Addiction
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Disclosure
• Dr. Mays is not on any drug advisory boards, paid for doing drug research, or otherwise employed, funded, or consciously influenced by the pharmaceutical industry or any other corporate entity.
• No off label uses of medications will be discussed unless mentioned in the handout and by the presenter.
• No funny business.

Agenda for Today
• Defining addiction
• Neuroanatomy and biochemistry
• Demographics
• Smoking
• Methamphetamine
• Marijuana and CBD
• Gabapentin
Death Rates

- Heart Disease 635,000 192/100,000
- Cancer 598,000 163/100,000
- Smoking 480,000 75/100,000
- Alzheimer’s 93,000 29/100,000
- Alcohol 88,000 28/100,000
- Overdoses 70,000 22/100,000
- Suicide 47,000 14/100,000
- Auto Accidents 38,000 9/100,000

Addiction

- Addictive disorders are chronically relapsing disorders characterized by compulsive use of the drug despite harm, loss of control over intake, and development of a negative emotional state when the drug is unavailable.
- Addictions involve continued behavioral engagement despite adverse consequences - they are disorders of misdirected motivation and impaired self-control.
- They involve dysfunction of 3 neurological systems:
  - The reward-antireward system (dopamine, midbrain)
  - The prefrontal cortex (executive functions, inhibition)
  - The amygdala (learning and memory)

Tolerance, Habituation, Addiction

- It is important to distinguish tolerance (the need for increasing amounts of a substance for the same effect), habituation (the adaptation of an organism to the chronic presence of a drug, often resulting in withdrawal symptoms if the drug is removed), and addiction. All organisms naturally experience tolerance and habituation to some substances, but only some develop addiction.
Addiction

- There are three primary states involved:
  - Binge/intoxication
  - Withdrawal/negative affect
  - Preoccupation/anticipation (craving)

Binge/Intoxication

- Alcohol causes the release of dopamine and opioid peptides in the ventral striatum (nucleus accumbens.) This is nature's primary reward mechanism, there to motivate us and direct our behavior to ensure our survival. The amygdala in the brain makes sure that we remember all the circumstances that led to this pleasurable experience. We become conditioned to the tastes and smells, environmental sights and sounds, people in the room, like Pavlov's dogs became conditioned to the sound of a bell before dinner.

Withdrawal

- As the drug wears off, the person enters the withdrawal phase — negative mood, inability to experience pleasure, increased sensitivity to stress, anxiety. Opioids produce this effect quite rapidly. This negative feeling propels the individual to want to use the drug again.
- Two processes lead the withdrawal/negative affect stage:
  - Loss of function in the reward system – neuroadaptation (e.g. down regulation of receptor sites)
  - Brain stress systems (cortisol) are recruited and strengthened that create aversive, or stress-like states that create an unpleasant, restless feeling.
Preoccupation/Anticipation Stage

• The executive functions of the cortex can be thought of as having a “go” system and a “stop” system.
• The “go” system consists of the anterior cingulate and dorsolateral prefrontal cortex and is responsive to the habits formed by the basal ganglia (striatum).
• The stop system consists of the ventrolateral and orbitofrontal cortex and usually inhibits the basal ganglia system.
• These are both modified by alcohol use.

Preoccupation/Anticipation Stage

• With repeated exposure, dopamine is released at the conditioned stimulus that predicts the reward, more than by the reward itself. This motivates our behavior and gets us to the place where they sell the drugs, to the emotional states that precede us getting high.

Preoccupation/Anticipation

• Dopamine pathways are not limited to reward and motivation, but are fundamental in the prefrontal cortex which regulates self-control, working memory, decision-making, and judgment. The basal ganglia-globus pallidus-thalamic-cortical loop engages dorsal striatum habit formation, which is the beginning of compulsive-like responding.
• The result is the disruption of our ability to make judgments based on changing circumstances, to seek out what is good for us and what is bad for us, and our resulting reaction of shame for our hopelessness and helplessness in trying to control ourselves.
Treatment Tip

- Addicted individuals tend to select preferentially small immediate rewards over larger delayed ones (delay discounting).
- Treatment of addictions that utilize small immediate rewards, such as contingency management do better than long term later rewards.

