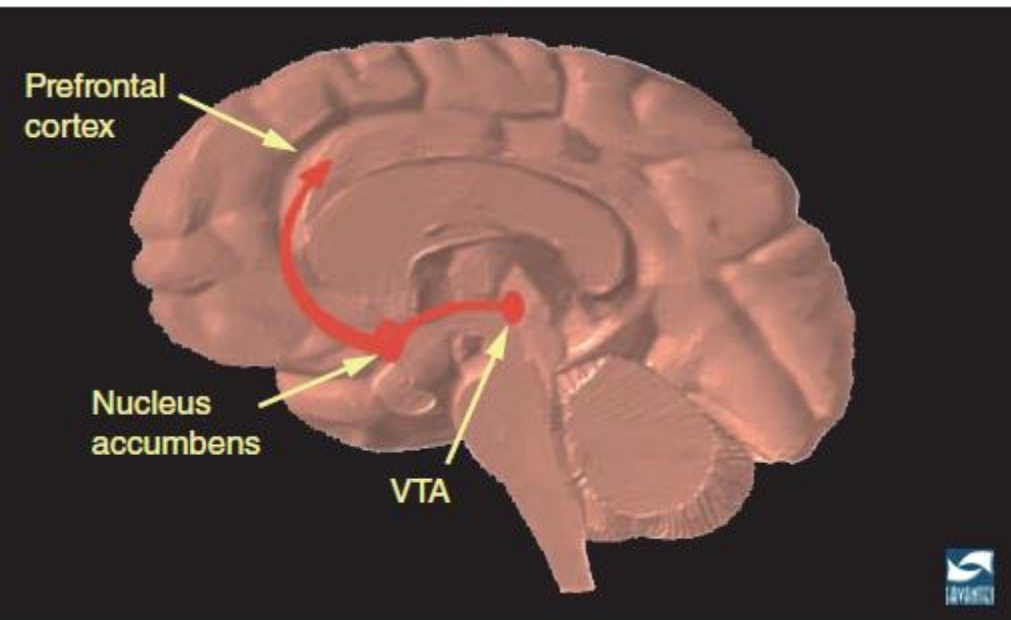


Substance-Related Disorders



Reward Pathway

- Virtually all substances of abuse appear to activate the *same* brain reward pathway, which is highlighted by dopaminergic neurotransmission arising in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NA) and prefrontal cortex (PFC). This pathway is also responsible for reinforcement of behaviors, focus, and learning.

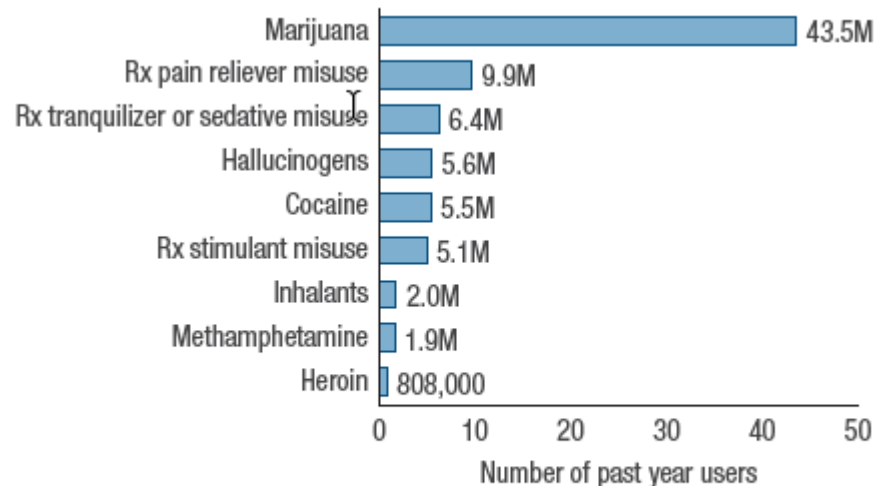


FIGURE 37-1. Past-year illicit drug use in the United States among individuals 12 years and older in 2018. (Data and figure

