THE "GOOD" DRUGS: CANNABIS, BENZODIAZEPINES, BZRAS, KRATOM

"NP … I need my (Metformin, lisinopril, Valtrex)."

"NP… but I need my cocaine for my mental health and sinus Issues."

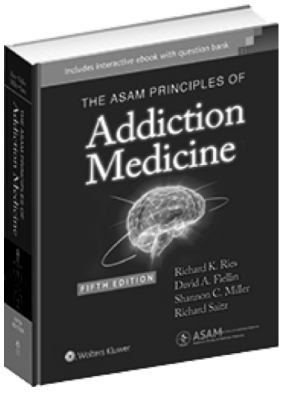
"NP… I need my Cannabis/Xanax/Kratom/Ambien for my Mental Health"

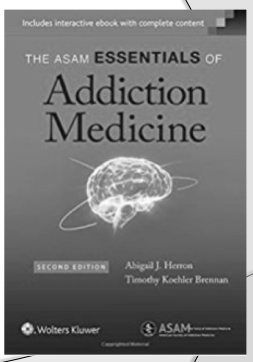
Martha Stewart

"But my Doctor has prescribed this medication for years."

Reaching a Conclusion

- At the end of each drug I will summarize with three things to help you make clinical decision:
  - Proven Efficacy
  - Risks to Patients
  - Risks to Provider





No Disclosures

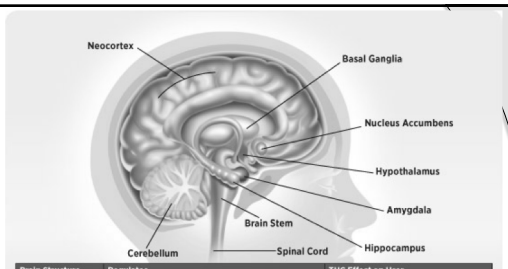
- No conflict of interests

Marijuana

Cannabinoids Pharmacology

- MOA: Activation of Cannabinoid receptors and many other potential downstream receptors.
  - Marijuana is a compound of 100- 500 chemicals only two of which are known: THC and CBD

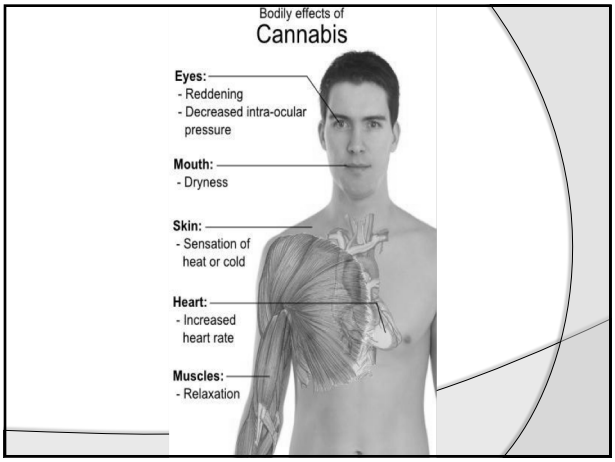
Herron, Abigail; Brennan, Timothy K. (2015). The ASAM Essentials of Addiction Medicine LWW. Kindle Edition.



Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	learning new information	impaired memory
Hypothalamus	eating, sexual behavior	increased appetite
Neocortex	complex thinking, feeling, and movement	altered thinking, judgment, and sensation
Nucleus Accumbens	motivation and reward	euphoria (feeling good)
Spinal Cord	transmission of information between body and brain	altered pain sensitivity

The brain structures illustrated above all contain high numbers of CB receptors

This slide is not completely accurate but gives good basic information



Not All Cannabis is the Same

- In the 60's THC was 0.1%
- Most THC now is at least 0.4 %
- Marijuana ("weed" or "grass") 6-12 %
- Sensimilla ("skunk") >13%
- *Cannabis resin ("hashish") >35%*
- Hash oil >50%

Herron, Abigail; Brennan, Timothy K. (2015). The ASAM Essentials of Addiction Medicine LWW. Kindle Edition.

Table 1. CNS and cardiovascular effects of THC and CBD.

	THC	CBD
Anticonvulsant	+	++
Muscle relaxant	++	+
Analgesic	++	+
Anxiolytic	±	++
Antipsychotic	–	++
Neuroprotective	+	++
Antiemetic	++	+
Sedation	+	–
Bradycardia	–	+
Tachycardia	+	–
Hypertension	+	–
Hypotension	–	+

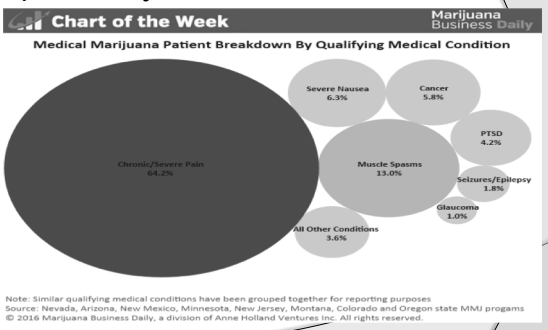
Adapted from Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Medical Hypotheses. 2006 Dec 31;66(2):234-46.

I question the anxiolytic and antipsychotic properties but more on that later.

FDA Approved Uses of Cannabis products

- Epidiolex (CBD)- approved for epilepsy in Lennox-Gastaut syndrome and Dravet syndrome
- Marinol [dronabinol] (a synthetic THC)- anorexia in AIDs and cancer nausea and appetite
- Cesamet [nabilone] (a synthetic THC)- anorexia in AIDs and cancer nausea and appetite

Medical Reasons For Use: As Reported by Users



https://mjbizdaily.com/chart-of-the-week-most-common-medical-conditions-of-registered-mmj-patients/

"I heard Marijuana has antipsychotic properties. I'd rather take that then have a side effect filled antipsychotic."

Cannabidiol has some antipsychotic properties. But NO big studies. Not ready for clinical use.

- Cannabidiol does have antipsychotic- like effects and at very high doses (1200-1500 mg) did seem to help in bipolar depression (but failed to control mania) but this was in some very small numbers of small studies (largest 88 people most < 20). Most of these studies were 4 weeks or less. Most are open label.
- It did well in a head to head study with amisulrpide of 42 patients for 28 days. Which doesn't say much due to number and length of treatment.
- A Cochrane review of these and more studies said there was "insufficient evidence for cannabis as an antipsychotic." It also details the significant methodological flaws in these studies. Cochrane Database Syst Rev. 2014 Oct 14;(10):CD004837. doi: 10.1002/14651858.CD004837.pub3. Cannabis and schizophrenia.Mcloughlin BC1, Pushpa-Rajah JA, Gillies D, Rathbone J, Variend H, Kalakouti E, Bartlanou K.
- I know some patients that prevent or minimize psychosis or depression with alcohol for a month. But I don't recommend it.

Iffland, K, and Grotenherme, F. (2017) An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. *Cannabis Cannabinoid Res.* 2(1):139-154.

Cannabidiol Products- unregulated

- A JAMA study looked at 84 cannabidiol (CBD) products sold on line and 14 had non-trivial levels of THC.

Bonn-Miller, M., Loflin, M., Thomas, B., Marcu, P., Hyke, P., and Vandrey, R. (2017) Labeling Accuracy of Cannabidiol Extracts Sold Online. JAMA. 318(17):1708-1709.

Marijuana Especially with THC Dramatically Increases Risk of Psychosis

- In a large multicenter Study of >2000 patients who regularly used of 10% THC or greater marijuana (which could be regular concentration in marijuana most patients access) saw a 5 fold increase of first episode psychosis. It was the most noticeable in Amsterdam where incidence of first episode psychosis could be reduced by >50 % if this strength THC was removed from the street. Forti, M., Quattrone, D., Freeman, T., Tripoli, T., Gayer-Anderson, C., and Quigley, H., et al. (2019) The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. https://doi.org/10.1016/S2215-0366(19)30048-3.
- One study of 2437 patients age 14 -24 those with predisposition to psychosis (history, genetic factors etc) 23% had psychotic features 4 years after their psychotic episode during cannabis intoxication and those without those factors 5-6%. Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H., and van Os, J. (2005) Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ.* 330(7481): 11. doi: 10.1136/bmj.38267.664086.63
- Especially age 15-18 but potentially up into 30s can induce permanent psychosis usually dose and strength dependent. Can be as high as seven fold increase risk of permanent psychosis. Herron, Abigail; Brennan, Timothy K. (2015). The ASAM Essentials of Addiction Medicine LWW. Kindle Edition.

Marijuana is the Most Likely Drug to lead to Permanent Psychosis

- Rates of permanent psychosis induced by drug
  - Lowest incidence rate is Alcohol use 4-5%
  - Amphetamine- 30%
  - Marijuana- 46%- evidence it worsens psychosis and may lead to earlier onset.
- Almost half the people in the world who used a drug and developed permanent psychosis did so because they used marijuana
- This again is most prominent in children up to age mid thirties.
- There are many theories it is connected with certain genetic risks.
- Older adults are less likely to develop.

Bousman, C., McKetin, R., Burns, R., Woods, S., Morgan, E., Atkinson, J., Everall, I., Grant, I. (2015) Typologies of Positive Psychotic Symptoms in Methamphetamine Dependence. *The American Journal on Addictions*, 24: 94–97.

Niemi-Pynttäri, J., Sund, R., Putkonen, H., Vorma, H., Wahlbeck, K., Pirkola, S. (2013) Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. *J Clin Psychiatry*.74 (1); e94-9

Does it help Schizophrenia? No.

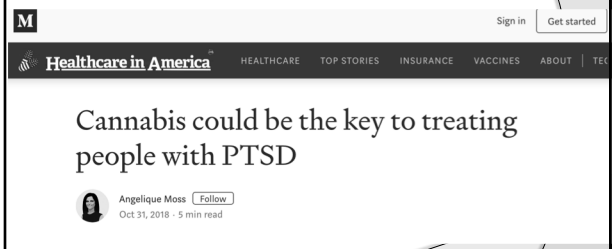
- Patients with Schizophrenia several hours after cannabis use have increased 1) learning and recall deficits; 2) positive, negative, and general schizophrenia symptoms; 3) perceptual alterations; 4) akathisia, rigidity, and dyskinesia; 5) deficits in vigilance; and 6) plasma prolactin and cortisol. Abi-Saabc, W., Madonickd, S., Forselius-Bielenb, K., Doerschf, A., Braleya, G., Gueorguievab, R. , Cooperg, T. and, Krystala, J. (2004) Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. https://doi.org/10.1016/j.biopsych.2004.12.006

Bipolar Disorder Effects

- "Marijuana use is associated with earlier age of onset of bipolar.
- It prolonged or worsened manic episodes.
- Increased likelihood of suicide attempt.
- A study of patients over a one year follow-up period after their first treatment for BD-I found that continued marijuana use was associated with elevated mood, but poorer global functioning. These relationships were not explained by differences in age, gender, premorbid functioning or baseline symptoms.
- It was associated with lower remission rates for depressive symptoms in women and for manic symptoms in men in one study.
- Furthermore, remission rates for depressive symptoms were lower in cannabis users prescribed mood stabilizers alone and remission rates for manic symptoms were lower in cannabis users prescribed olanzapine. The researchers note this may indicate that marijuana may diminish the effect of medications used to treat BD. This may be for several reasons but one could be CBDs interactions with many mood stabilizers and antipsychotics."

