce an instant feeling of well-being, confidence and euphoria. Dramatic behavioral changes can rapidly develop with stimulant use disorder. Chaotic behavior, social isolation, aggressive behavior, and sexual dysfunction can result from long-term stimulant use disorder.
	3. Amphetamines are metabolized in the liver via three different pathways. Amphetamine is a metabolite of methamphetamine.
	4. Amphetamine and phentermine are called “releasers.” They bind to transporters and trigger release of intracellular monoamines by reversing the normal direction of transport flux.
	5. MA has a prolonged half life and a long duration of action, which exceeds 6 hours.
	6. Effects are almost instantaneous when smoked or injected, while it takes 5 minutes after snorting or 20 minutes after oral ingestion to get a high.
	7. Effects include increased arousal and attention, suppression of appetite, and euphoria.
	8. Physiological changes with MA use include increased blood pressure, body temperature, heart rate, and breathing rate.
	9. Negative side effects include high body temperature, stroke, cardiac arrhythmia, stomach cramps, and shaking, as well as increased anxiety, insomnia, aggressive tendencies, paranoia and hallucinations.
	10. Discontinuing use of MA often results in a state of depression, as well as fatigue, anergia, and some types of cognitive impairment that last anywhere from 2 days to several months.

**VI**. **TREATMENTS**

1. Medication management:
	1. Methamphetamine Psychosis: Grelotti and colleagues (2010) noted that antipsychotic medications generally fail to ameliorate long-term post-MA psychosis attributable to chronic stimulant use. Clinical researchers have proposed consideration of ECT for such psychosis.
	2. Caution is advised (particularly haloperidol with possible seizure risk) in prescribing antipsychotic medications to acute MA induced psychosis.

Medications-Most controlled trials do not show efficacy for prevention of relapse of methamphetamine use.

1. Psychological treatments include TSF, contingency management, and CBT.

**Matrix Model**: Developed by NIDA/SAMHSA-a blended treatment approach that incorporates principles of CBT in individual and group settings, family education, motivation interviewing, and 12-step program participation. The manuals provide the structure and content for three-visit-per week, 16-week outpatient treatment experience, followed by a weekly social support group for 1 Year. This manualized therapy has been proven effective in reducing MA use during the 16-week application of the intervention, compared with treatment as usual.

**VII.** **STIMULANT INDUCED PSYCHOSIS VS. PRIMARY PSYCHOTIC DISORDER**

1. Methamphetamine (MA) use: has been associated with psychotic symptoms, including auditory and visual hallucinations, persecutory delusions, ideas of reference and disorganized speech.
2. Research has estimated that the prevalence of psychotic symptoms among MA users is between 13% and 24% (McKetin et al. 2006).
3. Methamphetamine psychosis typically follows a transient course, with symptoms subsiding once the user has stopped taking the drug. Some consumers can experience a prolonged psychosis that persists even after the drug has cleared from the body, with the majority of psychotic symptoms resolving within 1 month.
4. Some research has indicated that MA psychosis can develop into an enduring form of psychosis, with some reports noted that up to 30% of those with MA psychosis may have symptoms that continue up to 6 months following abstinence and other research indicating that abstinent MA-dependent users met criteria for a psychotic disorder at 3 years follow up (Wearne et al. 2018).
5. Several factors are associated with the presence, severity, and/or persistence of MA-related psychosis and include (Ma et al. 2018):
6. Intensity of MA use (amount, frequency, and form of MA use);
7. History of a psychotic disorder;
8. Family history of psychosis;
9. Family history of other mental illness;
10. Psychiatric comorbidity;
11. Experiencing childhood adverse events.
12. What is the possible relationship of MA use to schizophrenia?
13. Methamphetamine could induce schizophrenia by eliciting an underlying vulnerability/predisposition to a primary psychotic disorder; vs.
14. Methamphetamine-induced psychosis is a distinct syndrome from schizophrenia.
15. In their analysis of the lifetime experience of hallucinations and delusions associated with transient methamphetamine-related psychosis (MAP), persistent MAP, and primary psychosis, McKetin et al (2017) noted the following:
	1. Transient MAP was associated with persecutory delusions and tactile hallucinations.
	2. Persistent MAP was additionally associated with delusions of reference, thoughts interference and complex auditory, visual, olfactory, and tactile hallucinations. Primary psychosis was also associated with delusions of thought projection, erotomania and passivity.
	3. The lifetime symptom profile associated with persistent MAP was not significantly different to that of participants with a primary psychosis. This may reflect the precipitation of a primary psychosis in vulnerable individuals.
16. In their research, Wearne et al. (2018) noted that while there is considerable overlap in the behavioral and cognitive symptoms between MA psychosis and schizophrenia, there appears to be some evidence that suggests there are divergent aspects to each condition, particularly with acute MA psychosis. Schizophrenia appears to be associated with pronounced thought disorder, negative symptoms more generally and cognitive deficits mediated by the parietal cortex, such as difficulties with selective visual attention, while visual and tactile hallucinations appear to be more prevalent in acute MA-induced psychosis.