Three Phenomena Modulating Addiction

- Vulnerability
  - Sustained exposure to addicting drugs
  - Gene, environment, behavior interactions
- Motivational shift
  - Pleasure to craving
- Aberrant learning
  - Move to reflexive, rather than planned decisions

Addiction

- What clinicians see:
  - 1) uncontrollable, usually compulsive drug seeking and drug use, in spite of severe aversive consequences
  - 2) preoccupation with the drug, enhanced cue responsiveness
  - 3) the experience of craving, often for years or decades after abstinence has been obtained.
The Striatum (caudate, putamen, ventral striatum/nucleus accumbens)

- When we think we are choosing to do something, usually we are simply doing what we are programmed to do. The striatum is an important part of that programming. It receives input from all the reward circuits as well as the amygdala and, orbital frontal cortex, and anterior cingulate cortex.
- Neurons in the striatum integrate information about expected reward with motor information to guide behavior, including social rewards.
- Miswiring in the striatum is related to compulsive behavior (and addiction), tics, and problems with social connection.

Social Neurochemistry

- Social neurochemistry is linked to oxytocin, vasopressin, dopamine, and opioid receptors. Naloxone interferes with people's ability to feel connected. Acetaminophen reduces social pain.
- Endogenous opioids play an important part in the reward associated with social behavior and counteract the aversive consequences of social stress.
- Social epidemiology has established a strong link between poor social integration and behaviors that result in alcohol and drug use. Conversely, the level of social integration has been shown to be associated with decreased relapse risk among treatment-seeking drug users.

Striatum and Loneliness

- In other words, the striatum is linked to loneliness. Loneliness hypersensitizes us to the striatum reward system. We become restless, irritable, and impulsive. This is a setup for opioid use.
- People with exposure to social stress will experience relief of distress when taking drugs that directly or indirectly activate the opioid system such as heroin and oxycodone. Alcohol also increases endogenous opioid levels in humans.
Addiction and Social Integration

- During early stages of drug use, the drug is typically taken in a recreational, impulsive manner. However, as addiction develops, drug users become increasingly compulsive. Compulsive users become increasingly impaired in their ability to function socially. This results in further social marginalization and exclusion — factors that promote further drug use.
- During recovery, relapse triggers are typically social; conflicts in the workplace and the family, lack of social support and problems associated with low socioeconomic status.
- Isolation is related to relapse.

Social Integration = Treatment

- Social integration, by restoring normal function of endogenous opioid systems, may decrease drug use and relapse. Improving the social integration of drug users through opportunities for housing, jobs and meaningful relationships is therefore a neurobiologically specific and critically important way to decrease drug use.
- Reducing stigma is important, not just as a compassionate intervention, but also as a way to reduce social isolation.

Reprogram the Striatum

- The striatum can be reprogrammed away from drug seeking behavior, not just by punishment, but by opioid reinforcement of socialization.
- We need to create social and psychospiritual interventions that can provide these rewards.
The Biology in a Nutshell

- The brain registers all pleasures the same way: by the release of dopamine in the nucleus accumbens. The likelihood that the use of a drug or participation in an activity will lead to addiction is linked to the speed with which it promotes dopamine release and the reliability of that release.
- Dopamine not only causes the experience of pleasure, but plays a key role in learning and memory.

The Biology in a Nutshell

- Dopamine interacts with glutamate to take over the brain’s system of reward-related learning. The reward circuit includes areas involved in motivation and memory.
- Typically, we only get a “little shot” of dopamine when we get a reward, like earning a good grade, winning a race or being kissed. Opioids hijack this system and people can feel GREAT! without having to exert any effort.
- Addictive drugs can release 10x the amount of dopamine that natural rewards do and do it more reliably. Brain receptors become overwhelmed, producing less dopamine and dopamine receptors.

The Biology in a Nutshell

- Dopamine has less impact on the reward centers. The substance causes less pleasure. Compulsion takes over as the memory of the pleasure and the need to recreate it persists in spite of the decrease. Environmental cues receive more salience.
- 60% of people will relapse when they try to give up their substance, similar to relapse with hypertension and asthma.
**Glutamate Failure, a Failure to Learn**

- Glutamate is present in the connections between the nucleus accumbens and the prefrontal cortex. In addicts, glutamate receptors begin to malfunction and nearby glial cells fail to keep up normal levels of glutamate in the extracellular space.
- Addicts have a difficult time being flexible and changing habits. They are unable to learn that "When I use drugs, bad things happen." (a glutamate message from the prefrontal cortex to the n acc.)