. Stoner, Susan. Effects of Marijuana on Mental Health: Bipolar Disorder Considering Locked vs. Unlocked Treatment Facilities. Alcohol and drug abuse institute university of Washington.

"Marijuana Helps Soldiers and others with PTSD."



"It Lowers Anandamide"

- This is a non-specific neurotransmitter in the canabanoid system that some theorize is raided in healthy brain states. This is far from proven.

Canada Guidelines:

- Canada - Marijuana for PTSD
- However in their guidelines they report the evidence is "very low."
- There were only three studies of low quality and only two talked about symptoms other than sleep/nightmares.
- They were short term studies with serious methodological flaws.

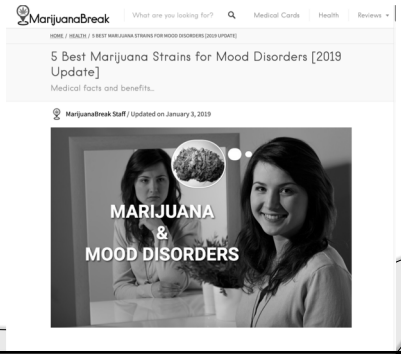
Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Jan. **Medical Marijuana for Post-Traumatic Stress Disorder: A Review of Clinical Effectiveness and Guidelines [Internet].**

Marijuana Worsens PTSD, Violence and Drug use in Patients

- A longitudinal study of >2,276 VA patients with PTSD studied from 1992-2011.
- Researchers were surprised to see increased violence over those not using or who stopped during the study.
- Symptoms of PTSD were worse than those not using or who stopped during the study.
- They were more likely to use drugs.

Wilkinson, S., Stefanovics, E., and Rosenheck, R. (2015) Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. J Clin Psychiatry. 76(9):1174-80. doi: 10.4088/JCP.14m09475.

"Marijuana helps my Depression and Anxiety."



"But I read this Positive Study for Mental Health."

- JAMA Metanalysis from 2015 and Cochrane reviews from up to 2018 some of the highest evidence found many of these studies to be highly biased, low quality, or unusable due to proper controls.

Whiting, P., Wolff, R., Deshpande, S., Nisio, D., Duffy, S., Hernandez, A., Keurentjes, J., Lang. S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood, M., and Kleijnen, J. (2015) Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 313(24):2456-73. doi: 10.1001/jama.2015.6358.

Latorracal, C., Pachecoll, R., Martimbiancoll, A., Pachitol A, and Riera, R. (2018) What do Cochrane systematic reviews say about the use of cannabinoids in clinical practice? Sao Paulo Med. J. vol.136 no.5 São Paulo Sept./Oct. 2018 http://dx.doi.org/10.1590/1516-3180.2018.0313210818.

Subjective Reports Give Some Evidence in the Short Term But…

- Self Reporting Medical Cannabis users 11,953 tracked sessions on an app were analyzed (3,151 for depression, 5,085 for anxiety, and 3,717 for stress). Medical cannabis users perceived a 50% reduction in depression and a 58% reduction in anxiety and stress following cannabis use. Two puffs were sufficient to reduce ratings of depression and anxiety, while 10+puffs produced the greatest perceived reductions in stress.
- High CBD (> 9.5%)/low THC (< 5.5%) cannabis was associated with the largest changes in depression ratings, while high CBD (> 11%)/high THC (> 26.5%) cannabis produced the largest perceived changes in stress.
- But there were no changes in the perceived efficacy of cannabis were detected across time. However, baseline symptoms of depression appeared to be exacerbated across time/tracked session.
- Take away: people who would self select for marijuana use, only 50-60% reduction of depression, anxiety and stress. However, this highly biased, self selecting, and high placebo responding group admitted to worsening depression with time. To get relief for anxiety they had to use extremely high doses of THC that have negative SEs and worsening depression. Drug induced euphoria?

Cuttler, C., Spradlin, A., and McLaughlin, R. (2018) A naturalistic examination of the perceived effects of cannabis on negative affect.
Journal of Affective Disorders www.elsevier.com/locate/jad

Marijuana Worsens Every Mental Health Disorder Even Those Being Treated with Proven Therapies

- "A review of twelve studies (with a total of 11,959 individuals) 4 studies with posttraumatic stress disorder one focusing on panic disorder, five with bipolar disorder and two depressive disorder. Across 11 studies, "recent" cannabis use (ie, any/greater frequency of use during the last 6 months) was associated with higher symptomatic levels over time relative to comparison groups (ie, no/lesser frequency of use). Ten of these studies further suggested that cannabis use was associated with less symptomatic improvement from treatment (eg, medication, psychotherapy for AMD)."

Mammen, G., Rueda, S., Roerecke, M., Bonato, S., Lev-Ran, S., and Rehm, J. (2018) Association of Cannabis With Long-Term Clinical Symptoms in Anxiety and Mood Disorders: A Systematic Review of Prospective Studies. J Clin Psychiatry 2018;79(4):17r11839.4088/JCP.17r11839

It Can Make Patients Significantly Worse

- For psychiatric patients, however, the picture is far bleaker. In the study, individuals with psychiatric or conduct disorders who used marijuana had double the risk of addiction; triple the risk of mood, anxiety, and attention deficit disorders; quadruple the risk of personality disorders and alcohol dependence; and cocaine dependence increased the risk by a factor of 6. Herron, Abigail; Brennan, Timothy K. (2015). The ASAM Essentials of Addiction Medicine LWW. Kindle Edition.

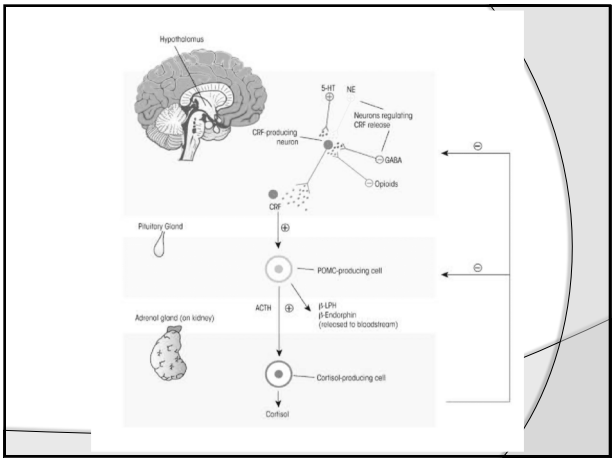
12-32 y/os are Particularly at Risk

- In 11 meta analyses 18-32 y/os who used cannabis were at a 37% increased risk of depression, 50 % increased risk of suicidal ideations and 346% increased risk of suicide attempts.
- The Surgeon General stated there is no safe dose of marijuana.

Gobbi, G., Atkin, T., T Zytynski, T., Wang, S., Askari, S., Boruff, J., Ware, M., Marmorstein, N., Cipriani, A., Dendukuri, N., and Mayo, N., (2019) Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young AdulthoodA Systematic Review and Meta-analysis. JAMA Psychiatry. doi:10.1001/jamapsychiatry.2018.4500

Rebound Anxiety

- Based on adaption made in the Brain and HPA continued use of Cannabis can raise base levels of anxiety due to down regulation of CB1R. Volkow, N., Hampson, A., and Baler, R. (2017) Don't Worry, Be Happy: Endocannabinoids and Cannabis at the Intersection of Stress and Reward. Annual Review of Pharmacology and Toxicology. 57:285-308.
- A Cannabis use at baseline was significantly associated with anxiety at follow-up in *N* = 5 studies adjusted for confounders (*OR* = 1.28, *95% CI*: 1.06-1.54, *p* = .01). The opposite relationship was investigated in only one study." Kedzior, K., Laeber, L. (2014) A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. BMC Psychiatry **14**:136 https://doi.org/10.1186/1471-244X-14-136.
- Most of my cannabis using patients agree that when they stop using Cannabis often their anxiety levels are higher than when they starting using.



Chicken or the Egg?

- Monozygotic twins where one uses Cannabis and one does not the user had higher risks of depression and suicidal ideation. Agrawal, A., (2017) Major depressive disorder, suicidal thoughts and behaviours, and cannabis involvement in discordant twins: A retrospective cohort study. Lancet Psychiatry Sep; 4:706. (http://dx.doi.org/10.1016/S2215-0366(17)30280-8)

Insufficient Evidence for Complex Neurological Conditions.

- "While there are trials that suggest potential benefit of cannabinoids for anorexia nervosa, anxiety, PTSD, psychotic symptoms agitation in Alzheimer's disease and dementia, Huntington's disease, and Tourette syndrome, and dyskinesia in Parkinson's disease, insufficient conclusion could be made due to the low quality of evidence as indexed by the Cochrane risk of bias, and underpowered samples." Lim, K., Mei, Y., and Lee, J. (2017) A Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders. Clinical Psychopharmacology and Neuroscience. 15(4): 301–312.10.9758/cpn.2017.15.4.301

Pain- Some Very Weak Evidence

- The oral spray containing tetrahydrocannabinol plus cannabidiol demonstrated some relief of neuropathic pain only.
- However one meta analysis of these studies says "Most studies were small, few reported outcomes beyond 2 to 3 weeks, and none reported long-term outcomes." Some of the bigger studies also had methodological flaws. Vita, M., Moskal, D., Maisto, S., and Ansell, E., (2018)Association of Cannabinoid Administration With Experimental Pain in Healthy Adults A Systematic Review and Meta-analysis. JAMA Psychiatry. 75(11):1118-1127. doi:10.1001/jamapsychiatry.2018.2503

Pain – Caveat* Maybe only Pain Perception

- JAMA review of 18 controlled studies (442 healthy participants) noted that Cannabis may not reduce actual pain intensity nor did it fix hyperalgesia conditions but by inducing euphoria it might make a small increase in pain threshold at initial pain onset and more importantly reduce how "unpleasant" or "intolerable" the pain was. Vita, M., Moskal, D., Maisto, S., and Ansell, E., (2018)Association of Cannabinoid Administration With Experimental Pain in Healthy AdultsA Systematic Review and Meta-analysis. JAMA Psychiatry. 75(11):1118-1127. doi:10.1001/jamapsychiatry.2018.2503
- In placebo controlled trials for MS spasticity and pain there was no decrease in spasticity but subjects reports reported a decrease in pain and spasticity. Zajicek, J., Fox, P., Sanders, H. et al. (2003) Cannabinoids for treatment of spasticity and other symptoms related to multiplesclerosis (CAMS study): multicentre randomised placebo-controlled trial.Lancet 362:1517–1526.
- The few positive studies of CBD alone showed an NNT of 5 for neuropathic pain. Other interventions with an NNT of 5 …SSRIs.
- https://www.psychiatrictimes.com/substance-use-disorder/cannabinoids-chronic-pain-opioid-alternative?rememberme=1&elq_mid=8189&elq_cid=1676900&GUID=F0EB92C9-73E9-461A-8D6C-BCD494947CBD

Pain – Caveat* Maybe only Pain Perception

- Mental health providers have for a long time been pushing for counseling and therapy and SSRIs in pain to help peoples tolerance for pain and seen great results. Reframing, finding purpose in pain and treating depression go a long way. These have great effect sizes and quality of evidence.
- Morley, S., Williams, A., and Eccleston, C. (2013) Examining the evidence about psychological treatments for chronic pain: Time for a paradigm shift? PAIN: Volume 154 - Issue 10 - p 1929–1931doi: 10.1016/j.pain.2013.05.049
- There are also many logical pathways for panic reduction by cannabis. The most likely is the known muscle relaxation. How about mastery of muscle relaxation exercises? It won't give you the munchies, psychosis, cognitive problems, or make you want to watch sponge bob.

