23 Detoxification Strategies

Ahmed Zaafran and Jennifer Kljajic

CONTENTS

INTRODUCTION

The late 1990s marked a turning point in America's crisis with opioid consumption. With a surge in opioid production by pharmaceutical companies, the medical community received reassurances from pharmaceutical companies that patients would not become addicted to opioid pain relievers. As a result, an increased prescription rate of opioids and other habit-forming medications played a major factor in the current opioid epidemic. The incidence of prescribed and non-prescribed opioid misuse increased prior to a clear understanding of the highly addictive nature of these medications. Despite efforts to thwart the current opioid epidemic in the United States, drug overdose deaths continue to increase.

From 1999 to 2017, almost 400,000 people died from an overdose involving any opioid, including prescription and illicit opioids.[1] In October of 2017, the U.S. Department of Health and Human Services (HHS) declared a public health emergency regarding the opioid crisis and initiated strategies to help tackle the many issues surrounding the epidemic.

Alongside the opioid crisis, another crisis that is gaining momentum involves benzodiazepines. According to the National Institute of Drug Abuse, more than 30% of opioid overdoses included benzodiazepines. A study published in the U.S. National Library of Medicine National Institute of Health suggests that benzodiazepine prescriptions increased by 67% between 1996 and 2013 and likely contributed to an increase in accidental dependence.[2]

Benzodiazepines, a central nervous system depressant, are often sought out alongside opioids due to similar mechanisms of action on the brain and body.

The current landscape includes two groups of individuals affected by the opioid and benzodiazepine crisis: those who are traditionally addicted, and those who are accidentally dependent.

TRADITIONAL ADDICTION

Traditional addiction, or substance use disorder, is the result of changes in the brain that result in a loss of control, compulsive use, intensive cravings, and continued use despite consequences. Individuals struggling with addiction have a hijacked and/or disabled dopamine reward system.[3] Lastly, they continue to use the drug despite negative consequences, such as poor health, and loss of relationships and/or employment. Those individuals are more at risk for overdose due to the synergistic effects of opioids and benzodiazepines. Furthermore, there are questions now as to whether some of the overdoses are actually intentional, due to the side effect of risk of suicide with benzodiazepines.[4]

ACCIDENTAL DEPENDENCE

On the other side of the spectrum, there are those who are accidentally dependent. Habit-forming medications such as opioids or benzodiazepines prescribed by a physician may lead to dependency and, without a careful de-prescribing plan, may also lead to addiction.

Despite maintaining a therapeutic dose in many cases, tolerance to the medication is a risk, and patients may start to experience withdrawal symptoms. As a result, increasing doses become necessary in order to achieve a similar therapeutic effect. While physical dependence is one problem, medication withdrawal often leads to physiological as well as mental health symptomology. Those symptoms may include depersonalization, derealization, panic attacks, and anxiety, which may last long after withdrawal.[5]

In both addiction and accidental dependency, with the mechanisms of opiate (opioid) and GABA (benzodiazepine) receptors being downregulated, dependency can set in as early as under a week.[6] Access to executive functioning skills in the frontal cortex such as judgment, planning, prioritizing, emotional control, self-monitoring, understanding different points of view, and attention span may become impaired. Additionally, areas such as the cerebellum, which includes motor control, balance, attention, language, processing procedural memories, and regulating fear and pleasure responses, are impacted.

Cumulatively, this disequilibrium within the central nervous system leads to impaired functioning, particularly in quality of life measures. Simple tasks such as writing grocery lists or running errands can be overwhelming due to the cognitive impairments from the medication during and after withdrawal.[7,8]

GENETICS

Genetic predisposition is a contributing factor in addiction. In a recent publication looking at human endogenous retrovirus-K HML-2 integration within RASGRF2, the authors note that gene expression may be altered simply by dealing with a stressor such as loss of loved one or loss of a job.[9] The epigenetics of the dopamine reward center increase the chance for addiction or dependency to set in.[9] Until recently, patients were being prescribed opioids and benzodiazepines for an indefinite time. A multi-agency approach, that includes hospital systems and government entities, is being taken diligently to solve this crisis.