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**Craving**

- There are several different kinds of craving:
  - Baseline: occurs without precipitants. It is instantly reversed, then quickly exacerbated by administration of the drug. It gradually diminishes during abstinence.
  - Stress-induced: more than just a psychological desire to escape discomfort. Stress induced craving is dependent on the release of corticotropin-releasing hormone (CRH). High CRH eventually leads to down-regulation of receptors on the adrenal glands, leading to low cortisol. Low cortisol predicts relapse in addicts. The hyperactive CRH response is probably conditioned by childhood stress (child sexual abuse, neglect, etc.)
  - Cue-induced: Cues may trigger intense craving after years of abstinence.

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**Salience**

- Consciousness is a whirlwind of different stimuli impinging on the brain. These events compete for attention. We think we are aware of what is happening around us, and we are choosing to focus on particular events. In fact, our attention to detail is quite poor, and our attention is usually directed by pre-conscious processes.
- Repeated use of addictive drugs reorganizes neurological circuits. Drug stimuli become over-valued in the prefrontal cortex and responses become more compulsive, less impulsive. There is reduced salience for non-drug motivational stimuli and a subsequent narrowing of goal choice to only those behaviors that are drug related. Decision making ability is reduced. Addicts instead focus on enhanced efforts to procure the drug.
Salience: From Recreation to Addiction

• The circuitry of motivational salience is activated by money in pathological gamblers, food in binge eaters, sexual stimuli in sexual compulsives, drug related cues in addicts.
• The change is from dopamine based behavior in the NAcc to glutamate based behavior from the cerebral cortex.
• At this point, enduring cellular changes have occurred. Often, these changes become greater with increasing periods of withdrawal!!

Behavioral Addictions

• Multiple lines of evidence support a relationship between substance addiction and behavioral addictions. Both share common core clinical features: compulsive engagement despite adverse consequences, diminished control, craving, common comorbidities, etc. In addition, laboratory studies are beginning to show that both kinds of disorders share a common chemistry and neurophysiology.
• Gambling addiction is included in DSM-5. Currently under investigation for inclusion are internet gaming addiction and sexual addiction. These are very controversial. What is the difference between an addiction and a self-destructive habit?

Neurobiology of Addiction Risk

• About 20% of people who are exposed to addicting drugs become addicted. The risk for addiction is related to complex interactions between biological factors (genetics, epigenetics, developmental attributes, neurocircuitry) and environmental factors (social and cultural systems, stress, trauma.)
• Genetics: about 50% of the risk for addiction. Most of these genes influence an individual's biologic response to substances of abuse or their metabolism.
• Epigenetics: long lasting neurological change can be established by early environmental factors: stress in the individual or the parent, loss, early substance exposure...
Environmental Factors

- Availability
- Social norms (smoking bans)
- Legal consequences
- Peer pressure
- Parents – use, attitudes, rules

SIBLINGS! A March 2019 paper in the *Am J Psych* showed through analysis of 65,000 individuals that drug abuse is not only transmitted through genetic influences in families, but also through a “contagious” process, e.g. by transmission of positive attitudes toward drugs and role models for drug initiation, as well as drug procurement. This transmission happens from parents, siblings, and cousins.

Neurodevelopment

- Neurodevelopment: The adolescent brain is not an adult brain and has not completed its development. It is more sensitive to reward/motivation, emotion circuitry and less controlled by the prefrontal cortex. Further, early exposure may impair the development of the prefrontal cortex, increasing the risk for addiction.

The Gateway Hypothesis

- The Gateway Hypothesis suggests that the developmental sequence of drug use starts with a legal drug and proceeds to illegal drugs.
- The Common Liability Hypothesis suggests that there is an underlying vulnerability for drug use in general.
- While both these may be true, there is new evidence that the Gateway Hypothesis may have more impact.
Evidence for the Gateway Hypothesis
(Kandel, NEJM, 9/4/14)

- Mice introduced to nicotine show a “priming” effect at the behavioral, molecular, and genetic level that enhances the effect of cocaine.
- Cocaine does not enhance the effect of nicotine.

Smoking

- 480,000 deaths annually, 30% of all cancer deaths, 20% of all deaths - leading cause of preventable morbidity and mortality worldwide. 20x this number suffer from a serious smoking related illness.
- 14% of American adults smoke. Most are nicotine dependent.
- Nicotine dependence begins in adolescence. Adults don’t start smoking, kids do.
- Smokers with brain damage to the insula were able to immediately quit smoking. This brain area turns a physical reaction into a feeling (craving).