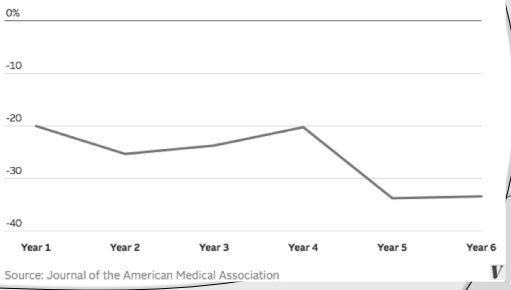
Pain – Head to Head

- The CBD NNH was 5-8 with motor impairment, altered cognitive function, altered perception being the most likely outcomes. For perspective the NNH for these symptoms in all other pain medications is NNH 20. Also for opioids the NNH for sedation (second most common harm) is 6. https://www.psychiatrictimes.com/substance-use-disorder/cannabinoids-chronic-pain-opioid-alternative?rememberme=1&elq_mid=8189&elq_cid=1676900&GUID=F0EB92C9-73E9-461A-8D6C-BCD494947CBD

Marijuana and Sedation

- Weekly to daily use of cannabis lead to some patients needing up to 220 % more Propofol to induce sedation for surgery. https://www.sciencedaily.com/releases/2019/04/190415172147.htm

Reduction in expected opioid deaths in states with medical marijuana laws, by year of implementation



It Helps Decrease Opioid Use? No. It Increases Risk of OD/Mortality.

- There was one study that noted a correlation between legal cannabis use in states and rate of opioid use. They put in several caveats that the data was not strong enough for conclusions.
- A replica study concluded below:
- "Not only did findings from the original analysis not hold over the longer period, but the association between state medical cannabis laws and opioid overdose mortality reversed direction from −21% to +23% and remained positive after accounting for recreational cannabis laws."

https://www.pnas.org/content/early/2019/06/04/1903434116

Cannabis and Opioids

- Survey by American Pain Association of 450 chronic pain patients on opioids with 176 augmenting with Cannabis endorsed no better pain control, increased anxiety, depression and other drug and alcohol use.
  American Pain Society Source Reference: Rogers A, et al "Opioid and Cannabis Co-Use among Adults with Chronic Pain: Relations to Substance Misuse, Mental Health, and Pain Experience" APS 2019; Abstract 177.
- Medical marijuana users are more likely to also abuse pain relievers, stimulants and tranquilizers. Caputi, T.; Humphreys, K., (2018)Medical Marijuana Users are More Likely to Use Prescription Drugs Medically and Nonmedically
  Journal of Addiction Medicine: Volume 12 - Issue 4 - p 295–299

Cochrane Reviews for Other Medical Conditions-

- Cochrane is a good standard for well researched and carefully scrutinized
- Evidence for Epilepsy- “Studies poorly reported – no conclusion can be drawn”
- Fibromyalgia- One study had “very low” evidence of pain reduction. One said it worsened depression and fatigue and one said there were serious adverse events and many withdrew from the study.
- AIDS Anorexia- No difference from placebo
- Nausea for adults with cancer- Moderate evidence for cannabinoid vs prochlorperazine and older mild to moderate anti-emetics

Latorraca, C., Pachecoll, R., Martimbiancoll, A., Pachitol A, and Riera, R. (2018) What do Cochrane systematic reviews say about the use of cannabinoids in clinical practice? São Paulo Med. J. vol.136 no.5 São Paulo Sept./Oct. 2018 http://dx.doi.org/10.1590/1516-3180.2018.0313210818.

Acute Intoxication SEs

- Acute cannabis use negative SE:
  - Sedation,
  - Lethargy
  - Intensification of ordinary sensory experiences
  - Perceptual distortion
  - Social withdrawal
  - Conjunctival hyperemia
  - Increased appetite
  - Dry mouth
  - Increased blood pressure and tachycardia
  - Acute bronchodilator effects have been reported.
  - Heart rate increases by 20-50% within a few minutes to a quarter of an hour have also been reported; this effect lasts up to 3 hours.

Karila, L., Roux, P., Rolland, B. Benyamina, A., Reynaud, M., Aubin, H., and Lançon, C. (2014) Acute and Long-Term Effects of Cannabis Use: A Review. Bentham Science Publishers 20, 000-0001 1381-6128/14

Cognitive Symptoms

- There were some noticeable changes in brain structure around memory, attention and impulsivity. THC blunted working memory, lengthened reaction time, and decreased accuracy of recall. These results had lasting effect. https://www.iwatch.org/ip20120514000003/2012/05/14/cannabis-cognitive-and-neuroanatomical-effects
- “Cannabis induces loss of internal control and cognitive impairment, especially of attention and memory, for the duration of intoxication. Heavy cannabis use is associated with reduced function of the attentional/executive system, as exhibited by decreased mental flexibility, increased perseveration, and reduced learning, to shift and/or sustain attention.” Lundquist, T. (2005) Cognitive consequences of cannabis use: Comparison with abuse of stimulants and heroin with regard to attention, memory and executive functionsBiochemistry and Behavior Volume 81, Issue 2, Pages 319-330
- Because of this some people will present with ADHD symptoms but this can be better explained by heavy cannabis use.
- This is one of the main reasons the surgeon general has said that there is no safe amount of this drug in adolescents.

Chronic SEs

- Potential for withdrawal lasting days to weeks and post acute withdrawal which may include; irritability, anger, or aggression; nervousness or anxiety; sleep difficulty (insomnia); decreased appetite or weight loss; restlessness; depressed mood; and physical symptoms causing significant discomfort, such as stomach pain, shakiness/tremors, sweating, fever, chills, and headache
- Gingival enlargement, with clinical characteristics similar to those of phenytoin-induced enlargement or Uvulitis and nicotinic stomatitis.
- Daily cannabis smoking is connected with worsening steatosis and fibrosis severity in chronic hepatitis C.
- Cannabinoid Hyperemesis Syndrome cyclic episodes of nausea and vomiting, and the learned behavior of hot bathing.
- Cannabis contains many carcinogenic substances, but it remains unclear whether it is a cause of lung cancer
- Cannabis has been linked, in a dose-dependent manner, to elevated rates of myocardial infarction and cardiac arrhythmias.
- The cannabinoid system opposes the autonomic nervous system, causing paradoxical vasoconstriction, a decrease in cardiac output and hypoxia and an increase in carboxyhemoglobin, an increased risk of infarction in coronary patients, an arrhythmogenic effect, and orthostatic hypotension
- Cannabis is one of the most frequent causes of arteriopathy in young adults. THC seems to have a direct toxic effect on blood vessels.
- Chronic cannabis use was associated with visceral adiposity and adipose tissue insulin resistance.
- Cannabis disrupts the menstrual cycle, suppressing oogenesis, and impairing embryo implantation and development in women and by increasing ejaculation problems, reducing sperm count and motility, and generating a loss of libido and impotence in men.
- Cannabis use during pregnancy is associated with an increased risk of adverse birth outcomes. Prenatal cannabis exposure influences brain development and may have long-lasting effects on cognitive functions. Cannabis use during pregnancy is related to diverse neurobehavioral and cognitive outcomes, including symptoms of inattention, impulsivity, deficits in learning and memory, and deficiencies in aspects of executive functions. The surgeon general said no amount of exposure of a fetus to marijuana is safe.
- Cannabis use significantly increased the risk of nasopharyngeal carcinoma.

Karila, L., Roux, P., Rolland, B. Benyamina, A., Reynaud, M., Aubin, H., and Lançon, C. (2014) Acute and Long-Term Effects of Cannabis Use: A Review. Bentham Science Publishers 20, 000-0001 1381-6128/14

Addiction

- It is estimated that about 9% of users become addicted to Marijuana.

Lopez-Quintero, C., Pérez de los Cobos, J., Hasin, D., Okuda M, Wang, S., Grant, B., Blanco, C. (2011) Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. May 1;115(1-2):120-30. doi: 10.1016/j.drugalcdep.2010.11.004.

Addiction is the Newest Risk of Lawsuit

- Between 2011 and 2016, the number of doctors punished by the DEA jumped more than five times. Nedelman,M. (2017) Doctors increasingly face charges for patient overdoses. https://www.cnn.com/2017/07/31/health/opioid-doctors-responsibleoverdose/index.html?r=https%3A%2F%2Fwww.google.com%2F
- Recently medical lawsuits suing providers for providing Addictive Substances has Increased. NSO insurance company reports 9.9 % of lawsuits were over a patient wrongful death and 9.7% for a patient becoming addicted. As likely to be sued for death as addiction.
- Second biggest payoff for NSO. 27% of allegations related to improper prescribing management of controlled drugs. You are highly likely to lose your case.

CNA and Nurses Service Organization. (2017). Nurse Practitioner Claim Report, 4th Edition. Retrieved from www.nso.com/NPclaimreport. Accessed October 26, 2017.

BUT WAIT! CBD = All Benefit/ No Risk!?

- More like Benefit?/ Risk?
- "Jordan Tishler, MD, an internist and professor at Harvard Medical School in Brookline, Massachusetts, and president of the Association of Cannabis Specialists, also believes that the benefits the average person is getting from CBD are likely placebo, and that it's THC that can really treat symptoms. "If you think about the general things cannabis is used for—pain control, nausea suppression, appetite stimulation, treatment of anxiety—that's all THC… in proper dosing and in proper timing that's actually working.'"
- It requires extremely high doses to get anything approaching an even slight therapeutic effect e.g. 600- 1200 mg and this was usually subjective oral report of benefit. Long term effects of high dose are unknown
- That would be >80-160 cups of CBD tea, >40-80 chocolate bars, and >25-50 CBD gummies.
- CBD is in a legal limbo and federal law enforcers still confiscate, fine and worse. As the article referenced below warns be careful traveling with it.

https://www.medicaleconomics.com/news/cbd-oil-trend?remembermeId=1&elq_mid=7108&elq_cid=1676900&GUID=F0EB92C9-73E9-491A-8D6C-BCD494947CBD

CBD Spray- Negatives

- The CBD NNH was 5-8 with motor impairment, altered cognitive function, altered perception being the most likely outcomes. For perspective the NNH for these symptoms in all other pain medications is NNH 20. Also for opioids the NNH for sedation (second most common harm) is 6.

Don't forget Drug interactions

- "THC is a CYP1A2 inducer. Theoretically, THC can decrease serum concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine(Flockhart 2007, Watanabe et al 2007).
- CBD is a potent inhibitor of CYP3A4 and CYP2D6.
  - As CYP3A4 metabolizes about a quarter of all drugs, CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin).
  - CYP2D6 metabolizes many antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone)."