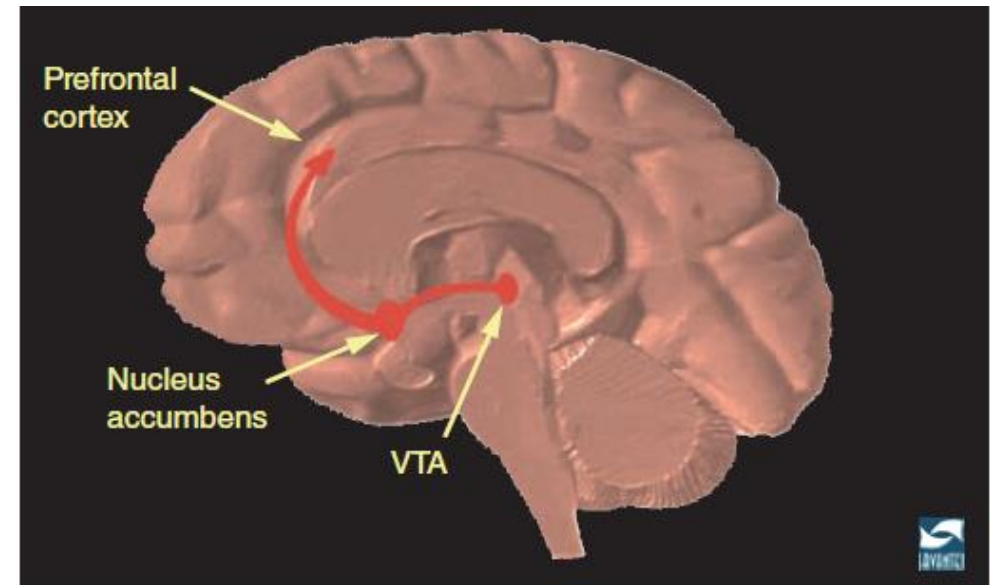


FIGURE 36-2. The mesocorticolimbic dopaminergic (ie, "reward") pathway. (VTA, ventral tegmental area.) (Data

Substance-related
disorders (addiction)
phase

**For treating, we mostly
need to treat all phases**

Treatment of
substance-related
disorders

Intoxication
Phase

Withdrawal
Phase

Craving
Phase

Intoxication
ttt

Withdrawal
ttt

long-term
relapse
Prevention

Substance-related disorders include

▪ Alcohol

▪ opioids

▪ Tobacco.

Table 37-3

Signs and Symptoms of Drug Intoxication for Select Substances^{6,10-13}

Drug	Behavioral Effects	Physiologic Effects
Alcohol	Disinhibition, euphoria, dysphoria, inappropriate aggressive or sexual behavior, impaired judgment; possibly progressing to somnolence and coma as the blood level increases	<p>Blood levels 0.02%–0.1% (20–100 mg/dL or 4.3–21.7 mmol/L): Slight impairment (eg, reaction time)</p> <p>Blood levels 0.1%–0.2% (100–200 mg/dL or 21.7–43.4 mmol/L): Significant impairment (eg, balance, speech, vision)</p> <p>Blood levels 0.2%–0.3% (200–300 mg/dL or 43.4–65.1 mmol/L): Marked ataxia, mental confusion, nausea, vomiting</p> <p>Blood levels 0.3%–0.4% (300–400 mg/dL or 65.1–86.8 mmol/L): Severe dysarthria, amnesia, hypothermia</p> <p>Blood levels > 0.4% (400 mg/dL or 86.8 mmol/L): Coma, decreased respiration or respiratory arrest, aspiration of gastric contents, airway obstruction by flaccid tongue, drop in blood pressure and body temperature</p>
Opioids	Drowsiness, sedation, slurred speech, impaired memory and attention, psychomotor retardation	Nausea, vomiting, respiratory depression (dose-related), stupor, coma, itching, miosis, hypothermia, bradycardia

Signs and Symptoms of Drug Withdrawal for Select Substances^{6,10-14}

Drug	Timeline	Symptoms
Alcohol	As levels decrease:	
	Early symptoms	Tremor, nausea, vomiting, tachycardia (> 110 beats/min), hypertension (> 140/90 mm Hg), headache, insomnia
	Peak (24 hours)	Seizure activity (usually 1 or 2 generalized tonic-clonic seizures, but can be numerous and possibly fatal)
	72–96 hours	Delirium tremens
	Onset at any time	Hallucinations (usually visual)
Opioids	For shorter-acting opioids (eg, heroin, morphine) withdrawal may begin 6–24 hours after last dose and last for about 1 week; with longer-acting opioids (eg, methadone) may take up to 2–4 days for withdrawal to emerge and will last longer	<p>EENT: lacrimation, mydriasis, rhinorrhea</p> <p>GI: nausea, vomiting, diarrhea</p> <p>Cardiovascular: increased heart rate and blood pressure</p> <p>CNS: irritability, restlessness, yawning</p> <p>Musculoskeletal: increased body temperature, piloerection</p>