There are many challenges in legislating change in regulations and guidelines for pain management while still addressing patient needs for adequate pain management. While it is imperative that the medical community works diligently to effectively taper patients off of habit-forming medications safely, it is equally important that patients needing complex pain management strategies are not left to suffer because of inadequate pain management regimes.

A lucid understanding of weaning and tapering strategies is crucial with this patient population. A mainstay methodology has been a cross over to a medication with a longer half-life. This allows for blood serum levels to stabilize. Further, the consensus has been to wean slowly to help mitigate the acute medication withdrawal process. Many primary care physicians and specialists do not have experience with the process and may do harm to the patient when attempting to remove these medications abruptly.

There are multiple strategies for tapering off of habit-forming medications, but only through a comprehensive approach, that includes behavioral health modalities with continuous support and empathy, will improved outcomes occur. The maintenance and containment of acute withdrawal symptoms that are seen alongside tapering strategies are of utmost importance, and the process may take months to years to successfully complete.

With the opioid and benzodiazepine epidemic garnering more national attention in the media, people are becoming more aware of the dangers of prescribing benzodiazepines and opioids concurrently. More education and mentoring of primary care physicians by specialists in addiction

medicine are needed to help patients wean off their opioid and benzodiazepine slowly and safely. In addition, recovery centers are struggling with discharge planning when sending patients back to rural communities that lack resources to support their sobriety and/or healing from addiction or dependency.

Likewise, there is a gap in professional services outside of traditional hospital systems to tackle this epidemic. With the vast resources available on the Internet today, many patients are turning to informal online support groups where individuals seek to help each other come off of habit-forming medications. These informal groups include moderators and peers helping each other manage the 24/7 daily withdrawal symptoms, and the positive results speak to the utility and efficacy of group therapy. Limitations include incorrect advice and the lack of professional experience, in addition to the risk of inter- and intrapersonal issues, bullying, and/or risk of secondary trauma from being exposed to extreme symptomology. Learned helplessness is also a potential outcome of these groups that can't be easily identified by moderators that may not be equipped to manage such group dynamics and incidents.

There is a great need to fill the gap in services and long-term recovery with professional support. Virtual medical teams that include recovery coaches that use cognitive behavioral therapy (CBT) and mindfulness, as well as wellness and health coaches supporting prescribing doctors and their patients, would be helpful since withdrawal and healing are known to be a long process. Inpatient residential programs are not as effective as previously thought without long-term support and recovery plans. Addiction is a chronic relapsing and remitting disease that takes months to years of treatment. In addition, there is evidence that it takes that long for the brain to heal, even from taking a drug as prescribed.

In addition, evidence-based tapering protocols such as those outlined in the Asthon Manuel, which is currently being introduced into legislation in New Jersey, are a great tool that could be used as a guideline. Dr. Heather Ashton, creator of the Ashton Manual, ran a clinic in the United Kingdom from 1982 to 1994 for benzodiazepine withdrawal. Her research is centered on the effects of psychotropic drugs including nicotine, cannabis, benzodiazepines, antidepressants, and others. In the manual, the half-life of benzodiazepines and directions for cross over to longer-acting benzodiazepines with respect to dosing are outlined.[10] Physicians are in need of best practices in tapering benzodiazepines at a measured pace. Much work is needed to combat the stigma associated with this process.

The neurological system is the slowest healing system in the body. When a nerve is damaged, it takes 6–9 months to regenerate. Benzodiazepines work on GABA receptors, which are key in nerve functioning. When a benzodiazepine is ingested, it modulates the GABA receptors all over the body. GABA also works in balance with glutamate, an excitatory neurotransmitter. Therefore, when someone stops a benzodiazepine, glutamate becomes the dominant neurotransmitter in the brain, causing a whole host of very uncomfortable symptoms such as muscle twitches, spasms, and/or seizures.