I had a patient who added CBD. He is on Risperdal, propranolol, and he was on an antihistamine. He developed akathisia, blood pressure dropped and he got dizzy, and his confusion increased with the anticholinergic effect.

https://doh.dc.gov/sites/default/files/dc/sites/doh/publication/attachments/Medical%20Cannabis%20Adverse%20Effects%20and%20Drug%20Interactions_0.pdf

Marijuana: Conclusions

- Proven Efficacy:
  - Moderate Evidence for cancer nausea but 5-hydroxytryptamine3-receptor antagonists, dexamethasone, and aprepitant, may have superior efficacy and fewer side effects. It should be saved for resistant patients or as a lower tier agent. It can lead also lead to Hyperemetic condition. Gary, M., Reisfield, M., and Robert L., DuPont, M. Recommend against the Medicinal Use of Marijuana https://pdfs.semanticscholar.org/5888/de4db73ca68c9576e3ed2eadbd3f8c2857d9.pdf
  - Approved for epilepsy in Lennox-Gastaut syndrome and Dravet syndrome, but mixed to poor evidence in other seizures.
  - Very Low Quality Evidence for short term (2-3 weeks) neuropathic pain control but mechanism of action could overlap with simple psychiatric intervention such muscle relaxation techniques and CBT or euphoria of "getting high."
  - Mixed to poor evidence in AIDS and cancer patients appetite stimulation (but in those conditions anything helps).

Marijuana: Conclusions

- Risk to Patient:
  - Worsens every mental health disorder in long term.
  - In vulnerable people (especially <35 with genetic risk) it can lead to permanent psychosis or bipolar disorder.
  - It can dramatically increase incidents of self harm, suicide, and violence in vulnerable patients.
  - Can lead to patients becoming addicted.
  - Can temporarily or permanently worsen cognitive function.
  - Potential for withdrawal lasting days to weeks and post acute withdrawal
  - Problems of mouth, throat and gums including certain types of cancer
  - Liver problems and worsening of certain liver conditions
  - Cannabinoid Hyperemesis Syndrome
  - Increased potential cancer risk
  - Increase risk of cardiac and vascular issues.
  - Increased visceral adiposity and adipose tissue insulin resistance.
  - Sexual and reproductive problems.
  - Risk to fetus and developmental disorders.

Marijuana: Conclusions

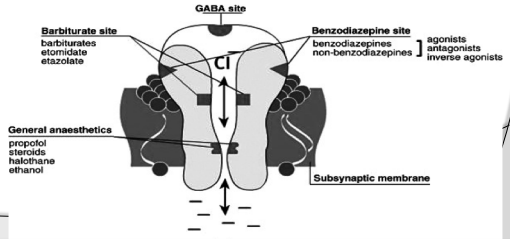
- Risk to Provider:
  - Outside of the few FDA approved treatments the contents of dispensary, online shops, and other distributors is questionable. How would you dose?
  - High risk of lawsuit for controlled substance without warning about all potential side effects. Some side effects are lethal (Cancer, cardiac, suicide/homicide) or permanently impairing (psychosis, cognitive)
  - High risk of lawsuit due to addiction.

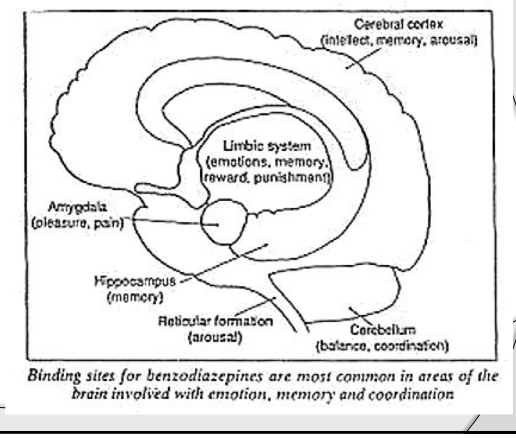
Benzodiazepines

Benzodiazepines (BZD)

- MOA in acute intoxication: Increase GABA signaling decreasing global activation but other signaling including increased dopamine in some areas.

Herron, Abigail; Brennan, Timothy K. (2015).The ASAM Essentials of Addiction Medicine LWW. Kindle Edition.





Binding sites for benzodiazepines are most common in areas of the brain involved with emotion, memory and coordination

What is It Approved to Treat

- 1st line treatment certain types of catatonia (actually lorazepam and not other BZDs)
- 1st line treatment Benzodiazepine/Alcohol withdrawal
- 1st line for immediate emergency seizure control
- 2nd line Acute Agitation (like they are tearing up your ER) dosing usually a few days at most. It can also make things worse.
- 2nd to 3rd line chronic seizure control
- 3rd line Panic Disorder – mostly adjunctive tx
- 3rd line Generalized Anxiety- mostly adjunctive tx
- 3rd line Social Anxiety disorder- mostly adjunctive tx
- 3rd line muscle spasm pain
- Off label specific intermittent but significant phobias (e.g. Fear of Flying)

That Leaves out:

- Depression
- All other anxiety disorders (PTSD, OCD, specific phobia)
- Schizophrenia
- Bipolar (except for acute mania agitation… again tearing up your ER)

It is Makes PTSD Worse

- One Metanalysis of > 5,000 patients with PTSD indicated that "BZDs are associated with specific problems in patients with PTSD: worse overall severity, significantly increased risk of developing PTSD with use after recent trauma, worse psychotherapy outcomes, aggression, depression, and substance use. .Guina, J., Rossetter, S., DeRHODES, B., Nahhas, R., Welton, R. (2015) Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. J Psychiatr Pract. 2015 Jul;21(4):281-303. doi: 10.1097/PRA.0000000000000091
- PTSD is cured most of the time by holding the distress in the body and using grounding techniques and working through thoughts in that moment. Benzodiazepines break down this process. I have treated some people that stopping the BZD literally fixed the patient or having a BZD prolonged symptoms.
- BZDs are prohibited in EMDR, an effective treatment for PTSD, and worsen effectiveness of Exposure therapies that do have evidence of helping.

Depression

- 81, 000 AD and BZD users were compared to > 600,000 AD alone for depression. At 6 months there is no difference between those started on AD vs AD and benzodiazepine.

  Bushnell, G., Stürmer ,T., Gaynes, B., Pate, V., and Miller, M. (2017) Simultaneous Antidepressant and Benzodiazepine New Use and Subsequent Long-term Benzodiazepine Use in Adults With Depression, United States, 2001-2014. JAMA Psychiatry. 74(7):747-755. doi: 10.1001/jamapsychiatry.2017.1273.

- In an old meta analysis adding a benzodiazepine did help some depressed patients anxious symptoms but was associated with greater drop out of treatment. However, any benefit was lost after 6-8 weeks when AD and AD + BZD had similar responses. Furukawa, T., Streiner, D., and Young, L. (2002) Antidepressant and benzodiazepine for major depression. Cochrane Database Syst Rev. 2002;(1):CD001026.
- A large study of > 300 patients showed patients did not improve with the addition of benzodiazepine and worsened in their anhedonia (inability to experience pleasure) Rizvi SJ, Sproule BA, Gallaugher L, et al. Correlates of benzodiazepine use in major depressive disorder: The effect of anhedonia. J Affect Disord. 2015;187:101-105.
- A known significant side effect of benzodiazepines is depression and is therefore never supposed to be monotherapy and can make the disorder worse. In fact it is surprisingly a very common factor in both melancholic and non-melancholic treatment resistant depression. I have often made patients better simply by deprescribing. Parker, G., and Graham, R. (2015) Determinants of Treatment-Resistant Depression: The Salience of Benzodiazepines. J Nerv Ment Dis.;203(9):659-63. doi: 10.1097/NMD.0000000000000348.

Schizophrenia

- "Benzodiazepine use was associated with a marked increase in mortality among patients with schizophrenia" in a study of 2588 patients.
- Overall risk of harm increased by 22% in most patients. It increased risk of hospitalization by 8% and ER visits by 12%.
- Adding an antidepressant reduced hospitalizations by 16%

  Tiihonen, J., Suokas, J., Suvisaari, J. (2012) Polypharmacy With Antipsychotics, Antidepressants, or Benzodiazepines and Mortality in Schizophrenia. Arch Gen Psychiatry. 69(5):476-83. doi: 10.1001/archgenpsychiatry.2011.1532.

Bipolar

- "Benzodiazepine use may be associated with greater risk for recurrence of a mood episode among patients with bipolar I and II disorder." Perlis, R., Ostacher, M., Miklowitz, D., Smoller, J., Dennehy, E., Cowperthwait, C., Nierenberg, A., Thase, M., and Sachs, G. (2010) Benzodiazepine use and risk of recurrence in bipolar disorder: a STEP-BD report. J Clin Psychiatry;71(2):194-200. doi: 10.4088/JCP.09m05019yel.
- "The incidence of subsequent long-term [BZD] use among bipolar benzodiazepine initiators is high. Patients on clonazepam, alprazolam or benzodiazepine/Z-drug polytherapy have the highest risk of becoming long-term users."

  Wingård, L., Taipale, H., Reutfors, J., Westerlund, A., Bodén, R., Tiihonen, J., Tanskanen, A., and Andersen, M. (2018) Initiation and long-term use of benzodiazepines and Z-drugs in bipolar disorder. Bipolar Disord. 20(7):634-646. doi: 10.1111/bdi.12626. Epub 2018 Feb 16.

OCD

- BZDs failed several RCTs and is not recommended especially if extinction/exposure therapy is being used.

  Hollander, E., Kaplan, A, Stahl SM. (2013) A double-blind, placebo-controlled trial of clonazepam in obsessive-compulsive disorder. World J Biol Psychiatry. 24(1):30-34.

  Crockett, B., and Churchill, E., and Davidson, J. (2004) A double-blind combination study of clonazepam and sertraline in OCD. Ann Clin Psychiatry. 16(3):127-132.

Borderline Personality disorder

- This group of often constantly suicidal, self harming, rapidly changing severe mood and risk taking patients are more likely to do the most dangerous behaviors or dysregulate if given a benzodiazepine.

Gardner, D., Cowdry, R. (1985) Alprazolam-induced dyscontrol in borderline personality disorder. Am J Psychiatry. 142(1):98-100.

Lekka, N., Paschalis, C., Beratis, S. (2002) Suicide attempts in high-dose benzodiazepine users. Comprehensive Psychiatry. 43,(6), 438-442. https://doi.org/10.1053/comp.2002.35912

Generalized Anxiety Disorder

- Meta-analysis of alprazolam, lorazepam, diazepam did not find that it was effective for even short term treatment.
- Most positive studies have at best mixed results, high potentially bias, or a failure to compare to first line treatment like SSRIs.

Martin, J. Sainz-Pardo, M., Furukawa, T et al (2007) Review: Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials. https://doi.org/10.1177/0269881107077355

Panic Disorder

- Recent Cochrane analysis in March 2019 says "Low-quality evidence shows a possible superiority of benzodiazepine over placebo in the short-term treatment of panic disorders. The validity of the included studies is questionable due to possible unmasking of allocated treatments, high dropout rates, and probable publication bias. Moreover, the included studies were only short-term studies and did not examine the long-term efficacy nor the risks of dependency and withdrawal symptoms." Breilmann, J., Girlanda, F., Guaiana, G., Barbui, C., Cipriani, A., Castellazzi, M., Bighelli, I., Davies, S., Furukawa, T., and Koesters, M. (2019) Benzodiazepines versus placebo for panic disorder in adults. Cochrane Database Syst Rev. 2019 Mar 28;3:CD010677. doi: 10.1002/14651858.CD010677.pub2.
- It worsens therapy outcomes which is the first line therapy.

  Spiegel, D., and Bruce, T. (1997) Benzodiazepines and Exposure-Based Cognitive Behavior Therapies for Panic Disorder: Conclusions from Combined Treatment Trials. Am J Psychiatry; 154: 773-781.
- In one 8 week study it did not help time to response but it did help with some early symptoms and patients reported feeling better.