Treatment of Alcohol Intoxication:

- Most cases of mild-to-moderate alcohol intoxication do not require medical treatment.
 - Providing a safe environment and reassurance until alcohol effects have dissipated is sufficient in most cases.
- If consciousness is impaired, give thiamine IV/IM at 100 mg/day for at least 3 days.
- Sedation with benzodiazepines has been used but, in the presence of alcohol, respiratory depression can be dangerous or even fatal.

Treatment of withdrawal syndromes

Alcohol Withdrawal :

❖ Uncomplicated Alcohol Withdrawal:

- *Uncomplicated alcohol withdrawal is the more commonly observed syndrome and, as the name implies, is not complicated by seizures, delirium tremens (DTs), or hallucinosis.*
- *Benzodiazepines are the treatment of choice for uncomplicated alcohol withdrawal.*
 - *The most commonly used benzodiazepines are lorazepam, diazepam, and chlordiazepoxide.*

- American Psychiatric Association (APA) guidelines recommend thiamine 50 to 100 mg per day for patients being treated for moderate to severe alcohol use disorders to prevent or treat adverse neurologic symptoms.
 - although other guidelines recommend higher doses (eg, thiamine 300 mg/day).
 - Thiamine must precede glucose-containing IV fluid administration to prevent Wernicke encephalopathy

❖ *Complicated Alcohol Withdrawal:*

- **Alcohol withdrawal seizures**, a medical emergency, should be treated in an inpatient setting. Withdrawal seizures are usually **generalized (tonic- clonic seizure)**.
- Management **consists of keeping the airway open and preventing self-injury during convulsions**.
- **Benzodiazepines are the treatment of choice.**
 - Give **diazepam 5 to 10 mg IV to terminate** a seizure if IV access is available. Repeat dose in 5 minutes if seizures persist. Alternatively, **lorazepam 4 mg IM** may be given.
- Avoid phenytoin for preventing or treating alcohol related seizures.
 - Alcohol withdrawal seizures result from γ -aminobutyric acid (GABA) and glutamate abnormalities secondary to chronic alcohol intake. However, phenytoin affect sodium channel rather than GABA/Glutamate, so its ineffective in alcohol-related seizure.
- **Alcohol Withdrawal Delirium (DTs)**: DTs is a medical emergency necessitating hospitalization. Signs and symptoms include **hallucinations, delirium, severe agitation, fever**, increased blood pressure and heart rate, and possible **cardiac arrhythmias**.
- **benzodiazepines** are the treatment of choice.
 - Administer **thiamine** according to the previously described guidelines.

Maintenance Treatment

Alcohol Use Disorder:

- The FDA-approved medications to treat alcohol use disorder are **naltrexone** (oral and depot), **acamprosate**, and **disulfiram**.
- **Naltrexone** (50 mg once daily) is a competitive opioid receptor antagonist that **decreases alcohol intake, craving** for alcohol, and **alcohol-induced euphoria** (ie, reduces positive reinforcement of drinking).
- Administered as 380 mg once monthly of **Naltrexone** (long-acting IM), results in significantly greater reductions in heavy drinking days.
 - Recently, gabapentin and topiramate

Opioid Intoxication

- *Opioids encompass a wide range of substances, including naturally occurring (eg, morphine) and synthetic (eg, oxycodone).*
- *Acutely intoxicated patients usually present with nausea, vomiting, respiratory depression, miosis, euphoria, slow heart rate, low blood pressure, hypothermia and constipation.*
 - *Seizures may occur with certain agents, such as meperidine.*
- *One strategy is to reverse intoxication using naloxone 0.4 to 2 mg IV every 2 to 3 minutes up to 10 mg.*