**OPIOID USE DISORDERS AND “OTHER” DRUGS**

**I. OVERVIEW**

1. There are three types of opioid receptors: mu; kappa; and delta. The **mu receptor** is the receptor most associated with the pleasurable reactions associated with compounds that activate it (i.e. agonists).
2. Definitions:
3. **Opioid**-refers to the entire class of compounds that bind to one or more types of opioid receptors.
4. **Opiate**-used only to refer to a ***subset of opioids***, namely the natural products of the opium poppy (especially thebaine and morphine).
5. **Semisynthetic opioids**: modifications of a naturally occurring opiate: heroin from morphine; buprenorphine and oxycodone from thebaine.

Heroin is an opioid drug made from morphine, a natural substance taken from the seed pod of the various opium poppy plants grown in Southeast and Southwest Asia, Mexico, and Colombia. Heroin can be a white or brown powder, or a black sticky substance known as black tar heroin. Other common names for heroin include *big H*, *horse*, *hell dust,* and *smack*.

Some people mix heroin with crack cocaine, a practice called *speedballing*.

1. **Synthetic opioids**: fully synthetic compounds: methadone and fentanyl.

**II**. **HISTORICAL OVERVIEW**

1. Harrison Act (1914): prohibition on prescription of narcotics (opioids) to individuals with an opioid use disorder. Many physicians were prosecuted with fears of opioid prescribing developing. An increase in drug trafficking and crime associated with opiate (heroin) and cocaine misuse.
2. 1974: First methadone maintenance programs for opioid use disorder.
3. DATA 2000: Office based treatment of opioid use disorder with buprenorphine (see below for more detail).

**III. EPIDEMIOLOGY**

* 1. Researchers studied data from more than 59,000 pharmacies, accounting for nearly nine out of 10 prescriptions nationwide. Based on its analysis, the CDC says more than **2 million Americans who consumed prescription opioids** had an opioid use disorder. The [**disease’s overall economic burden**](https://www.ncbi.nlm.nih.gov/pubmed/27623005) — such as the cost of substance abuse treatment, health care and legal cases — cost the U.S. more than $78 billion a year.
	2. Prescription opioid use:
	3. During a single ten year period, 1999-2010, the volume of addictive opioid painkillers sold in the US skyrocketed by 400%. The amount of opioids prescribed in 2015 was enough for every American to be medicated around the clock for three weeks.
	4. The amount of opioids prescribed in the United States began to decrease in 2011. However, in 2015, it remains approximately three times as high as in 1999 and nearly four times as high as the amount distributed in Europe in 2015.
	5. These decreases might reflect growing awareness among clinicians and patients of the risks associated with opioids. Throughout this period, however, the average duration of opioid prescriptions increased, in part because of the continued increase in longer opioid prescriptions (≥30 days) through 2012, followed by a stabilization of the rate, and a substantial decrease in shorter prescriptions (<30 days) after 2012. This pattern, along with the trends in overall numbers of opioid prescriptions, might reflect fewer patients initiated on opioid therapy after 2012, whereas patients already receiving opioids were more likely to continue receiving them. Patients are at risk for continuing opioids long-term once they have received them for >5 days, and are unlikely to discontinue opioids after they have received them for 90 days. highlighting both the importance of minimizing unnecessary initial opioid exposure and potential challenges in reducing opioid use among patients already receiving them.
	6. Despite reductions in opioid prescribing in recent years, opioid-involved overdose death rates continue to increase. However, these increases have been driven largely by use of illicit fentanyl and heroin. There is no evidence that policies designed to reduce inappropriate opioid prescribing are leading to these increases. Combined implementation of mandated provider review of PDMP data and pain clinic laws reduced the amount of opioids prescribed, prescription opioid-involved overdose deaths, and all opioid-involved deaths. The policies were also associated with reductions in heroin overdose deaths that were not statistically significant. By reducing the number of persons exposed to opioids and the subsequent risk of opioid use disorder these policies might reduce the number of persons initiating illicit opioid use in the longer term.
	7. Heroin epidemiology:
	8. According to the National Survey on Drug Use and Health (NSDUH), in 2016 about 948,000 Americans reported using heroin in the past year,[1](https://www.drugabuse.gov/publications/research-reports/heroin/references) a number that has been on the rise since 2007. This trend appears to be driven largely by young adults aged 18–25 among whom there have been the greatest increases.
	9. The number of people using heroin for the first time is unacceptably high, with 170,000 people starting heroin use in 2016, nearly double the number of people in 2006 (90,000). In contrast, heroin use has been declining among teens aged 12–17.
	10. Approximately 23% of individuals who use heroin develop opioid addiction.
	11. Prescription Opioids and Heroin:
	12. Prescription opioid pain medicines such as OxyContin® and Vicodin® have effects similar to heroin. Research suggests that misuse of these drugs may open the door to heroin use. Nearly 80 percent of Americans using heroin (including those in treatment) reported misusing prescription opioids first.
	13. While prescription opioid misuse is a risk factor for starting heroin use, only a small fraction of people who misuse pain relievers switch to heroin. According to a national survey, less than 4 percent of people who had misused prescription pain medicines started using heroin within 5 years.This suggests that prescription opioid misuse is just one factor leading to heroin use.