What is needed is to follow a conservative protocol that facilitates a patient–physician relationship that is patient-centered. Empowering patients through education and planning is the crux of a successful tapering regimen. It is important to educate physicians and collaborate in a way that includes innovative methodologies such as digital health programs as well as the use of compounding pharmacies to measure accurate dosing and reductions. A common tapering strategy is based on the Ashton method and suggests no more than a 10% medication reduction every 2 to 4 weeks to help stave off severe withdrawal symptoms.[10] Compounding the medication into a liquid titration or capsules can simplify the process and allow for more accurate dosing. However, some individuals need slower tapering such as 2.5% every 7–10 days or 5% every 2 weeks. Some individuals need to cut 2.5% and hold until their symptoms stabilize so they can make their next cut/taper.

What is very important to note is that blood serum levels need to be stable throughout the day so that the individual tapering can maintain some manageable level of activities of daily living in between dose reduction. Practitioners in methadone clinics have known this for years, and

benzodiazepines need the same amount of careful discernment in keeping individuals stable as they taper. Due to the half-life of the medication, it is important to factor that into the taper. If someone is taking alprazolam, they need to dose four times daily due to the approximate 6-hour half-life. Lorazepam in general is dosed three times daily due to the 8-hour half-life, and clonazepam is dosed twice daily due to the 12-hour half-life. Diazepam is dosed once daily due to 30-hour half-life. The half-life of all of these drugs is approximate due to inter-individual variability in metabolism and excretion rates. When tapering, a person would need to make even cuts across the doses. For example, if someone is taking 1 mg of Ativan a day (individual doses of 0.33 mg three times daily), a 5% dose decrease would be 0.316 mg three times daily for a total of 0.95 mg, and then the next step would be 0.3 mg three times daily for a total of 0.9 mg with a duration hold at each level anywhere from 7 to 14 days or holding until the withdrawal symptoms stabilize. The only accurate way of performing these dose tapers is to have the dose compounded at a compounding pharmacy or prescribing the liquid form of these medications for accurate measurement.

The need for daily support during this long process is crucial as indicated earlier with individuals looking to the informal groups on the Internet such as Benzo Buddies and closed Facebook groups for support and advice. Professional virtual support is much needed to provide privacy, confidentiality, and accessibility to those who may be homebound by temporary symptoms of agoraphobia, living in rural areas, or who are struggling to make it through the workday due to vestibular challenges, weakness, and/or stress-induced triggers to use again and/or panic attacks. Helping people understand their severe symptoms and identify the use of coping tools during withdrawal as well as the use of problem-solving skills to navigate the red tape around withdrawal will increase the chance of success. A person's radical acceptance of the severe symptoms is crucial to help manage daily challenges that present often for many months to sometimes years. Some are at risk of taking their own life due to the severity of the withdrawal symptoms. This process can only be done with sufficient support; sending someone home with a tapering plan and a follow-up check in 1–2 months is not sufficient.

The use of virtual recovery coaches, collaboration between doctors, and a virtual medical team are just some of the many ways to address this gap in services where behavioral health techniques to support emotional states in conjunction with patients' personalized tapering protocols can be taught and implemented. The introduction, practice, and tracking of coping tools such as affirmations, positive self-talk, and cognitive behavior therapy (CBT) techniques such as reality testing and journaling are also useful. Additional tools working with fears and feelings, such as Jin Shin Jyutsu, which include breathing techniques, grounding exercises, meditation, visualization, emotional freedom technique (tapping), and guided imagery, can be taught and modeled virtually to help in coping with some of the withdrawal symptoms.

Furthermore, assisting people in withdrawal with accessing community resources, such as community acupuncture and traditional acupuncture, along with the framework of Maslow's Hierarchy of Needs in mind, will help them to connect with others in the community and meet the need for the sense of belongingness. Likewise, daily reminders about the importance of keeping things simple by getting back to the basics in life such as eating nutrient-dense food and drinking clean purified water help to meet the physiological needs for feeling well. According to Maslow, one cannot connect with others unless one's physiological and security needs are met.[11]

Individuals in acute withdrawal are often weak, nauseous, and dizzy. Focusing on helping individual function by assessing their basic physiological needs, helping to simplify their life to meet their basic needs while in withdrawal, and accepting temporary limitations and setbacks are all very crucial to a successful healing journey. It can be a very long process, and living with the hundreds of symptoms in withdrawal 24/7 can be exhausting. Even during slow tapers, individuals experience a multitude of symptoms that affect activities of daily living.