Opioid Withdrawal

- *Withdrawal from opioids is commonly described by patients as resembling “a bad case of the flu.” Symptoms include :*
 - **EENT**: lacrimation, mydriasis, rhinorrhea
 - **GI**: nausea, vomiting, diarrhea
 - **Cardiovascular**: increased heart rate and blood pressure
 - **CNS**: irritability, restlessness, yawning
 - **Musculoskeletal**: increased body temperature, piloerection
- *In severe withdrawal, either buprenorphine (partial μ -opioid receptor agonist) or methadone (ie, full μ -opioid receptor agonist) are recommended for detoxification.*
 - *Methadone is also widely used to treat women during pregnancy*

Table 37-6**Sample Regimen^a for Buprenorphine Induction
Treatment of Opioid Withdrawal and Long-Term Relapse
Prevention⁸**

Day	Buprenorphine Sublingual/Buccal Dosage
1	2–4 mg every 2 hours (maximum, 8 mg on first day)
2	Start with total day 1 dose; additional 2–4 mg every 2 hours (maximum, 16 mg)
3	Start with total day 2 dose; additional 2–4 mg every 2 hours (maximum, 32 mg)
4–5	Maintain on dose required to alleviate withdrawal symptoms ^b

Table 37-7**Symptoms-Based Treatment Approach for Opioid
Withdrawal^{8,10,27}**

The following are examples of medications for withdrawal symptoms that cause distress:

1. Insomnia: trazodone 75–200 mg at bedtime
2. Headache, muscle aches, or pain: acetaminophen 500–1000 mg every 6 hours
3. Noradrenergic hyperactivity: clonidine 0.1–0.2 mg every 6–8 hours (not to exceed 1.2 mg in 24 hours) lofexidine 0.54–0.72 mg every 6 hours (not to exceed 2.88 mg in 24 hours)
4. Abdominal cramps: dicyclomine 10–20 mg every 6 hours
5. Diarrhea: loperamide 2 mg every 6 hours

Opioid Use Disorder:

- After conclusion of withdrawal, patients may not feel their usual selves for some time and could **relapse to using opioids**, just to “**feel normal**.”
- Long-term use of opioids **results in brain changes**, and the brain might not readily return to its prior homeostasis. **The goal of treatment** is to encourage **stability**, both in the body and in the **patient's life**.
- ***Opioid Agonists*** **Methadone** and **buprenorphine**, are first-line medications for maintenance treatment.
- ***Opioid receptor antagonist:*** **long-acting naltrexone (monthly dose)** can be used

Tobacco Cessation:

- ***Nonpharmacologic*** Behavioral treatment, delivered by a variety of clinicians, increases abstinence rates. **The 5 As model**
 - **Ask** about tobacco use.
 - **Advise** to quit.
 - **Assess** willingness to make a quit attempt.
 - **Assist** in quit attempt.
 - **Arrange** follow-up.
- **Electronic cigarette** use has grown considerably in recent years. They appear to contain toxins similar to those found in tobacco

Fagerström Test for Nicotine Dependence	Assesses extent of nicotine tolerance, dependence, and craving	6 items Higher scores may predict greater difficulty quitting 0–2: very low 3–4: low 5: moderate 6–7: high 8–10: very high
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- *Pharmacologic of Tobacco Cessation :*
- Nicotine replacement therapy (NRT), bupropion, and/or varenicline.
- Nicotine patch:

Cigarettes smoked per day:	
>10 cigs/day: Step 1(Weeks 1-6): 21mg/day Step 2 (Weeks 7-8): 14mg/day Step 3(Weeks 9-10): 7mg/day	<10 cigs/day: Step 1 (week 1-6): 14mg/day Step 2 (weeks 7-8): 7mg/day

- Duration: 8–10 weeks

- *Bupropion* sustained-release:
 - *Dosing: 150 mg once daily for 3 days, then 150 mg twice daily.*
 - *1–3 days: 150 mg once daily*
 - *then 150 mg twice daily for 3-6 months*
 - *Start 1–2 weeks before quit date.*
- *Varenicline:*
 - *Dosing:*
 - *1–3 days: 0.5 mg once daily*
 - *4–7 day: 0.5 mg twice daily*
 - *then 1 mg twice day for 3-6 months*

Start 1 week before quit date.

Second-Line Medications for smoking cessation:

- Clonidine :
 - Results from a meta-analysis of six trials showed that clonidine increased smoking cessation rates by 9%.
- Nortriptyline : 25-75mg/day (10-28 days before smoking cessation).
 - Nortriptyline is also considered to be efficacious as a second-line agent for smoking cessation.