**IV. OPIOID INTOXICATION MANAGEMENT**

* 1. In a retrospective analysis of consecutive cases of presumed opioid overdose by emergency services, 16% were either dead or in full cardiopulmonary arrest at the time of the initial emergency medical service evaluation.
	2. The level of tolerance to opioids can have a significant effect on an individual’s risk of opioid overdose. In addition, tolerance to respiratory to depression may be slower than tolerance to euphoric effects, thus explaining why overdose occurs so often, even among “experienced” opioid users.
	3. DSM-5 notes intoxication includes pupillary constriction plus one or more of the following:

1. Drowsiness or coma

2. Slurred speech

3. Impairment in attention or memory.

* 1. “Heroin Overdose Syndrome”: triad of altered mental status; depressed respiration, and miotic pupils.
	2. Management:
1. Immediate supportive management with availability of adult advanced cardiac life support. Make sure there is adequate ventilation.
2. Toxicology looking for other drugs. Opioid use and overdose may be complicated by the effects of substances employed to “cut” drugs purchased on the street. Scopolamine has been noted in many cases.
3. **Naloxone hydrochloride (Narcan)-a pure opioid antagonist**: **0.4 to 0.8 mg IV** initially, repeated as necessary. The onset of action of Narcan to reverse overdose effects is **approximately 2 minutes**. For patients with an incomplete naloxone response, a **trial of 2 mg of naloxone** is warranted.

V. **OPIOID WITHDRAWAL SYNDROME**

1. **Daily use in significant quantities over 2-3** weeks generally is required to produce a withdrawal syndrome, although previously dependent individuals develop the withdrawal syndrome more quickly upon relapse. As use continues, so does withdrawal severity (therefore, important to ask how long person has been using opioid).
2. DSM-5 withdrawal criteria (3 or more of the following)
	1. Dysphoric mood
	2. Nausea or vomiting
	3. Muscle aches
	4. Lacrimation (increased tears) or rhinorrhea (runny nose)
	5. Pupillary dilation, piloerection (goose bumps), or sweating
	6. Diarrhea
	7. Yawning
	8. Fever
	9. Insomnia
3. Rapidly metabolized drugs, such as heroin, are associated with more severe shorter-lived withdrawal, whereas drugs that dissociate slowly from the opioid receptor (e.g. buprenorphine) or that are slowly metabolized (e.g. methadone) are associated with a less intense, longer withdrawal syndrome.
	1. Heroin symptoms manifest 8-12 hours after last use, beginning with intense craving and anxiety, but possibly also with profound dysphoria and agitation. Withdrawal symptoms peak 2-3 days after last dose and should resolve by day 5.
	2. Longer acting drugs, such as methadone, may not produce a withdrawal syndrome until 2-4 days after last use
4. **Protracted withdrawal syndrome**-regardless of the opioid, after acute withdrawal the individual may experience a protracted withdrawal syndrome, with subtle, pernicious mood and sleep disturbances that last 6-8 months. This may include mild abnormalities in vital signs and continued craving. However, there is no universal definition of this syndrome.

**VI METHADONE MAINTENANCE TREATMENT-AGONIST TREATMENT**

1. What is “Methadone” (Dolophine)?
	1. A medication that acts on the mu receptor to block the effects of opioids. (Schedule II drug).
	2. Is present at levels to maintain alertness without withdrawal symptoms, craving, or drug preoccupation throughout a 24-hour dosing interval.
	3. Methadone can be diverted as a drug of abuse.
2. Why prescribed methadone? Methadone maintenance has been shown to:
	1. Decrease mortality
	2. Reduce illicit drug use
	3. Reduce seroconversion to HIV
	4. Reduce criminal activity
	5. Increase engagement in socially productive activities
3. Who can prescribe Methadone?

Methadone must be dispensed to the patient at a Substance Abuse and Mental Health Services Administration (SAMHSA)-certified opioid treatment program (OTP) facility—with daily doses provided at the clinic—until the patient is deemed stable enough to receive take-home doses.

Barriers to accessing this treatment include limited geographical locations of OTPs, transportation difficulties, and policies that preclude the use of methadone.

1. What is the recommend dose?
	1. Federal regulations require that the **initial dose of methadone is no more than 30 mg** and may be lower in patients in whom low tolerance might be expected.
	2. A total dose of **no more than 40 mg may be given on the first treatment day** unless the program physician documents in the patient’s record that 40 mg did not suppress opioid abstinence symptoms.
	3. A significant portion of the previous dose remains in tissue stores with daily dosing. **Thus, levels of methadone increase daily, even without an increase in dose**.
	4. Studies have reported deaths during the first 10-14 days of treatment, particularly when induction doses are high (more than 50 mg and when the patient is also ingesting sedatives.
	5. The maintenance phase begins once a stable dose is established. Outcomes with methadone medication are dose related; lower doses (20-40 mg/day) are effective at suppressing opioid withdrawal but may not suffice in decreasing craving or blocking the effective of other opioids. Most patients receiving methadone maintenance do well on a dose range of **80 to 120 mg/dl**.
	6. Patients initially attend the clinic 6 or 7 days per week. For days that the patient is not required to attend the clinic, a “take-home” dose of mediation is provided. In the United States, it is possible for patients to receive up to a month’s worth of take-home doses of methadone, although this number of take-home doses is permitted no earlier than the third year of treatment.