  Katzelnick, D., Saidi J, Vanelli, M., Jefferson, J., Harper, J., and McCrary, K. (2006) Time to response in panic disorder in a naturalistic setting: combination therapy with alprazolam orally disintegrating tablets and serotonin reuptake inhibitors compared to serotonin reuptake inhibitors alone. Psychiatry (Edgmont). Dec;3(12):39-49.

Social Anxiety Disorder

- Clonazepam did better than placebo in monotherapy while causing some persistent dizziness in some. The best study was a 75 patients for 10 weeks the others had < 30 patients. All studies were vs placebo.

  Davidson, J., Potts, N., Richichi, E., et al. (1993) Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol.13:423-8.
- In the only published placebo- controlled study of alprazolam for SAD, only 38% of patients were considered responders, which did not differ significantly from the response rate with placebo, and symptoms had returned 2 months after discontinuation of alprazolam.

  Blanco, C., Bragdon, L., Schneier, F. and Liebowitz, M. (2013) Some patients have worsening social phobia on these meds as mentioned above. The evidence-based pharmacotherapy of social anxiety disorder. International Journal of Neuropsychopharmacology, 16, 235–249. f CINP 2012 doi:10.1017/S1461145712000119
- In a large controlled study where patients who did not respond to sertraline were augmented with placebo or augmented with clonazepam patients did not show statistical level of improvement with either. The best response was to give the sertraline more time. Pollack, M., Van Ameringen, M., Simon, M., Worthington, J., Hoge, E. (2014)https://doi.org/10.1176/appi.ajp.2013.12101353

Prescribing Guidelines

- Almost all guidelines including for benzodiazepines recommend that if you rx a benzodiazepine that it would be for 2-8 weeks
- UK guidelines indicates that more than 2 weeks is unjustified.
- Long term use is defined by some as > 60 days to >6 months. Almost all guidelines strongly warn against use for this timeframe or longer.

Martin, J. Sainz-Pardo, M., Furukawa, T et al (2007) Review: Benzodiazepines in generalized anxiety disorder: heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials. https://doi.org/10.1177/0269881107077355

BZDs The Bad

BZDs Interfere with Therapy

- Especially anxiety disorders like panic disorder respond as first line to therapy.
- APA guidelines for treatment of Panic Disorder: “One large randomized controlled trial showed that although adding alprazolam to exposure therapy marginally enhanced gains during acute treatment, patients who received the combination relapsed more after treatment withdrawal compared to those who received exposure plus placebo. Another small study showed that patients taking benzodiazepines had poorer memory for the educational material presented in CBT than patients who were taking no medications.”.

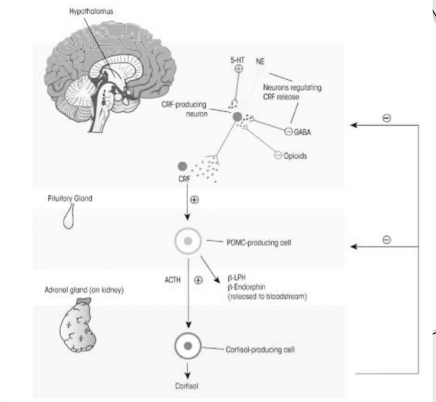
PRACTICE GUIDELINE FOR THE Treatment of Patients With Panic Disorder https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf

Worsening Mood symptoms

- Impairs the grief response. One study even showed that diazepam worsened sleep in grief.

Byrne, G., and Raphael, B. (1994) A longitudinal study of bereavement phenomena in recently widowed elderly men. *Psychol Med.* 24:411–421

- Throwing off the HPA axis. These drugs long term may increase anxiety/withdrawal like sxs.
- As mentioned above may worsen depression.



Post Acute Withdrawal and Rebound Anxiety

- This state can lead to month or months of:
  - Irritability
  - Decreased Sleep
  - Distractibility (decreased cognition)
  - Anxiety and anxious psychomotor agitation
  - Increased goal directed activity (going out late looking for drugs)
  - Increased risk taking related to trying to "feel again" and impaired judgment/cognition related to post drug dysphoria.
  - Muscle tension
  - HTN
  - The opposite of any good benefits you got from the drug
  - Rarely: hallucinations

Disinhibition

- For some benzodiazepines disinhibit causing increased risk taking, dangerous behaviors, or lack of control over impulsiveness.
- 76% of overdose patients had a benzodiazepine prescription

Carol, P. (2002) Benzodiazepines and disinhibition: a review. Psychiatric Bulletin, Volume 26, Issue 12, pp. 460-462. https://doi.org/10.1192/pb.26.12.460

Kripke, D. (2018) Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. Version 3. F1000Res. 2016; 5: 918. doi: 10.12688/f1000research.8729.3

1/3 of intentional ODs and Suicide Attempts Involve a Benzodiazepine and It is More Lethal in OD Than Most Psychotropics. Why give to people at high risk… ie anxious and depressed?

Ait-Daoud, N., Hamby, A., Sharma, S., and Blevins, D. (2018) A Review of Alprazolam Use, Misuse, and Withdrawal. J Addict Med. 12(1):4–10. doi: 10.1097/ADM.0000000000000350

Cognitive Side Effects

- Long term memory especial verbal memory can become impaired even at standard therapeutic dosing. Results in cognitive tests improved but were still poor 6 months after stopping use.

Curran H. Tranquillising memories: a review of the effects of benzodiazepines on human memory. Biol Psychol. 1986;23:179–213. 6. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs. 2004;18:37–48. [PubMed] [Google Scholar]

Respiration Risk

- Among individuals with chronic obstructive pulmonary disease (COPD), adverse effects is estimated 30%.
- Benzodiazepine administration has been shown to depress central respiratory drive and chemoreceptor responsiveness to hypercapnea Rudolf, M., Geddes, D., Turner, J., Saunders, K. (1978). Depression of central respiratory drive by nitrazepam. Thorax 33(1):97-100; Beaupre, A., Soucy, R., Phillips, R., Bourjouin, J. (1988) Respiratory center output following zopiclone or diazepam administration in patients with pulmonary disease. Respiration;54(4):235-40 .
- Benzodiazepines also decrease arousability from sleep which may prolong the duration of hypoventilation or contribute to aspiration. Berry, R., McCasland, C., Light, R. (1992) The effect of triazolam on the arousal response to airway occlusion during sleep in normal subjects. Am J Respir Crit Care Med;146(5):1256-60.
- BZDs drugs have been shown to decrease inspiratory and expiratory respiratory muscle strength. Jolly, E., Aguirre, L., Jorge, E., Luna, C. (1996) Efecto agudo del lorazepam sobre los musculos respiratorios en los pacientes con EPOC estable. [Acute effect of lorazepam on respiratory muscles in stable patients with chronic obstructive pulmonary disease]. Medicina (B Aires) 56(5):472-8
- BZDs have been reported to exert effects on the lower esophageal sphincter. They decrease lower esophageal sphincter pressure. Rushnak, M., Leevy, C. (1980) Effect of diazepam on the lower esophageal sphincter. A double-blind controlled study. Am J Gastroenterol;73(2):127-30
- Benzodiazepines have been reported to provoke intracellular acidosis in alveolar macrophages, leading to impaired cytokine production and bacterial phagocytosis. This leads to increased deaths from Pneumonia. Sanders, R., Godlee, A., Fujimori, T., et al. (2013) Benzodiazepine augmented γ-amino-butyric acid signaling increases mortality from pneumonia in mice. Crit Care Med;41(7):1627-36.
- Peripheral Gaba receptors can lead to aspiration and GERD sxs. Akinci, M., Schofield, P. (1999) Widespread expression of GABAA receptor subunits in peripheral tissues. Neurosci Res. 35(2):145-53

Motor Vehicle Accidents

- BZDS may double rate of involvement in fatal accidents

Rudisill, T., Zhao, S., Abate, M., Coben, J., Zhu M. (2014) Trends in drug use among drivers killed in US traffic crashes, 1999–2010. Accid Anal Prev.70:178–187. doi: 10.1016/j.aap.2014.04.003.

Reaction Time

- Even for a short term use which doesn't always resolve if you stop, reaction times were significantly worse if patients were taking more than 2.5 mg of lorazepam, 10 mg of diazepam, 1 mg of alprazolam or equivalent.

Manthey, L., van Loenen-Frösch,F., Giltay, E., van Veen,T., Glashouwer, K., Penninx,B., and Zitman, G. (2014) High dose benzodiazepines prolong reaction times in chronic users who have major depressive and/or anxiety disorders. Br J Clin Pharmacol. 77(3): 571–577.

Geriatrics Risk

- On the BEERs list of medications not to be used with caution in Geriatrics.
- There may be only one in thirty studies that showed it helped with anxiety in geriatrics. That was of oxazepam for 4 weeks. Only 1 of 5 studies showed it helped with behavioral issues in dementia. Gerlach, L., Wiechers, I., Maust, D. (2018) Prescription Benzodiazepine Use Among Older Adults: A Critical Review. Harv Rev Psychiatry. 26(5):264-273. doi: 10.1097/HRP.0000000000000190.
- Falls can increase sometimes as much as 50% on benzodiazepines especially long acting e.g diazepam. Ray, W., Griffin, M., Schaffner, W., Baugh DK, and Melton, L. (1987) Psychotropic drug use and the risk of hip fracture. N Engl J Med. 316:363–369.

Cancer Risk in Long Term use?

- A longitudinal case controlled study of >42,000 cases showed:
  - Clonazepam (HR, 1.15; 95%CI, 1.09-1.22) were associated with a higher risk for cancers.
  - Moreover, specific cancer risk among BZDs use was observed significantly increased 98% for brain, 25% for colorectal, and 10% for lung, as compared with non-BZDs use.
  - Diazepam, chlordiazepoxide, medazepam, nitrazepam, and oxazepam are safe among BZDs use for cancer risk."
  - This is correlational data that has been questioned but not completely dismissed.

Iqbal, U., Nguyen, P., Syed-Abdul, S., Yang, H., Huang, C., Jian, W., Hsu, M., Yen, Y., Li, Y. (2015) Is long-term use of benzodiazepine a risk for cancer? Medicine (Baltimore). 94(6):e483. doi: 10.1097/MD.0000000000000483.

Rebound Insomnia

- When stopping a benzodiazepine it can impair sleep significantly for days to weeks afterward.

Soldatos, C., Dikeos, D., and Whitehead, A. (1999) Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies. Int Clin Psychopharmacol. 14:287–303.

Risk in Pregnancy

- Clear risk of miscarriage almost doubling the risk (from 6 % at placebo to 10-11%). Less risk with antipsychotics.
- It is known to impact fetal development in animals.
- Worse risk is in the first trimesters.
- Women taking this medication need to be on birth control or warned not to start a family until d/ced.

Source Reference: Sheehy O, et al "Association between incident exposure to benzodiazepines in early pregnancy and risk of spontaneous abortion" JAMA Psychiatry; DOI: 10.1001/jamapsychiatry.2019.0963.

Risk of Addiction

- It can develop from 1-2 weeks of use including at least moderate withdrawal symptoms especially lipophilic and rapidly on-setting versions like Xanax.
- 17.1% of benzodiazepine users misused their meds. NICE guidelines say the abuse rate could be as high as 30 %. Contrast this with the 21-29 % of opioid misuser in chronic pain. Or contrast that with the abuse rates of Alcohol at 6-8% .