Patience and support are central to sustaining the long-term healing of the central nervous system. Having access to family support systems fosters a sense of belongingness. According to the Rat Park Study by Bruce Aleksander, that sense of belonging has profound implications. Recovery was

found to be more likely if individuals had connections with others and were involved in engaging activities in their environment.[12] Daily support keeps these areas in perspective through techniques such as motivational interviewing and can help keep those in recovery focused.

Services like Lucid Lane are helpful in long-term discharge planning from recovery centers for traditional addiction and partnering with those afflicted with accidental dependency, but they are only able to scratch the surface of the need at this point. The need is growing as we enter an epidemic emerging from the shadows of the opiate crisis. Clients facing arrested development, unhealed trauma, nutritional deficiencies, and/or genetic mutations, such as the MTHFR gene that has been indicated in mental health,[13] virtual ongoing support as well as daily on the ground support is much needed to fill the gap in services for long-term recovery. Through a holistic and comprehensive approach that includes personalized medication tapering strategies, and behavioral health techniques, along with innovative digital health programs, a cohesive effort needs to be made to combat the global epidemic caused by the uncontrolled misuse and overprescribing of habit-forming medications such as benzodiazepines and opioids and to support education in deprescribing practices.

REFERENCES

1. Bohnert A., Guy G., Losby J. Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline. *Ann Intern Med* 2018; 169(6): 367–375. doi:10.7326/M18-1243
2. Bachhuber M.A. Hennessy S. Cunningham C.O., Starrels J.L. Increasing Benzodiazepine Prescriptions and Overdose Mortality in the United States, 1996–2013. *Am J Public Health*. 2016 April; 106(4): 686–688. Published online April. doi:10.2105/AJPH.2016.303061
3. Hauser K.F., Knapp P.E. Opiate Drugs with Abuse Liability Hijack the Endogenous Opioid System to Disrupt Neuronal and Glial Maturation in the Central Nervous System. *Front Pediatr.* 2018; 23(5): 294. doi:10.3389/fped.2017.00294
4. Rocket I.R.H., Caine E.D., Connery H.S., et al. Mortality in the United Stated from Self-Injury Surpasses Diabetes: A Prevention Imperative Injury Prevention. Inj Prev 2019; 25(4): 331–333. Published online 27 August 2018. doi:10.1136/injuryprev-2018-042889
5. Busto U., Sellers E.M., Naranjo C.A., Cappell H., Sanchez-Craig M., Sykora K. Withdrawal Reaction after Long-Term Therapeutic Use of Benzodiazepines. *N Engl J Med* 1986; 315(14): 854–859. https://www.ncbi.nlm.nih.gov/pubmed/3092053
6. Shah A., Hayes C.J., Martin B.C. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017; 66(10): 265–269. doi:10.15585/mmwr.mm6610a1
7. De Vries T.J., Shippenberg T.S. Neural Systems Underlying Opiate Addiction. *J Neurosci* 2002; 22(9): 3321–3325.
8. NIDA. Drugs, Brains, and Behavior: The Science of Addiction. 20 July 2018. Retrieved from https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction. Accessed on 13 February 2019.
9. Karamitros, T., et al. Human Endogenous Retrovirus-K HML-2 Integration within RASGRF2 Is Associated with Intravenous Drug Abuse and Modulates Transcription in a Cell-Line Model. *Proc Nat Acad Sci* 2018; 115(41): 10434–10439.
10. Ashton H. Benzodiazepines: How They Work & How to Withdraw, the Ashton Manual. 2002. Benzo.org.uk. Retrieved from http://benzo.org.uk/manual/bzcha01.htm. Accessed on 3 March 2019.
11. McLeod S.A. Maslow's Hierarchy of Needs. 2017. Retrieved from www.simplypsychology.org/maslow.html
12. Peele S. *The Meaning of Addiction*. Lexington, MA: DC Heath; 1985: 77–96.
13. Wan L., Li Y., Zhang, Z. et al. Methylenetetrahydrofolate Reductase and Psychiatric Diseases. *Transl Psychiatry.* 2018; 8(1): 242. Published online 5 November 2018. doi:10.1038/s41398-018-0276-6