E. Side effects:

1. Side effects at therapeutic dose include: increased sweating, constipation, drowsiness, decreased sexual interest, hypogonadism in men. Persons maintained on a steady dose of methadone do not appear to have problems with performance or clinically significant cognitive impairment. There are variable findings in regard to methadone and QTc prolongation.
2. Signs of methadone overdose are: respiratory depression; cognitive impairment; QTc prolongation; Torsades de Pointes.
3. How long should someone be on methadone?

In general, for successful rehabilitation, length of treatment with methadone is best seen in terms of years rather than months. For many patients, 5 to 10 years-or even a lifetime-of methadone maintenance may be required.

Studies suggest that **only 10-20% of patients who discontinue methadone are able to remain abstinent.**

1. Withdrawal from methadone maintenance:
	1. If patients chose to terminate methadone maintenance, methadone should be withdrawn slowly over 3-6 months.
	2. The dose should be decreased by 5-10 mg/week until it reaches 25 mg once a day. Below 25 mg the patient may have more difficulty because withdrawal can occur within 24 hours. Spilt dosing, if possible, is sensible at this point.

**VI. BUPRENORPHINE-AGONIST THERAPY SCHEDULE III MEDICATION**

1. Buprenorphine, approved in 2002 by FDA to treat opioid dependence, is available at OTPs but is most often prescribed by physicians in office-based settings. Thus, in theory, it can be more accessible than methadone.
2. To prescribe buprenorphine, physicians need limited special training and so all physicians may not currently be able to prescribe it. Physicians also need to be granted a waiver by the U.S. Drug Enforcement Agency (DEA) from regulations that otherwise prohibit them from treating people with opioid dependence in office settings and, at maximum, can only treat up to 100 patients at a time. Currently, mid-level practitioners (e.g., nurse practitioners, physician assistants) are not eligible for DEA waivers to prescribe buprenorphine.
3. Buprenorphine offers several benefits to those with opioid dependency and to others for whom treatment in a methadone clinic is not preferred or is less convenient.
4. Physicians must apply to SAMHSA to provide buprenorphine treatment beyond the 30-patient limit for up to 100 patients with opioid dependency. In 2016, congressed approved physicians getting a waiver to treat up to 275 patients with buprenorphine.
5. For treatment purposes, buprenorphine is combined with naloxone in **a 4:1 ratio**. This helps prevent the medication from being diverted for injection because if given IV, the naloxone can precipitate withdrawal. The exception to giving buprenorphine with combined naloxone is for pregnant women.
6. The FDA has approved the following buprenorphine products:
* Bunavail (buprenorphine and naloxone) buccal film
* Suboxone (buprenorphine and naloxone) film
* Zubsolv (buprenorphine and naloxone) sublingual tablets
* Buprenorphine-containing transmucosal products for opioid dependency
1. How Buprenorphine Works:
2. Buprenorphine has unique pharmacological properties that help: a. Lower the potential for misuse; b. Diminish the effects of physical dependency to opioids, such as withdrawal symptoms and cravings; c. Increase safety in cases of overdose.
3. Buprenorphine is an **opioid partial agonist**. This means that, like opioids, it produces effects such as euphoria or respiratory depression. With buprenorphine, however, these effects are weaker than those of full drugs such as heroin and methadone.
4. Buprenorphine’s opioid effects increase with each dose until at moderate doses they level off, even with further dose increases. This **“ceiling effect”** (approximately 32 mg) lowers the risk of misuse, dependency, and side effects. Also, because of buprenorphine’s long-acting agent, many patients may not have to take it every day.
5. Buprenorphine treatment happens in three phases:
6. **The Induction Phase** is the medically monitored startup of buprenorphine treatment performed in a qualified physician’s office or certified OTP using approved buprenorphine products. The medication is administered when a person with an opioid dependency has **abstained from using opioids for 12 to 24 hours and is in the early stages of opioid withdrawal**. For those patients taking longer acting opioids, such as methadone, the provider will need to wait **up to 36 hours** before beginning treatment. It is important to note that buprenorphine can bring on acute withdrawal for patents who are not in the early stages of withdrawal and who have other opioids in their bloodstream.

**Most patients will require their first 2-4 mg dose approximately 12 hours after their last dose of opioids, and another 2-4 mg approximately 1 hour later.**

**For most patients, 8 mg will suffice on the first day; heavier users may need up to 12 mg.**

Some physicians are now prescribing Buprenorphine treatment via telepsychiatry. In such cases, physicians should be conservative and start with a 2 mg dose and slowly increase the dose until stabilization is achieved.

1. **The Stabilization Phase** begins after a patient has discontinued or greatly reduced their misuse of the problem drug, no longer has cravings, and experiences few, if any, side effects. The buprenorphine dose may need to be adjusted during this phase. Because of the long-acting agent of buprenorphine, once patients have been stabilized, they can sometimes switch to alternate-day dosing instead of dosing every day.

**After day 1, daily doses of 8-16 mg will sufficiently alleviate symptoms.**

**FDA approved dose range is up to 24 mg (combined with 6 mg naloxone) a day.**

**Buprenorphine given alone is relatively safe; however, when combined with other respiratory depressants, such as benzodiazepines, death may result.**

1. **The Maintenance Phase** occurs when a patient is doing well on a steady dose of buprenorphine. The length of time of the maintenance phase is tailored to each patient and could be indefinite. Once an individual is stabilized, an alternative approach would be to go into a medically supervised withdrawal, which makes the transition from a physically dependent state smoother. People then can engage in further rehabilitation—with or without MAT—to prevent a possible relapse.

