



The Overlooked Risks of Benzodiazepine Use: Forgotten Dangers of a Commonly Prescribed Medication

Catherine M. Pittman, Ph.D., HSPP

Professor and Licensed Clinical Psychologist

Saint Mary's College

Notre Dame, Indiana

9th Annual Drug Abuse Symposium, Noblesville

Sponsored by the Office of the Indiana Attorney General

October 30th, 2018

A Helpful Drug?

When individuals have difficulty with stress or with sleeping what is the most typical response?

Often they approach their family doctor, who attempts to treat the anxiety or refers them to a psychiatrist. In either case, it is very likely that a medical (psychopharmacological) solution may be offered.

The solution offered is often benzodiazepines. In the U.S., the percentage of adults who filled a benzodiazepine prescription increased by 30% between 1996 and 2013 (Marcus et al., 2016). Yet we are often not considering the consequences.

If the person is prescribed benzodiazepines, short term relief is obtained, but if use continues, tolerance develops, and increasing dosages may be required. Dependence on benzodiazepines is very likely, and do we warn patients of this?

The truth is that we often don't...

Most Commonly Dispensed Benzodiazepines in US

<u>Medication</u>	<u># of prescriptions in 2011</u>
alprazolam (Xanax)	49 million
lorazepam (Ativan)	28 million
clonazepam (Klonopin)	27 million
diazepam (Valium)	15 million
temazepam (Restoril)	8.5 million

Source: Drug Enforcement Administration bulletin, January 2013

Common Benzodiazepines

<u>Trade Name</u>	<u>Generic Name</u>
Xanax	Alprazolam
Klonopin	Clonazepam
Valium	Diazepam
Ativan	Lorazepam
Halcion	Triazolam
Librium	Clordiazepoxide
Restoril	Temazepam
Tranxene	Clorazepate



Common Z-Drugs

Drugs with effects similar to benzodiazepines but designed for use in treatment of insomnia because they don't have detrimental effects on sleep architecture

<u>Trade Name</u>	<u>Generic Name</u>
Ambien	Zolpidem
Sonata	Zalepion
Lunesta	Eszopiclone
Intermezzo	Zolpidem



Mechanism of Action of Benzodiazepines

Benzodiazepines modulate activity of gamma-aminobutyric acid, an inhibitory neurotransmitter also known as GABA.

They bind to GABA receptors and increase the receptors' affinity for GABA by making the receptor site more sensitive to being activated. (A process known as positive allosteric modulation.)

GABA receptors are inhibitory, making neurons less likely to fire.

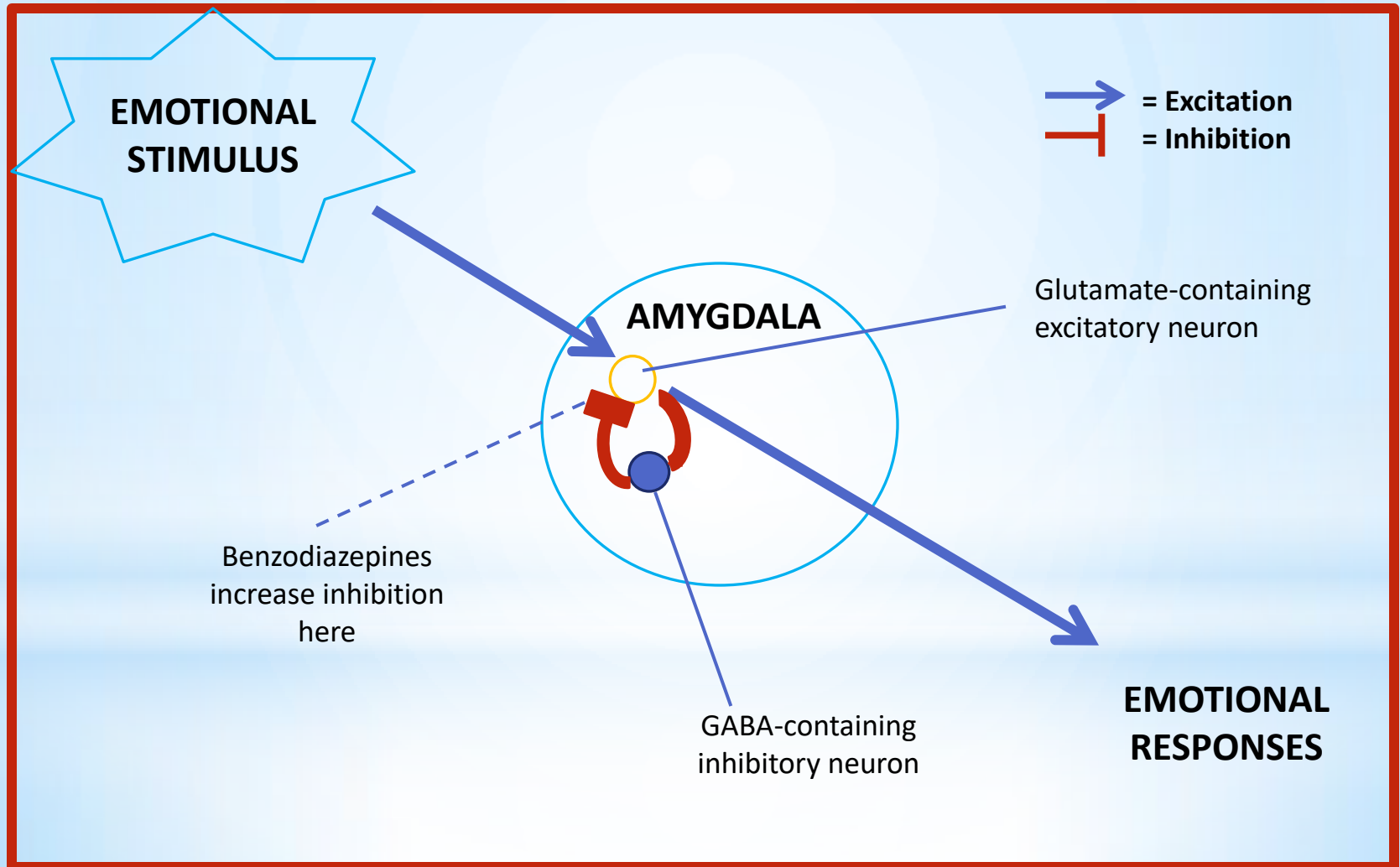
Benzodiazepine provides a “GABA boost,” facilitating inhibition