Vowles, K., McEntee, M., Julnes, P., Frohe, T., Ney, J., van der Goes, D. (2015) Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 156(4):569-576. doi:10.1097/01.j.pain.0000460357.01998.f1. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics.
National Institute for Clinical Excellence. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. www.nice.org.uk/guidance/ta77. (last accessed 10 May 2018).

High Potency/ Rapid onset Most Risk

- Xanax in particular but diazepam has a similar onset and potency.
- Rapid powerful responses hits the reward seeking pathway uniquely.
- But oddly the exception to the rule is Clonazepam has a unique amount of abuse potential that continues to baffle.

Salzman C. (1991) The APA Task Force report on benzodiazepine dependence, toxicity, and abuse. Am J Psychiatry. 148(2):151-152.

Alprazolam

- The number one most prescribed psychotropic drug.
- The second most common drug involved in ED visits related to drug misuse.
- More toxic in overdose.
- Even following manufacturers guidelines to taper it often leads to severe withdrawal symptoms even with use lasting days to weeks.
- Withdrawal can be worse including more cases of delirium and psychosis.
- Rebound anxiety is uniquely higher than other benzodiazepines. 27% of patients in one study had rebound anxiety that was worse than pretreatment panic symptoms. 35% had new somatic symptoms.
- Dr. Allen Francis the chair of the DSM IV writes in his book “Saving Normal.” “There is no clinical purpose for this drug [Xanax]… and it often does more harm than good.”
- Make this a Schedule II drug?

Ait-Daoud, N, Hamby, A., Sharma, S., and Blevins, D. (2018) A Review of Alprazolam Use, Misuse, and Withdrawal. J Addict Med. 12(1): 4–10. doi: 10.1097/ADM.0000000000000350

The Rate of Rxing These Meds is up but not by Psych Providers

- Prescribing has doubled among primary care providers who now make up > 52% of all prescriptions.
- Psychiatric prescribers only make up 30% of prescriptions.
- Primary care also quadrupled the amount of benzodiazepine and opioids prescribed together despite black box warning.

Agarwal, S., and Landon, B. (2019) Patterns in Outpatient Benzodiazepine Prescribing in the United States. JAMA Netw Open. 2(1):e187399. doi: 10.1001/jamanetworkopen.2018.7399.

New Prescription Epidemic?

- NPR- “America’s Other Prescription Drug Problem” Apr 2018 *https://www.npr.org/.../benzodiazepines-america-s-other-prescription-drug-problem*
- NBC News –”Dangers of rising benzo prescriptions raise alarms of next drug crisis”July 2018 *https://www.nbcnews.com/.../dangers-rising-benzo-prescriptions-raise-alarms-next-dru...*
- Washington Post- The prescription drug epidemic no one's talking about Jan 2019 *https://www.washingtonpost.com/.../prescription-drug-epidemic-no-ones-talking-about/*
- Psych Congress- Are Benzodiazepines the Next Opioid Crisis? *https://www.psychcongress.com/article/are-benzodiazepines-next-opioid-crisis*
- MD Who Wrote About Opioid Epidemic says BZDs next opioids *https://www.statnews.com/2018/02/22/benzodiazepines-drug-epidemic/comment-page-1/*
- Even Dr. Drew (So it must be true)- https://www.youtube.com/watch?v=0WIn9V1mIGQ.

Even if There is No Epidemic

From An Actual Lawyer's Page

Possible Medical Negligence

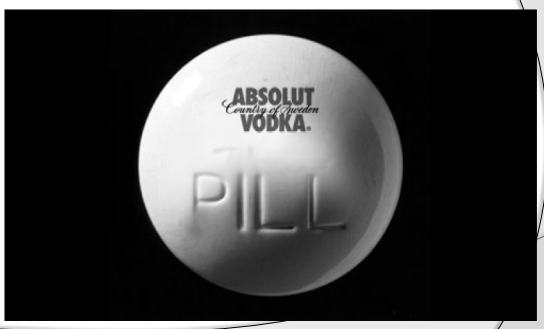
The issue of medical negligence associated with benzo use most commonly come up in the context of withdrawal and overdose. In the case of withdrawal, a medical provider that fails to properly account for the dangers of withdrawal from benzos with resulting serious injury or death is almost by definition guilty of medical malpractice.

The same would hold true for doctors that prescribe benzos to patients known (or who the medical provider should have known) were likely to use the drugs in combination with alcohol or other dangerous drug combinations. Remarkably, there are mental health professionals who prescribe benzos knowing full well that their patient has alcohol and/or drug addiction issues. In fact, it may be that the patient is being treated for those very issues when he or she is prescribed benzos. Without proper precautions to protect the patient, this is inexcusable.

Have a Drink

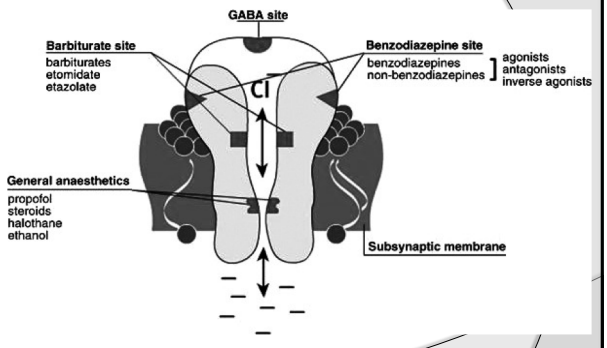
It Works for Anxiety But Would You Prescribe it?

BZD = Alcohol in Pill Form



- "Studies of genetic differences in sensitivity to sedative drugs and development of tolerance and cross-tolerance between these drugs indicate that actions of ethanol are similar (but not identical) to those of benzodiazepines."

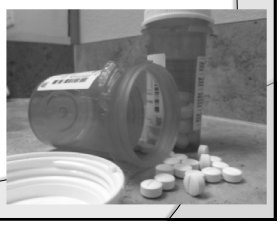
Harris, R. (1990) Distinct actions of alcohols, barbiturates and benzodiazepines on GABA-activated chloride channels. Alcohol. 7(3):273-5.



Mechanism of Action is the Same in Benzodiazepines and Alcohol

- The safety profile may be just a little better for benzodiazepines.
- This is why benzodiazepines tapers are used to detox alcohol withdrawal, something that alcohol was used for in the past.
- A drink definitely helps acute anxiety for some.
- Would you prescribe a drink? Is it good evidence based treatment?

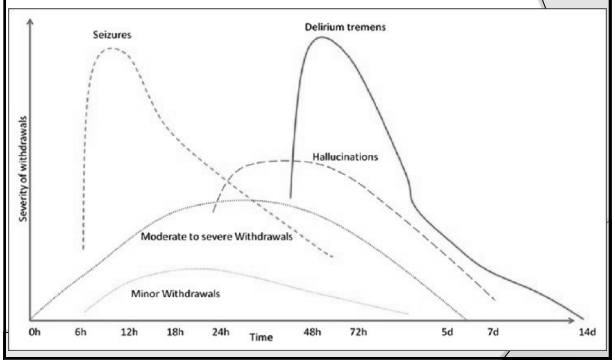
"I transferred to your care from Dr. Prescribes-a-lot so I am on 6 mg of Xanax a day. I need you to fill it or I'll go into withdrawal/commit suicide/not be able to function."



You are not liable for the poor prescribing of another provider. There is considerable risk for you to continue another providers high risk medication.

1. If treatment has been longer than 6-8 weeks and they have had or are at risk for an adverse reaction (car wreck, OD, fall, pneumonia, complications of PTSD/COPD, become dependent) you are liable and do not have much justification. You continued the rx past what most literature and guidelines recommend.
2. Not filling an antidepressant, antipsychotic, or mood stabilizer may be questionable but not continuing a third line treatment that you are unsure is necessary is not malpractice.
3. Also just like obtaining a patient on Clozaril, high dose mood stabilizers, etc you can always say you don't have the expertise to handle such a patient. After two weeks of benzodiazepines you are well within your right as a non-psych prescriber to say you are out of your depth.

Know Withdrawal



Benzodiazepine Withdrawal

- Life threatening withdrawal happens for most benzodiazepines 6-12 hours after significant reduction in blood level but obviously this can be slightly longer with benzodiazepines with longer half-life.
- After 72 hrs from the initiation of withdrawal most life threatening symptoms are past depending on half life.
- If someone comes to you off benzodiazepines for 5-7 days without severe symptoms there is almost no risk of life threatening symptoms. Outside of this window for withdrawal there is serious harm to stop these medications.

What About in the Window of Withdrawal or Your Lack of RX Will put them There?

- Refer to the ER. BZD withdrawal is an emergency condition. Autonomic instability and seizures are the most likely negative outcome.
- You must teach the symptoms of withdrawal and when to go to the ER, but you must do this with all BZDs patients.
- The above is the extent of your obligation, unless you prescribed the medication.

Doing More: To Taper or Not to Taper

- Shouldn't a taper be given?
  - If you do you are responsible for the patient, side effects, and withdrawal make sure you have the resources or educate about when to go to the ER..
  - It is considerable risk to give a taper for someone on high dose benzodiazepine and most likely there are issues (medical and psychiatric) that hospitalization may help. 6 mg of Xanax is not a routine PCP visit.
  - You can instruct them on a taper of what they have left which helps use up, reduce the harms overall.
- Give an Anticonvulsant. This can prevent the most worrisome side effects. Then instruct to go to the ER with symptoms.
  - There is evidence that Carbmazapine, Depakote and gabapentin can help prevent the most serious symptoms of withdrawal. They are not substitutes for proper withdrawal treatment however. Myrick, H., Malcolm, R., Randall, P., Boyle, E., Anton, R., Becker, H., and Randall, C. (2009) A double-blind trial of gabapentin versus lorazepam in the treatment of alcohol withdrawal. Alcohol Clin Exp Res. 33(9):1582-8. doi: 10.1111/j.1530-0277.2009.00986.x.
  - Gabapentin also has indications in anxiety which may help with post acute withdrawal increase activation and anxiety and potentially the underlying anxiety. Berlin, R., Butler, P., and Perloff, M. (2015) Gabapentin Therapy in Psychiatric Disorders: A Systematic Review. Prim Care Companion CNS Disord. 17(5): 10.4088/PCC.15r01821.
  - Pregabalin has evidence in most of the anxiety disorders and withdrawal but does still have a abuse potential

Before Benzodiazepines Consider Alternatives

- Gabapentin
- Pregabalin
- Hydroxyzine
- Quetiapine
- Propranolol

Pregabalin

- Head to head comparison of benzodiazepine (either Ativan 6 mg or alprazolam 1.5 mg) vs Pregabalin 300 mg or >150 mg. Pregabalin was superior to benzodiazepine.
  - Benzodiazepines reduced 5 of 14 Hamilton Anxiety scale ratings items
  - Pregabalin 300 mg but greater than 150 mg reduced 13 of 14. Doses higher than 300 mg had less effect. Lydiard, R., Rickels, K., Herman, B., and Feltner, D. (2010) Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. Int J Neuropsychopharmacol. 13(2):229-41. doi: 10.1017/S1461145709990460.
- It can also help with neuropathic pain.
- It does still have some abuse potential but not as much as benzodiazepine and its general side effect profile is less.
- It is a first line option in Canadian guidelines https://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-14-S1-S1

Quetiapine

- Quetiapine- Actually the most effective for treating in reviews for severe anxiety symptoms but obviously comes with sedation, weight gain and more. Bandelow, B., Michaelis, S., Wedekind, D. (2017) Treatment of anxiety disorders. Clin Neurosci. 19(2):93-107
- Dose at 25 mg ½ to 1 po TID prn anxiety
- Quetiapine 50 mg- 300 mg up titrate by 50 mg every 1-2 nights to ideal dose. 200 mg or less is more sleepy than 300 mg.
- For most patients getting proper therapy this can usually be a short term treatment of 1 month and usually less than a year. Typically 3-6 months.