H. When buprenorphine is being tapered, 2 mg increments are typically used. Gradual, rather than more rapid withdrawals are probably more effective though there is limited research.

**VII. NALTREXONE-SCHEDULE III-OPIOID ANTAGONIST THERAPY**

* 1. Naltrexone is **an opioid antagonist**, a medication that binds to and effectively blocks opioid receptors.It prevents receptors from being activated by agonist compounds, such as heroin or prescribed opioids, and is reported to reduce opioid cravings and to prevent relapse.Patients need to be informed that this medication will prevent them from feeling the euphoric effect or pain relief they previously felt when they took an opioid. Both methadone and buprenorphine are controlled substances, whereas naltrexone is not.
	2. Naltrexone can be prescribed by any healthcare provider who is licensed to prescribe medications. Special training is not required; the medication can be administered in OTP clinics. Practitioners in community health centers or private office settings can also prescribe it for purchase at the pharmacy. These factors may improve access to treatment for opioid dependence.
	3. Naltrexone requires that patients be abstinent from opioids for a period prior to induction. Such abstinence can be difficult for patients to achieve. Retention in treatment has sometimes been problematic when patients are asked to adhere to daily doses of oral naltrexone.A monthly injection of naltrexone, instead of daily dosing, may improve patients’ adherence to their medication regimens.
	4. Patients who have been treated with extended-release injectable naltrexone may have reduced tolerance to opioids and may be unaware of their potential sensitivity to the same, or lower, doses of opioids that they used to take. If patients who are treated with extended-release injectable naltrexone relapse after a period of abstinence, it is possible that the dosage of opioid that was previously used may have life-threatening consequences, including respiratory arrest and circulatory collapse.
	5. Naltrexone displaces heroin or prescribed opioids from receptors to which they have bound, which can precipitate withdrawal symptoms.Therefore, complete detoxification from opioids before initiating or resuming extended-release injectable naltrexone is necessary to prevent withdrawal. At least 7–10 days without opioid use is recommended before beginning extended-release injectable naltrexone.
	6. Patients have better treatment outcomes when naltrexone-based treatment is combined with behavioral therapies.The efficacy of extended-release naltrexone has been established when given in conjunction with behavioral support; it has not been studied as a sole component of treatment.

**VIII.** **HALLUCINOGENS AND CLUB DRUGS**

* 1. Psychoactive substances that produce a profile of changes in thoughts, perceptions, and emotions often including a profound alteration in the perception of reality. Despite the term hallucinogen, frank visual and auditory hallucinations are uncommon, although perceptual alterations (i.e. illusions) are common.
	2. Many hallucinogens are schedule as Schedule I compounds, ie. compounds having high abuse potential and no accepted safe medical use.
	3. **Classic hallucinogens**: agonists at postsynaptic serotonin type 2 receptors (primarily 5-HT 2A).