Physical Effects of Smoking

- Nicotine reduces stress, increases relaxation, modulates mood, enhances vigilance, improves cognition, lowers weight, and is pleasurable.
- Tar and toxic products cause cancer and lung diseases.
- Nicotine causes sleep disturbance, worsens CAD, arrhythmias, peripheral vascular disease, peptic ulcer, delays wound healing, reduces birth weight, exacerbates diabetes.
Smoking and Mental Illness

- Habitual smoking is common among individuals with psychiatric disorders, who consume 45% of all cigarettes in the U.S.
- Rates:
  - Substance abusers - 90%
  - Schizophrenia - 83%
  - Bipolar Disorder - 69%
  - Depression - 46%
Amphetamine/ Methamphetamine Use

- Non-cocaine stimulants are the most widely abused illicit drugs in the world after marijuana. US rates are increasing significantly.
- Although MA has many properties in common with cocaine, there are some important differences:
  - Duration: 8-24 hours vs. 20-30 minutes
  - Production is a relatively simple process. Most comes from Mexico.
  - Cost is about 25% of the cost of cocaine
  - Users spend more time under the influence on more days of the week. Intolerable negative consequences are slower to appear.
  - MA has a more complicated neurological effect. It blocks dopamine reuptake, but also destroys the vesicles in the neuron.

Amphetamine/ Methamphetamine Use

- Investigations in animals show that as many as 50% of dopamine producing cells can be damaged even after low levels of MA use. Serotonin containing nerve cells may be damaged even more extensively.
- The list of other adverse effects associated with MA use is extensive and includes neurological, cardiovascular, respiratory, psychiatric, social and other physical effects.

Amphetamine/ Methamphetamine Use

- In CA, offenders diversion programs show 50% with primary meth abuse (vs. cocaine at 14%). Cocaine is more popular on the East Coast.
- Midwestern states and Southeast have witnessed epidemics of meth labs and trafficking, where meth is more popular than cocaine. Meth tends to be used more in rural areas, cocaine in urban areas.
- Fentanyl is now being found in cocaine and meth.
- Several large treatment studies have found women>men.
- Meth use is common among patients on medication for opioid use disorder.
Prescription Stimulants

• Stimulants are approved for treating ADHD. Among high school and college students, Adderall particularly is viewed as a “smart pill,” though they don’t improve mastery or memory. College students are twice as likely to abuse Adderall as non-college peers. The drugs increase focus, decrease appetite, and decrease the sleepiness. Curiously, most users report that taking them doesn’t improve their grades.
• Students who misuse Adderall are also significantly more likely to abuse marijuana, cocaine, benzodiazepines, painkillers, and alcohol.

Prescription Stimulant Use in Adults

• During the past decade, 55% of prescriptions for stimulants have been written for people over the age of 19.
• The rapid increase in diagnoses for adult ADHD has probably been fueled by loosening criteria for adult ADHD in DSM-5 and a strong push from the pharmaceutical industry.
• 16 million adult Americans used a prescription stimulant over the last year, 5 million misused it (to increase alertness, e.g.) and 400,000 met the criteria for a use disorder.
• Misuse is strongly associated with the use of alcohol and other drugs. Any use of stimulants is associated with depressive episodes and suicidal ideation.

Misuse of Prescription Stimulants

• Webpages: “How to convince your shrink you’ve got ADHD” “How to get your doctor to prescribe Adderall in 5 easy steps”, etc.
• Symptoms must start before 12, be present in 2 or more settings, substantially impair the person, and can’t be better explained by something else.
• Genuine ADHD is a disabling condition and it should leave some sort of paper trail.
• Are we at the beginning of a story like the oxycodone story, with safe prescription medication leading to a terrible epidemic of addiction?
Meth Addiction

• Many opioid users are in treatment with methadone or buprenorphine begin to use amphetamines. (60% in San Diego, 40% in Vermont...)

• Meth users do not recognize that they are addicted to amphetamines like they recognize they are addicted to opioids – they don’t feel withdrawal sickness. They say they use because they like it, not because they are addicted. They are ambivalent about the need to stop.

• Users are unaware that they are severely dysfunctional with significant brain damage including cognitive impairment, memory problems, prefrontal cortex damage, anhedonia, and frequent triggers to irresistible craving. This will last through 6 months of abstinence. There is also multiple psychiatric comorbidities (depression, anxiety, PTSD).

Amphetamine Abuse Treatment

• Heavy users need inpatient or residential treatment. This high risk group includes those who inject, those taking high doses, the homeless, those younger than 21, men who have sex with men (meth is frequently used in conjunction with sexual activity in this cohort), and individuals already on medications for opioid disorder.