Gabapentin

- It has evidence in anxiety, withdrawal, and cravings in alcohol use. Pande, A., Davidson, J., Jefferson, J., Janney, C., Katzelnick, D., Weisler, R., Greist, J., Sutherland, S. (1999) Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol. 19: 341-348.
- It has a similar pathway to pregabalin with significantly less side effects and abuse potential.
- It can be used in treatment of PTSD and exposure therapies.
- It is used as second line in Canadian guidelines. https://bmcpsychiatry.biomedcentral.com/articles/10.1186/1471-244X-14-S1-S1
- Gabapentin 100-900 mg one po up to TID prn anxiety

Hydroxyzine HCL or PAM

- In head to head comparison with Librium it was just as effective. Guaiana, G. et al. Cochrane Database Syst Rev. (2010) Hydroxyzine for generalised anxiety disorder. (12):CD006815. doi: 10.1002/14651858.CD006815.pub2.
- It is very effective for many and side effects are very minimal. There is almost no dependency are rare sedation and dry mouth most common side effect
- Usual dosing 25-100 mg one to three times a day

Propranolol

- One meta- analysis reported "More specifically, our meta-analyses found no statistical difference between the effects of propranolol and benzodiazepines on anxiety and panic attack frequency."

Steenen,S., van Wijk, A., van der Heijden, G., van Westrhenen,R., de Lange,J, and de Jongh, AD. (2016) Propranolol for the treatment of anxiety disorders: Systematic review and meta-analysis. J Psychopharmacol. 30(2): 128–139. doi: 10.1177/0269881115612236

- Usually dosed: Propranolol 20- 60 mg BID anxiety

Other Anxiety Treatments

- First Line-
  - SSRI and SNRI
  - Therapy
- Buspirone

Prescribing BZDs- Consideration

- Long Acting VS Short Acting
  - Long acting
    - More likely to provide continual anxiety relief
    - Less likely in general to develop dependence or counter therapeutic use pattern ("I feel bad I pop pill").
    - Easier to titrate. Constant level slowly leaving the system which decreases chances of withdrawal even the milder post acute withdrawal.
    - Significantly more likely to develop cognitive side effects
    - Much higher risk of falls, impaired driving.
    - Easy to get higher levels as drug accumulates before it is fully eliminated. E.g. If half life is > 12 hrs and it is dosed daily then each day there is more drug in the system.
  - Short acting
    - Often is fast acting.
    - Is more rapidly eliminated so less likely to be impaired hours later.
    - Less cognitive side effects in the long term.
    - More likely to have rebound anxiety
    - More likely to cause euphoria or the instant relief that can lead to dependence.
    - Withdrawal symptoms much faster to come on when medication is stopped.
- How Lipophillic
  - The more lipophilic the quicker it hits the brain producing slightly faster relief and much more likely to produce euphoria and dependence

Prescribing BZDs: My Top Two Choices- Low Lipiphilia

- Oxazepam- Short acting but it has theoretically less abuse potential due to slow absorption and being lipiphilic. It is also safer in frail patients and safe with hepatically impaired patients.

Lilea, J., Stoops, W., Wagner, F., Glaser, P., Rush, C. (2005) Oxazepam does not modulate the behavioral effects of d-amphetamine in humans. Pharmacology Biochemistry and Behavior. 82(2): 270- 279.

- Librium – Also slowly absorbed/ less lipiphilic but longer acting. It has a huge half-life (100 hrs) and therefore is almost self tapering as it slowly leaves the system creating few peaks and troughs. A few doses can create an easy safe taper. However, it can build up in the system leading to total drug present being elevated. It also gives the brain little break from being effected by the drug.

Benzodiazepine Equivalency

Approximately Equivalent Oral Doses, mg		Time to Peak Level, hours	Half-life, hours
Alprazolam (Xanax)	0.5–1	1-2	12
Chlordiazepoxide (Librium)	10–25	1-4	100
Clonazepam (Klonopin)	0.25–0.5	1-4	34
Diazepam (Valium)	5–10	1-2	100
Lorazepam (Ativan)	1–2	1-4	15
Oxazepam (Serax)	15–30	1-4	8
Temazepam (Restoril)	10–20	2-3	11
Triazolam (Halcion)	0.25–0.5	1-2	2

https://emedicine.medscape.com/article/2172250-overview

A Proper and Recommended Taper

- Convert current BZD to Librium (earliest and one of the most established detox BZDS) or oxazepam (if liver compromised or for short acting).
- Reduce dose by 10 % or 12.5 mg of Librium per week until 2/3 rds or 3/4 ths complete with taper then slow down to potentially to 10% or 12.5 mg of librium every 10 -11 days.
- Example: pt using Xanax 4 mg/day. (This may require inpatient to start) Librium 25 mg TID with a 12.5 mg dose mid-day x7 days then 25 mg TID x 7 days then BID with a 12.5 mg dose mid-day x 7 days then BID x7 days then 12.5 mg qAM and 25 mg qhs x 10 days then 25 mg x 10 days then 12.5 mg x 10 day. Whew! 2 months later safely weened.
- This is an over-simplification. Individual patients need individual treatment. What if they have break through symptoms?
- You must weigh pro-cons with your patient. I personally do not know many providers who trust their benzo overusing patients to follow these instructions.

If You are Going to Initiate BZD Treatment: Pearls

- Give two weeks at a time when possible.
- Give low dose to start. (e.g. Librium 10-25 mg one a day or oxazepam 15 mg 1-2 po BID prn anxiety.)
- Give Librium or oxazepam to limit abuse potential.
- Rule out and note in chart contraindications mentioned above (respiratory problems, PTSD, Borderline PD, most mental health disorders etc)

Benzodiazepines: Conclusion

- Efficacy:
  - 1st line treatment in physical and psychiatric conditions:
    - Acute Seizure control
    - Catatonia (lorazepam only)
    - Alcohol/BZD acute withdrawal in the first 72 hrs to 7 days
    - Acute Immediately Dangerous Agitation (treatment not last more than a few days)
  - 3rd Line chronic Seizures
  - 3rd Line for the below anxiety disorders after failures of or greater risk in starting usually safer alternatives (hydroxyzine, gabapentin, pregabalin, quetiapine) for 2 weeks NTE 8 weeks while antidepressant and therapy is being started or changed. Must rule out PTSD, Borderline PD, bipolar, schizophrenia or contraindicated medical conditions (e.g. respiratory problems, fall risk, high risk with potential worsening cognition):
    - Social Anxiety disorder (clonazepam only proven)
    - Treatment resistant panic disorder while patient is not in Exposure Therapy
    - Treatment resistant anxious depression in patients who treatment adherence is a greater concern than risk of increased depression/anhedonia.
    - Treatment resistant generalized anxiety disorder

Benzodiazepine: Conclusion

- Risk to Patients
  - Increase risk of impaired driving even at normal therapeutic doses.
  - Increase risk of respiratory compromise especially in at risk populations.
  - Increase risk of falls especially in at risk populations.
  - Impaired cognition that may be long term.
  - Worsening or increase risk of negative outcomes almost all mental health disorders.
    - Increase risk of depression/anhedonia
    - Increased risk of negative behaviors/impulsivity
    - Increased risk of hospitalizations in some disorders
    - Increased risk of self harm in some disorders
  - Sedation
  - Risk of disinhibition
  - Potential for rebound anxiety after treatment
  - Risk of withdrawal and post acute withdrawal which can be life threatening or worse than original disorder.
  - May make first line treatments like therapy less effective.
  - Risk of addiction
  - Potential cancer risk?

Benzodiazepines: Conclusion

- Risk to Provider- Provides Multiple Liability Risks:
  - Provides significant risk for patient death (e.g. respiratory, falls, crashes, risk taking behaviors) in at risk populations even at therapeutic levels
  - Lethal in OD or misuse
  - Can lead to permanent impairment (e.g. cognitive)
  - Can lead to risk of addiction
  - Current high publicity about misuse
  - Current attention by lawyers

Benzodiazepine Receptor Antagonist

Benzodiazepine receptor antagonists

- MOA: act as positive modulators of the effects of GABA agonists on the GABA a receptor. They work on selective alpha and beta subunits of the receptor. The net is a more selective for sedation with less amnesiac, anxiolytic, and less tolerance in general.
- Drugs in the class are zolpidem, zopiclone, eszopiclone, and zalephon

Ries, R.,Fiellin, D.,Miller, S.,Saitz, R. The ASAM Principles of Addiction Medicine (p. 124). LWW. Kindle Edition.

Zolpidem

- Comes in short acting dosed at 5- 10 mg. Rarely effective or justified over 10 mg.
- CR version 6.25-12.5 mg.
- Particularly in Zolpidem, women do not metabolize the drug the same and have higher plasma levels.

Roehrs, T., and Roth, T. (2016) Gender Differences in the Efficacy and Safety of Chronic Nightly Zolpidem. J Clin Sleep Med. 12(3):319-25. doi: 10.5664/jcsm.5574.

Eszopiclone

- 1-3 mg one po qhs
- Longer acting to keep a patient asleep
- Significant potential for an odd metal taste in mouth on awakening.

Zalephon

- 5- 10 mg one po qhs
- Has least side effects in some studies as low as placebo
- Some studies did not show robust response for 5 mg.
- Good for initiating sleep and less likely to cause daytime impairment even when given during middle waking.
- Newest approved drug so not many studies or longer term evaluation.

Common Side Effects

- Amnesia
- Dizziness,
- Sedation
- Headache
- Nausea
- Taste perversion (worst with eszopiclone).

Sateia, M., Buysse, D., Krystal, A., Neubauer, D., and Heald, J. (2017) Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 13(2): 307–349.

Warning!

- Biased studies: When studies the Z drugs literature is full of biased and poorly run studies.
- AASM Review downgraded zolpidem and eszopiclone due mainly to this.
- Be careful of positive studies.

Sateia, M., Buysse, D., Krystal, A., Neubauer, D., and Heald, J. (2017) Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 13(2): 307–349.

Zolpidem: How Much Better?

- Some studies showed a subjective change of only 7 minutes earlier onset of sleep compared to placebo. It was 22 minutes measured polysomnography.
- In Quality of life measures did not significantly differ (-36) compared to placebo (-33)

Huedo-Medina, T., Kirsch, I., Middlemass, J., Klonizakis, M., Niroshan Siriwardena, A. (2012) Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration
BMJ 345 doi: https://doi.org/10.1136/bmj.e8343

Quality of evidence

- "Because sponsorship bias is in the direction of greater effects for industry sponsored trials, our results might overestimate the effects of Z drug hypnotics for treating adult insomnia."

Huedo-Medina, T., Kirsch, I., Middlemass, J., Klonizakis, M., Niroshan Siriwardena, A. (2012) Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration

BMJ 345 doi: https://doi.org/10.1136/bmj.e8343

Eszopiclone: How Much Better?