1. *Tryptamine* based: LSD, LSA, psilocybin, DMT, 5-Methosy-DMT, AMT

2. *Phenethylamine* based Mescaline; DOM

* 1. **Entactogen hallucinogens**: MDMA
	2. **Dissociative anesthetic hallucinogens**: PCP; Ketamine, DXM
	3. **Atypical hallucinogens**: Salvinorin A; scopolamine
	4. The National Institute on Drug Abuse has identified the following compounds as club drugs: LSD, ketamine, MDMA, methamphetamine, GHB, and flunitrazepam (Rohypnol.
	5. The most commonly associated long-term risk of classic hallucinogen use is hallucinogen persisting perception disorder (HPPD), frequently referred to as “flashbacks.”
	6. **MDMA-Ecstasy (Methylene-Dioxy-Methamphetamine): Schedule I drug**
		1. A synthetic drug that is structurally similar to both amphetamine and mescaline (therefore has both stimulating and hallucinogenic properties).
		2. Promotes release of serotonin and other monoamines and prevents reuptake of serotonin.
		3. Typically taken in oral form and onset of effects occur 30-60 minutes later.
		4. Has a mix of mood-enhancing, stimulant-like and hallucinogenic effects. Increases empathy and good feelings for others.
		5. Psychiatric adverse effects can generally be managed with interpersonal support and administration of benzodiazepines in a case of extreme agitation.
		6. Most significant risks are physiological and can include serious cardiac complications, hyperthermia, and hyponatremia. May also cause “lock jaw” (trismus) and teeth grinding, anorexia, diaphoresis, hot flashes, and “disco dump.”
		7. There is little conclusive evidence that MDMA causes neurotoxicity of clinically relevant impairments in brain function at doses (100-200 mg) or total exposures ranging from one to three sessions.
	7. **Gabba-Hydroxybutyrate (GHB):** Known as “liquid ecstacy”-highly regulated Schedule III drug
		1. GHB is popular because of its reputed aphrodisiac, disinhibitory, and amnesic effects; short duration of action; absence of “hangover” and nondetectabiltiy by standard drug screens. People refer to GHB as giving them “the greatest sex ever.”
		2. GHB is taken orally as a liquid and effects begin within 15 minutes of ingestion and last 2 to 4 hours.
		3. At low doses, GHB produces relaxation, euphoria, sedation, disinhibition, sociability, and anterograde amnesia.
		4. Higher doses produce somnolence, confusion, and hallucinations. Higher doses may case incontinence, myoclonic movements, bradycardia, hypotension, hypothermia, generalized tonic-clonic seizures and coma. Overdose is a real danger because the lethal dose is only five times greater than the recreation dose. Also, has a synergistic effect with alcohol/other sedatives.
		5. Chronic GHB use leads to a withdrawal syndrome that resembles sedative-hypnotic withdrawal. Withdrawal is rare but severe and may require treatment with benzodiazepines. Most patients who overdose from GHB recover completely.
	8. **PCP and Ketamine: dissociative anesthetics**
		1. In contrast to classic hallucinogens, dissociative anesthetics have considerable addiction liability.
		2. Exerts its action by blocking NMDA glutamate receptors.
		3. Results in distorted perception of the body, the environment, and time.
		4. Lack of responsive awareness to pain and the general environment.
		5. Acute effects of ketamine tend to be less severe and of shorter duration than those of PCP.
	9. **Bath Salts (Cathinone Derivatives)**
		1. Synthetic cathinones, more commonly known as "bath salts," are human-made stimulants chemically related to cathinone, a substance found in the khat plant. Khat is a shrub grown in East Africa and southern Arabia, where some people chew its leaves for their mild stimulant effects. Human-made versions of cathinone can be much stronger than the natural product and, in some cases, very dangerous.
		2. Synthetic cathinones usually take the form of a white or brown crystal-like powder and are sold in small plastic or foil packages labeled "not for human consumption." They can be labeled as "bath salts," "plant food," "jewelry cleaner," or "phone screen cleaner."
		3. Much is still unknown about how synthetic cathinones affect the human brain. Researchers do know that synthetic cathinones are chemically similar to drugs like amphetamines, cocaine, and MDMA.
		4. Synthetic cathinones can produce effects that include:
* paranoia—extreme and unreasonable distrust of others
* hallucinations—experiencing sensations and images that seem real but are not
* increased friendliness
* increased sex drive
* panic attacks
* excited delirium—extreme agitation and violent behavior

 **LABORATORY TESTING/MONITORING OF SUBSTANCE USE**

1. **LABORATORY DIAGNOSIS**
2. Four scenarios when testing helpful:
3. Overdose or trauma in the emergency setting
4. Assist in initial diagnosis of a substance use disorder
5. Monitor abstinence during treatment program
6. Monitor treatment adherence in patients taking prescribed controlled substances
7. Basic definitions:
8. Point of contact:
9. False positive: a test that indicates a substance is present in the sample when it is not.
10. False negative: a test that indicates a substance is not present in the sample when it is.
11. Cut off levels: Cutoff levels were established to help minimize false-positive results especially in workplace drug testing (eg, passive inhalation of marijuana causing positive results; poppy seeds ingestion causing positive opiate results). Results lower than the established cutoff values are reported as negative. Therefore, a negative result does not indicate that a substance is not present, but that the concentration was lower than the established cutoff concentration.

Although clinicians should be aware of federal cutoff values for substances of abuse, they should recognize that the federal cutoff concentrations were established for use in the workplace in which higher cutoff concentrations may be necessary to avoid false-positive results. However, in medical practice, lower cutoff values may be necessary particularly when testing for medication adherence.

1. Adulterants:

“In vivo” adulterants: what a person can take/consume before giving a urine specimen. Can include pills, capsules, or drinks.

“In vitro” adulterants: products that are *added* to the urine to change result. Adulterants can include common products such as bleach, vinegar, liquid detergents, table salt and baking soda. Testing the pH of urine can help determine if an adulterant has been added. There are commercial adulterants that are sold that can get around tested pH changes so federal testing requires the use of testing for one or more of these adulterants. Validity dipsticks are available to test for adulterants and can be used in clinical or non regulated settings; however, many clinical labs do not test for adulterants.

1. Clinician should have basic knowledge of:
2. Which drugs are detected by the tests ordered?
3. How long is the drug detected after use?
4. Which substances give a false positive or false negative?
5. Body fluids for testing
6. Urine: most common source of testing for drugs of abuse. Both parent drug and metabolites may be detected in urine specimens and are usually in higher concentrations than in blood or serum samples. Drug detection times are longer in urine (i.e, 1 day up to several weeks) than in blood or serum samples.

Pros: Collected easily and non-invasively; drugs often present

Cons: Even when observed urine specimens are easily adulterated or substituted

1. Blood:

Pros: more accurate than urine testing for quantifying recent ingestion. Less likely to be adulterated or substituted

Cons: present in the blood for much shorter period of time than urine; invasive; higher risk of infection to person obtaining the specimen.

1. Oral fluid: includes saliva, fluid from gingiva etc.

Pros: non invasive; can be directly observed without privacy concerns; less likely to have adulterations; measurements of drug concentrations closely approximate circulating concentrations in the plasma.

Cons: drugs present in oral fluid for shorter time than in urine; contamination from recently smoked or ingested drugs can occur.