GABA is widely used throughout the CNS, and a specific type of GABA receptor, the GABA_A receptor, is the primary inhibitory receptor in the brain.

GABA_A is involved in many processes throughout the body, e.g., the regulation of fear, anxiety, muscle tension, and memory functions.

Benzodiazepines have widespread effects on a variety of processes.

Benzodiazepines Inhibitory Effect



Common Uses of Benzodiazepines

- U.S. has the highest volume of benzodiazepine sales in the world...
- Most frequently prescribed medication for anxiety disorders, including Generalized Anxiety Disorder and Panic Disorder (Pull & Damsa, 2008)
- Most common use by primary care practitioners is in treatment of insomnia
- College students' use is rising (Kleykamp et al., 2010)
- Often administered along with selective serotonin reuptake inhibitors (SSRIs) in initial stage of treatment for anxiety or depression
- Used for anticonvulsant effect in seizure disorders
- Prescribed to promote muscle relaxation
- Prescribed to reduce agitation often associated with psychotic disorders

Beneficial Effects of Benzodiazepines

- Quickly absorbed; some achieve peak levels within 30 minutes
 - Physicians and patients are pleased with short term results
 - Quick and effective relief from anxiety, emotional distress
 - Quick reduction of muscle tension and agitation
- Have anticonvulsant effect for seizure disorders
- Reduced anxiety often experienced when used in first weeks of antidepressant use (Furukawa, Streiner, & Young, 2001)
- Can be an effective sleep aid. Meta-analysis revealed decrease in time to fall asleep is about 4 minutes, and increased sleep time is approximately one hour (Holbrook, Crowther, Lotter, Cheng, & King, 2000).
- These medications are inexpensive because they are off patent

Detrimental Effects of Benzodiazepines

- Side effects: sedation, daytime drowsiness, ataxia, dyscoordination, slurred speech, decreased attention, and impaired memory and cognitive performance
- Relapse rates of 50% or higher are typical for most disorders when meds are discontinued (Spiegel & Bruce, 1997)
- With prolonged use-
 - Physiological dependence can occur as soon as 4-6 weeks, when a person is taking the prescribed dosage (Spiegel & Bruce, 1997)
 - Tolerance occurs and increased dosage is required with prolonged use
 - Dependence and withdrawal effects occur
- Continued use impairs cognitive performance (Bierman et al., 2007), especially as duration of use continues
- Side effects are especially of concern in elderly population because they result in falls, cognitive impairments

The Withdrawal Process

- Benzo withdrawal is a complicated, difficult process that is difficult to predict, but has the potential to have long-term debilitating effects
- Empirical study of the process of withdrawal from benzodiazepines has revealed a rather large number of varied symptoms, which are difficult to recognize as indicators of withdrawal.
- The Benzodiazepine Withdrawal Symptom Questionnaire has been used to investigate the symptoms reported, and common factors that have been found include perceptual and sensory disturbances, muscular pain, cognitive dysfunction, malaise, dysphoric mood, and memory loss (Couvee & Zitman, 2002).
- Evidence suggests that the clusters of symptoms may be different as the withdrawal process proceeds (Couvee & Zitman, 2002).
- More studies have been conducted abroad than in the U.S., despite higher rates of prescription in the U.S.
- The discontinuation syndrome that long-term users experience is known to be severe and prevent successful withdrawal (Lader, 2009).