- Meta-analytic integrations of participant-reported data on sleep efficacy outcomes demonstrated better results for eszopiclone compared to placebo: a 12-minute decrease of sleep onset latency (mean difference (MD) -11.94 min, 95% confidence interval (CI) -16.03 to -7.86; 9 studies, 2890 participants, moderate quality evidence), a 17-minute decrease of wake time after sleep onset (MD -17.02 min, 95% CI -24.89 to -9.15; 8 studies, 2295 participants, moderate quality evidence) and a 28-minute increase of total sleep time (MD 27.70 min, 95% CI 20.30 to 35.09; 10 studies, 2965 participants, moderate quality evidence).

Huedo-Medina, T., Kirsch, I., Middlemass, J., Klonizakis, M., Niroshan Siriwardena, A. (2012) Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration BMJ 345 doi: https://doi.org/10.1136/bmj.e8343

Zalephon: How Much Better?

- 9.5 min reduction in mean sleep latency versus placebo
- 21.5 min of total sleep time

Sateia, M., Buysse, D., Krystal, A., Neubauer, D., and Heald, J. (2017) Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 13(2): 307–349.

Effectiveness Compared

- Zolpidem is often thought to have better efficacy but:
  - Six RCTs compared zaleplon with zolpidem. One RCT found that 10 mg zaleplon per night resulted in statistically significant shorter sleep onset latency than 5 mg zolpidem (median time 31 minutes versus 42 minutes). National Institute for Clinical Excellence. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. www.nice.org.uk/guidance/ta77. (last accessed 2 December 2014)

Head to Head with BZDs for Sleep

- No statistical difference in effectiveness between BZDs and Z- drugs.
  - National Institute for Clinical Excellence. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. www.nice.org.uk/guidance/ta77. (last accessed 2 December 2014)

Duration of Use

- The labels of all these medications indicate that use is for days to two weeks with a maximal of 4 weeks including taper.
  - National Institute for Clinical Excellence. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. www.nice.org.uk/guidance/ta77. (last accessed 2 December 2014)

Guidelines for Chronic Use

- The best guidelines say there is only weak evidence of chronic use of any medication for sleep. CBT-I is has the best evidence according to the American College of Physicians and American Academy of Sleep Medicine.
- The Z-drugs are on par with suvorexant, ramelteon, doxepin, which may have less SEs.

Sateia, M., Buysse, D., Krystal, A., Neubauer, D., and Heald, J. (2017) Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 13(2): 307–349.

Z-Drug Complex Sleep Behaviors, Some Lethal

- The FDA reviewed 20 reported deaths related to these drugs; causes included carbon monoxide poisoning, drowning, falls, hypothermia, car accidents with the patient driving, and apparent suicide. Additionally, the agency reviewed 46 reports of nonfatal injuries, including near-drowning, burns, falls, gunshot wounds, and apparent suicide attempts. Such behaviors were observed even when patients were taking the drugs for the first time and at the lowest doses. Zolpidem is the most likely to caus. https://www.jwatch.org/fw115371/2019/05/01/insomnia-drugs-get-boxed-warning-complex-sleep-behaviors?query=pfwTOC&jwd=000020099349&jspc=

Zolpidem in Overdose

- 25% of ODs with a benzodiazepine receptor agonist (BZD or z- drug) used zolpidem.

Kripke, D. (2018) Hypnotic drug risks of mortality, infection, depression, and cancer: but lack of benefit. Res. 5: 918. doi: 10.12688/f1000research.8729.3

Increased Depression?

- Data is mixed some studies saying yes, some, some saying no and some (particularly with escopiclone) say it improves mood. Kripke, D. (2007) Greater incidence of depression with hypnotic use than with placebo. BMC Psychiatry. 7: 42.

Rebound Insomnia

- There is clear evidence in sleep studies of physiological rebound insomnia stopping zolpidem. It was more mild than triazolam. Soldatos, C., Dikeos, D., Whitehead, A.. (1999) Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies. Int Clin Psychopharmacol.14:287–303.
- Three months of use usually lead to some withdrawal symptoms when taking 10 mg of zolpidem. Lemoine, P., Allain H, Janus C, and Sutet P. (1995) Gradual withdrawal of zopiclone (7.5 mg) and zolpidem (10 mg) in insomniacs treated for at least 3 months. Eur Psychiatry. 1995;10 Suppl 3:161s-5s. doi: 10.1016/0924-9338(96)80098-8.
- There is less rebound effect with eszopiclone. Rösner, S., Englbrecht, C., Wehrle, R., Hajak, G., and Soyka M. (2018)Eszopiclone for insomnia. Cochrane Database Syst Rev. 2018 Oct 10;10:CD010703. doi: 10.1002/14651858.CD010703.pub2.
- Zalephon also has little rebound insomnia Ebbens, M. and Verster, J. (2010) Clinical evaluation of zaleplon in the treatment of insomnia. Nat Sci Sleep.; 2: 115–126.

Z-Drugs Some Less to No Driving Impairment

- Studies on zaleplon in healthy subjects have not been shown to cause significant residual impairment leading to traffic accident risk with early or middle-of-the-night dosing.
- They are mixed on zolpidem with increased risk up to 50% to none detected. It is dose and time dependent (10 mg or greater taken < 8 hrs from waking highest risk.)

Brandt, J., and Leong, C. (2017) Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. Dec; 17(4): 493–507 doi: 10.1007/s40268-017-0207-7

Z –Drug- Falls

- Rates of Falls and Fractures are similar to benzodiazepines. Brandt, J., and Leong, C. (2017) Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. Drugs R D. Dec; 17(4): 493–507 doi: 10.1007/s40268-017-0207-7

Z Drug: Respiratory Problems

- Unclear if Z- drugs are better or worse but several studies of OSA showed significant less risk than benzodiazepines. Mason, M., Cates, C., and Smith, I. (2015) Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. Cochrane database Syst Rev.

Cognitive effects

- Results of several metanalyses showed a medium effect sizes for zolpidem on measures of verbal memory, attention, and smaller effects on speed of processing. There could be also some generalized negative cognitive effects.
- There is not enough data on eszopiclone and zalephon.

Stranks, E. and Crowe, S. (2014) The acute cognitive effects of zopiclone, zolpidem, zaleplon, and eszopiclone: A systematic review and meta-analysis. Journal of Clinical and Experimental Neuropsychology. (36) 7: 691-700.

Zolpidem May Worsen PTSD Nightmares/Memories

- Zolpidem worsened 28 veteran's nightmares and negative memories when compared to xyrem and placebo.

Mednick, S., McDevitt, E., Walsh, J., Wamsley, E., Paulus, M., Kanady, J., and Drummond, S. (2013) The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. J Neurosci. 6;33(10):4494-504. doi:10.1523/JNEUROSCI.3127-12.2013. PubMed PMID: 23467365

Dependence

- Zolpidem when compared with triazolam it did score similarly in drug liking, there is some rebound insomnia, some but less anxiety on withdrawal, and rare seizures. Tolerance, euphoria, and severe withdrawal symptoms are less. But head to head even with zopiclone there is significant abuse potential which has lead to increased restricted use in France. Rousselet, M., Feuillet, F., Gerardin, M., Jolliet, P., Hardouin, J., and Victorri-Vigneau, C. (2017) The French addictovigilance network clinical assessment: Z-drugs, true false twins. Expert Opin Drug Saf.;16(9):1063-1069. doi: 10.1080/14740338.2017.1346084..
- Zalephon was significantly less risk according to the Nice guidelines

Z-Drugs: Conclusion

- Efficacy:
  - 2nd line treatment in Sleep. It has less side effects than benzodiazepines and different risks from Seroquel, tricyclic antidepressants, and other sleep aids.

Z- Drugs: Conclusion

- Risk to Patients
  - Increase risk of impaired driving even at normal therapeutic doses with normal dosing (10 mg of Zolpidem) and potentially with others but less than BZDs.
  - Increase risk of falls especially in at risk populations.
  - Impaired cognition with Zolpidem that may be long term but unknown for the others.
  - Dangerous sleep behaviors have been identified even at low doses even on the first night or first several nights
  - Sedation
  - Risk of disinhibition though less than BZDs.
  - Risk of withdrawal which can be life threatening or worse than original disorder though less than BZDs
  - May increase trauma nightmares.
  - Potential risk of addiction/dependence with zolpidem though significantly less.

Z- Drug: Conclusion

- Risk to Provider- Provides multiple liability risks:
  - Provides significant risk especially with new black box warning about sleep behaviors
  - Lethal in OD or misuse
  - Can lead to permanent impairment (e.g. cognitive)
  - Can lead to risk of addiction
  - Current high publicity about misuse
  - Current attention by lawyers

Kratom

Kratom

- It is a combination of 25 alkaloids.
- At low doses it is a stimulant (like meth or Khat) at 1- 5 gm
- Otherwise at > 5 mg it has impact on opioid receptors Kappa, mu and delta and even has alpha 2 properties. These lead to sedation, pain relief, and most of the effects/SE of opioids.
- It does have anti-inflammatory effects.
- It has a short half-life which makes withdrawal sooner.

Most data pulled from Penders, T., and Stanciu, C. Kratom a Substance of Growing Concern. Presentation givenon Nov 28, 2018.

Reason for use

- 68% reported for pain and 65% for mood.
- There are no clinical trials supporting either. There are no trials period.

Kratom- SE

- In addition to classic stimulant symptoms at low doses and classic opioid sxs at high:
  - Skin hyperpigmentation
  - Hepatotoxicity
  - Insomnia
  - Weight loss
  - Impaired memory
  - Increase prolactin
  - Increased risk of seizures

Henningfield,, J., Fant, R., and Wang, D. (2018).The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology (Berl). 235(2): 573–589. doi: 10.1007/s00213-017-4813-4

LaBryer, L., Sharma, R., Chaudhari, K., Talsania, M., Scofield, R. (2018) Kratom, an Emerging Drug of Abuse, Raises Prolactin and Causes Secondary Hypogonadism: Case Report. J Investig Med High Impact Case Rep. doi: 10.1177/2324709618785022

Deaths and Poisoning

- There are increased calls for Kratom poisoning.
- Most actual deaths are due to adulterants or mixing with other drugs.
- Death rates are lower with this drug than opioids but it is uncertain why.
- There are at least 36 deaths related to Kratom alone.

Henningfield., J., Fant, R., and Wang, D. (2018) The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology (Berl). 235(2): 573–589. doi: 10.1007/s00213-017-4813-4

Dependence

- 55% of Kratom users appear to become dependent

Kratom: Conclusion

- Efficacy:
  - No Clinical Proven efficacy
  - Theoretically it can help with withdrawal and pain (but so could heroin)
  - Theoretically help with energy and create euphoria (but so can meth or cocaine)

Kratom: Conclusion

- Risk to Patients
  - Risk of overdose.
  - Risk of addiction potentially higher than opioids
  - Risk of stimulant like effects and opioid like effects.
  - Insomnia
  - Weight loss
  - Impaired memory
  - Increase prolactin (male breasts and lactation)
  - Increased risk of seizures

Kratom: Conclusion

- Risk to Provider- Provides multiple liability risks:
  - Soon to be controlled substance with unknown effects.
  - Little justification at this time to promote but definitely needs to be studied because it may be less dangerous than alternative. However, we just do not know if it has other side effects worse than other illicit drugs.