1. Sweat: many drugs are secreted into sweat and patches can be applied to the skin to absorb sweat and measure drug secretion.

Pros: represents secretion over an extended period of time.

Cons: sweat can be collected in only relatively small amounts, and quantification of drug levels is limited by the ability to quantify the total amount of sweat secreted.

1. Hair: Hair grows approximately 1 cm per month.

Pros: can be collected easily and non invasively; adulteration and substitution less likely than with urine.

Cons: cannot identify recent ingestion because significant amounts of drug are not found in hair until 1 to 2 weeks after use. Cosmetic treatments and ultraviolet light exposure can lead to decreasing concentrations of the drug in hair over time. Concentrations of drugs in hair are low requiring more sensitive essays.

1. Laboratory methods for testing:
2. Initial drug tests or screening tests are performed using immunoassay technology and are conducted in the laboratory or onsite with point-of-care testing (POCT). In these tests, an antibody is designed to detect a specific target, which may be a specific class of drug, parent drug, or metabolite. Commercial immunassays from different manufacturers use various antibodies and not all assays share the same cross-reactivities. Immunoassays allow for a large number of specimen screens to be completed and provide relatively rapid results. Unfortunately, immunoassays will detect substances with similar characteristics, resulting in cross-reactivity leading to false positive results. All initial testing conducted with immunoassays need to be considered presumptive, and clinicians need to use clinical judgment, patient history, and collaborative information to decide whether confirmatory testing is necessary for optimal patient care.
3. Confirmatory testing: Can be performed using gas or liquid chromatography to separate the drugs in the specimen followed by spectroscopy to identify the substances. These techniques can identify and quantify extremely small amounts of drugs or metabolites. This testing is more expensive but less susceptible to false positive or false negative results.
	* + 1. **TESTING TO IDENTIFY ALCOHOL USE**
	1. Breath testing: relies on PoC (point of collection) test kits.
4. Alcohol is easily quantified in breath.
5. Resistant to cheating and far easier to collect than urine, oral fluid, or hair.
6. Alcohol in breath: short detection window, usually less than 12 hours.
	1. Oral fluid (saliva):

Generally identifies alcohol/drug use within the 12 to 24 hours prior to sample collection.

* 1. Blood:
1. **Direct markers**: Direct markers include blood ethanol itself, as well as alcohol derivatives.
	1. **Alcohol blood level:** Alcohol is rapidly metabolized by the liver, so alcohol concentrations in the blood decrease rapidly, typically to zero within a few hours after the last drink
	2. **Phosphatidylethanol (PEth)** is an abnormal cellular membrane phospholipid and was discovered for the first time in mammalians in 1983, being detected in the brain, kidney, liver, skeletal muscle, and heart of rats **chronically exposed to ethanol.**

PEth in blood also seems to be promising for characterizing the drinking pattern (i.e., identifying binge drinking episodes) and differentiating light-moderate drinking from abstinence. Total phosphatidylethanol exhibits high diagnostic sensitivity and specificity for detecting **active chronic excessive drinking behaviors**, with a regular daily alcohol intake (DAI) of more than 60 g. (PEth) can be detected in blood **for up to two weeks of sobri**ety.

Of the long-term biomarkers, PEth, which is formed only in the presence of ethanol and is thus a very specific alcohol biomarker, demonstrated the highest sensitivity for the detection of **current regular alcohol consumption**, and was found positive about twice as often as CDT.

Positive PEth testing following positive EtG/EtS results confirms recent drinking.

* 1. **Fatty acid ethyl esters (FAEEs):** Only in **heavy drinkers**, are elevated concentrations of FAEEs observed at days 2 to 4. FAEEs are of limited value for the detection of prior single ethanol intake.
1. **Indirect markers:**
	1. **Liver function tests:** these tests suffer from **low sensitivity for early detection of risky drinking,** and the specificity is only moderate because many cases of elevated levels are unrelated to alcohol consumption.
	2. **Mean corpuscular volume (MCV):** Chronic drinking increases MCV
	3. **Carbohydrate-deficient transferrin** (**CDT**) is a laboratory test used to help detect heavy ethanol consumption. Transferrin is a serum protein that carries iron through the bloodstream to the bone marrow. Elevated levels of CDT suggest **recent alcohol abuse**, especially if other liver-associated enzymes (such as γGT) are elevated. CDT levels are less sensitive when there has been alcohol abstinence for greater than 1 week. Although ***recent* heavy alcohol use** is most commonly associated with elevated CDT, certain rare liver disorders can also increase levels of CDT. CDT levels are less useful for detecting alcoholism in patients with other liver diseases.
	4. Urine
2. Quantitative level of alcohol (and drugs) in urine is heavily influenced by recent fluid consumption. Therefore, urine alcohol/drug levels do not equate with blood levels and are read as positive or negative.
3. Urine alcohol concentration lags the blood concentration of alcohol at the time of urination.
4. The detection window for urine alcohol tests generally is 12 hours or less.
5. Biomarkers of alcohol use are important new testing options for alcohol. These biomarkers include ethyl glycol or ethyl sulfate and are found in urine for 3-5 (sometimes 7) days following consumption of alcohol. A negative test for EtG establishes that the person has not used alcohol in the past 5 to 7 days.
6. Urinary EtG/EtS is useful to detect or rule out **recent intake** of even small amounts of alcohol.
7. Use of hand sanitizers and hair products containing large percentage of ethyl alcohol have been blamed for false-positive EtG results in urine.
	1. Sweat testing:
8. Unlike other testing, sweat testing is prospective.
9. Person wears a patch that cannot be replaced without noticeable puckering at the edges of the device.
	1. Hair
10. Head hair grows at the average rate of about 0.5 inch each month, thus producing a record of drug use over the preceding 90 days. However, it takes about 1 week for hair to grow from the base of the follicle to a point at which it can be snipped at the level of the scalp. Therefore, there is not record in hair of drug or alcohol use in the week prior to sample collection.
11. Hair biomarkers (in contrast to urine) can be used to distinguish between light, moderate, and heavy use of drugs and alcohol.
12. Use of strong bleach and hair coloring procedures have been blamed for false negative EtG hair test results.
13. Studies of EtG and FAEE levels in hair have demonstrated the analytical ability to differentiate social alcohol consumers from heavy drinkers.
14. Neither hand sanitizers nor mouthwashes confound hair tests for EtG or FAEE.
15. There is no evidence of racial bias in hair testing, which was an earlier concern based on studies that mice who were give an antipsychotic drug, had higher concentrations of this drug in mice black hair vs. mice white hair.