• Contingency management is the only treatment with any success. Cash is a trigger, so use vouchers, gas cards, grocery cards, etc...

• Triggers for craving include going to the clinic, standing in a drug line at the clinic, being in certain parts of town, being around friends who use, getting a call from their drug dealer, boredom.

• Holding on to the next reward is often enough to help an individual get through the craving episode.

• Counseling is not particularly helpful.

Current Legal Status

• In 1970, marijuana (cannabis sativa – a form of hemp) was established as a schedule I drug: “no currently accepted medical use and a high potential for abuse.”

• 1 in 8 adults smoke marijuana, more than 40% of adults have tried it at some time.

• The majority of states allow some form of medical use.

• Nine states + Washington D.C. have legalized recreational use.
Medical Safety

- The leading causes of death from substances are from alcohol and tobacco, not because they are more dangerous than opioids or marijuana, rather because they are legally available to everyone.
- We don’t know much about the safety of marijuana, which is primarily inhaled. Smoking-related diseases take a long time to develop. And adolescents will be using it during a particularly vulnerable period of development. Rates of substance use among teens have fallen for every substance except marijuana. 21% of US adolescents have used marijuana, 40% of high school seniors.

Cannabis Use

- Cannabis is the most commonly used illegal drug in the US - about 15 million people use it.
- Most users do not develop any problems, but a subset do - 9% develop dependence. In addition, users experience such accompanying problems as drugged driving arrests, accidents (cannabis in the blood increases the risk of a fatal car crash 2.8x) and mental health problems. Adolescent marijuana use is related to later development of depression. The risk is dose related and gender related (girls more than boys.)

Biochemistry

- A marijuana plant contains more than 500 chemicals. The two most studied are THC and cannabidiol.
- THC: responsible for most of the effects on the central nervous system. THC receptors are prevalent in the cortex, hippocampus, and cerebellum. Hence we see fragmented thought, memory problems, and coordination problems in chronic use.
- Cannabidiol: less is known about this chemical – it may be primarily a sedative. It binds to glia, not neurons. It also has anti-emetic, anti-inflammatory and even antipsychotic effects. However, since cannabidiol leads to less THC availability, it is bred out by growers.
Medical Benefits

- Because marijuana is a schedule I controlled substance, there is little to no scientific research about it. There are 3 cannabis-derived chemicals approved for human use:
  - Dronabinol (Marinol): chemotherapy induced nausea/vomiting and AIDS related anorexia
  - Nabilone (Cesamet): same. Both these drugs are second-line treatments due to side effects. They may also be useful for neuropathic pain and glaucoma.
  - Nabiximols (Sativex): spasticity associated with multiple sclerosis. May also work as the two above.
- The evidence for these benefits is inferior to evidence the FDA requires for other prescription medications.

Medical Benefits Summarized

Sci Am Mind (May/June 2014)

- Cancer: reduces chemotherapy induced nausea, increases appetite. Not considered 1st line due to side effects and better prescription drugs available.
- Epilepsy: may inhibit seizures. No good human evidence.
- Glaucoma: lowers eye pressure. Prescription drugs have been found to be more effective and longer lasting.

Medical Benefits Summarized

Sci Am Mind (May/June 2014)

- Multiple Sclerosis: decreases muscle stiffness and other symptoms. There aren’t really other good choices available, so this may be an important use.
- Pain and inflammation: may help as an adjunct to other medications for neuropathic pain (pain caused by damaged neurons.)
Medical Benefits Summarized
Sci Am Mind (May/June 2014)

- These clinical results do not consider improvement in overall quality of life. Users report improved mood, decreased anxiety and insomnia as invaluable additional benefits to this drug. Many of the traditional pharmaceutical treatments have unpleasant side effects that marijuana may not have.

Problems With Potency and Contamination

- The average potency of marijuana in the 1960’s and 1970’s was 1% THC. Medical marijuana dispensaries offer marijuana with a potency as high as 20%. “Vaping” may increase the concentration even more.
- Marijuana may be contaminated by molds, fungi, or herbicide.