**VIGNETTE: “I only had one drink!”**

A NGRI acquittee is returned to the hospital from CONREP when a CONREP worker noted alcohol on his breath during a group home visit. The patient readily admitted that a fellow patient gave him a “shot of whiskey”, which he had just tried that one time. He is adamant that that was his first “taste” after six months of complete sobriety in the community. The treatment team is struggling whether the patient is ready to return to the community. There is no evidence or report of other alcohol use and the patient states this was just “my first slip.” He adds that he was about to call his sponsor when the CONREP worker showed up and again exclaims, “I only had one drink.”

What tests might the treatment team consider to verify his account?

**III. CANNABIS TESTING**

1. Casual use: Up to 10 days in urine. 50% positive in hair samples.
2. Heavy use: Up to 30 days in urine. 85% positive in hair samples.
3. Weight loss gives serial Utox spike.
4. Dronabinol gives positive test.
5. Passive inhalation gives negative test.

**SUMMARY**

1. Substance use is risk factor most associated with aggression and violence.
2. Evidence-based treatments are important factor in decreasing violence risk from substances.
3. Laboratory monitoring is key to assisting in relapse prevention and requires detailed understanding of factors resulting in false positives and false negatives.

**General references**:

Arsenault L, Moffit TE, Casp A, et al.: Mental disorders and violence in a total birth cohort: results from the Dunedin study. Arch Gen Psychiatry 57:979-986, 2000

Dugre JR, Dellazizzo L, Giguere C et al. Persistency of cannabis use predicts violence following acute psychiatric disorder. Frontiers in Psychiatry.8:176, 2017

Galanter M, Kleber HD, Brady K: The American Psychiatric Publishing Textbook of Substance Abuse Treatment, DSM-5 Education. AAPI Press: Washington, D.C., 2015

Heron AJ, Brennan TK: The ASAM Essentials of Addiction Medicine. Wolter Kluwer, New York: 2015.

**Cannabis References:**

Fergusson DM, Boden JM: Cannabis use and later life outcomes. Addiction: 103:969-976, 2008

Kadden RM, Litt MD, Kabelo-Cormier E, et al: Abstinence rates following behavioral treatments for marijuana dependence. Addict Behav 32:1220-1236, 2007

Meier MH, Caspi A, Ambler A, et al.: Persistent cannabis users show neuropsychological decline from childhood to midlife. PNAS, August 27, 2012

Solowij M, Stephens RS, Roffman RA, et al: Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA: 287: 1123-1131, 2002

Stanger C, Budney AJ, Kamon JL, et al: A randomized trial of contingency management for adolescent marijuana abuse and dependence. Drug Alcohol Depen 105:240-247, 2009

Starzer M, Nordentoft M, Hjorthoj C: Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis

**Stimulant references**:

Ma, J, Li, SD, Wang, TU, et al.: Relationship between the duration of methamphetamine use and psychotic symptoms: a two-year prospective study. Drug and Alcohol Dependence. 187: 363-368, 2018

McKetin R, McLaren J, Lubman DI, et al.: The prevalence of psychotic symptoms among methamphetamine users. Addiction 101:1473-1478, 2006

McKetin R, Baker AL, Dawe S, Voce A, Lubman DI: Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. Psychiatry Research 251:349-354, 2017

McKetin R, Gardner J, Baker AL, et al.: Correlates of transient versus persistent psychotic symptoms among dependent methamphetamine users. Psychiatry Res 238:166-171, 2016

Potivn S, Pelletier J, Grot S, Herbert C, et al.: Cognitive deficits in individual with methamphetamine use disorder: A meta analysis. Addictive Behaviors: 80:154-160, 2018

Wearne TA, Cornish JL: A comparison of methamphetamine-induced psychosis and schizophrenia: a review of positive, negative, and cognitive symptomatology. Frontiers in Psychiatry, 9:1-21, October 2018