Cognitive Deficits

- The cognitive effects of cannabis often persist after acute intoxication (as does psychomotor impairment.) It isn’t clear what the mechanisms of action are that underlie the impairment, nor whom will be affected the most, nor whether cognitive ability improves with abstinence.
- It is hypothesized, not proven, that users brain reserve capacity may be impaired, even if cognitive testing is normal.
- 2 major prospective cohort studies found a decline in IQ from childhood (13) to adulthood among regular users (4-5 “joints”/week.) This may or may not be reversible if adults stop smoking.
Psychosis and Marijuana

• There are no long-term, randomized, placebo-controlled trials. However, there have been 7 prospective, longitudinal studies. Three meta-analyses have indicated that the increased risk of psychosis following marijuana use has an odds ratio of 1.4-2.9. The risk is dose-related and increases up to 7 for daily marijuana smokers.

• However, in countries where public health issues are closely tracked (e.g. Sweden), an increase in marijuana use has not been found to be correlated with an increase in schizophrenia incidence. This may be taken as evidence that marijuana probably does not cause schizophrenia but may trigger it in vulnerable people.

Neurologic Changes

• Chronic heavy marijuana use has structural and functional consequences in the orbitofrontal cortex via cannabinoid receptors. These changes represent less efficient energy use by the brain. They may reflect greater myelination and may alter synaptic pruning. Marijuana is neurotoxic.

• A 2015 study in Neuropsychopharmacology showed epigenetic changes in rats passed on to offspring even when the cannabis exposure occurred well before mating.

Youth

• Even for youth who start smoking later than 18, the data is those who smoked regularly as teenagers, make 66% as much as the average person at the age of 30. This probably has to do with the effect on education.

• In terms of psycho-social development, teens who smoke a lot may believe that they are developing autonomy by doing something adults do not approve of, but probably are not accomplishing the hard task of becoming independent and developing intimate relationships.
Colorado and Teen Use

- After marijuana was legalized for medical use in 2009, teens admitted to substance abuse treatment were more likely to have high amounts of marijuana metabolites in their urine, and there has been an increase in automobile fatalities among teenage drivers with marijuana in their system.

Withdrawal and Treatment

- Cannabis withdrawal syndrome is well established and is more psychological than physiological. Symptoms include depression, irritability, appetite suppression, and headaches. In heavy users, there may be diarrhea and other intestinal discomfort, including nausea and vomiting. Cannabis withdrawal symptoms may last 3–7 days, depending on the amount of prior use.
- N-acetylcysteine (NAC) is a health supplement that has effects on the neurotransmitter glutamate. It may have an effect on the treatment of cannabis-dependent adolescents. There is some preliminary evidence that gabapentin may also be beneficial.
- Since there is no good evidence that pharmacotherapy helpful in reducing cannabis use, treatment involves a combination of motivational interviewing, help with detox, and behavioral strategies.

CBD Oil

- Cannabidiol is a derivative of marijuana that has recently become available as a prescription drug (Epidiolex.) It is FDA approved for 2 rare forms of childhood epilepsy.
- It is also available as a health food “supplement” for the last 10 years.
CBD Oil

• CBD does not cause a "high" but some people consider it to be somewhat tranquilizing.
• It may have neuroprotective properties and lower the risk of psychosis and anxiety that is caused by THC. A CBD product is undergoing trials as a treatment for schizophrenia. It has also reduced social anxiety in several trials.
• CBD oil is legal in all states as long as its made from hemp. Purity is a gamble. (check out Consumer Labs or the FDA web site.)
• Dosages for psychiatric use range from 300mg/day to 1200/mg day. A 300 mg dose is $20-$50 over the counter.

Bottom Line on CBD

• There is not much good evidence to endorse or warn against CBD.

Treatments

• Gabapentin has traditionally been thought to be a nonaddictive medicine. It is FDA approved for seizure disorders and certain kinds of nerve pain. Off-label uses have included alcohol withdrawal, anxiety, mood instability, insomnia, somatoform disorders, and withdrawal symptoms from opioids.
• It acts to inhibit glutamate, norepinephrine. It does not bind to GABA, benzodiazepine, opioid, or cannabinoid receptors. It is thought that gabapentin may increase dopamine activity and may indirectly potentiate other drugs of abuse.
• In 2013 a study reported that 15% of individuals in Appalachia being treated for opioid abuse were using gabapentin to get "high."
Abuse Potential of Gabapentin

- A 2016 article found 26% of an incarcerated population with opioid use disorder abused gabapentin compared to 4% who did not abuse opioids.
- Typically, gabapentin is abused only after abuse of another substance has begun.
- Withdrawal symptoms occur within 12 hours to 7 days after last use and include agitation, confusion, sweating, GI problems, insomnia.