The Withdrawal Process

- No medications exist to help in the withdrawal process when patients are attempting to taper their benzodiazepines.
- Although those withdrawing from opiates have suboxone or methadone, there is no way to blunt the withdrawal symptoms.
- If stopped too quickly, benzodiazepines can result in seizures or even death.
- Empirical study of the process of withdrawal from benzodiazepines has revealed a rather large number of varied symptoms.
- If a person is experiencing respiratory depression caused by benzodiazepines, there is a drug, flumazenil, that can reverse the respiratory depression, but it is not readily available in the way that Narcan has become. First responders don't typically have it.
- Most physicians do not recognize benzodiazepine withdrawal, and many are not aware of it or do not believe it exists.
- Only a few physicians are prepared to assist patients dealing with benzodiazepine withdrawal.
- Withdrawal can take years and resources available to patients during the long-term process are extremely limited.

Introducing

BenzoBuddies

- BenzoBuddies (BB) is a internet forum founded in 2004 by a British man after his withdrawal from Rivotril (clonazepam or Klonopin), which he was originally prescribed to treat myoclonus, a seizure disorder. They provided us a great opportunity for research...
- The mission of BB is to provide information and support for members who question their dependency on their medication and may want to plan and execute benzodiazepine withdrawal.
- The site is an online peer support group and no medical professionals are affiliated with the site.
- Members typically use screen names to remain anonymous.
- About 73% participate with gender undeclared, with 12% identified as male and 15% identified as female (Pittman & Youngs, 2013).
- BB currently has over 15,000 members internationally. The members come primarily from the U.S. (72%), with 9% from Canada, 5% from the U.K., and about 3% from Australia. There are also members from Japan, Germany, France, India, Spain, etc.



- Members of BenzoBuddies often feel they get support in coping with dependence from the BenzoBuddies site.
- Members describe themselves as “dependent” or “accidental addicts” because they feel they are addicted to benzodiazepines despite (or because of) following dosage regimens prescribed by their doctors.

- Many members report seeking online support via BB because the medical community failed to recognize or failed to offer treatment for their cluster of benzodiazepine withdrawal symptoms.
- We received numerous requests from them asking us to educate the professional treatment community about the dangers of benzodiazepines.

Demographics of American Participants

Total sample = 493 *Note that this is a nonrandom sample, and should not be taken to represent all benzodiazepine users or all those who wish to discontinue benzodiazepines.

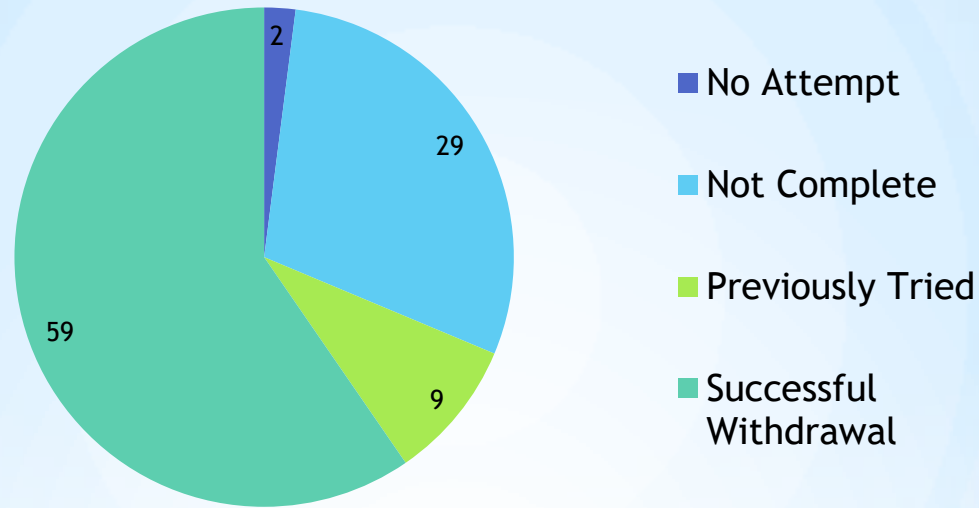
Of those who gave complete demographic information:

	13%	18-29 years
	18%	30-39 years
65% Female	19%	40-49 years
35% Male	32%	50-59 years
	15%	60-69 years
	3%	Over 70 years

They were prescribed benzodiazepines as early as age 11 and as late as age 86. Benzodiazepine use started as early as 1979 or before, and as late as 2012.

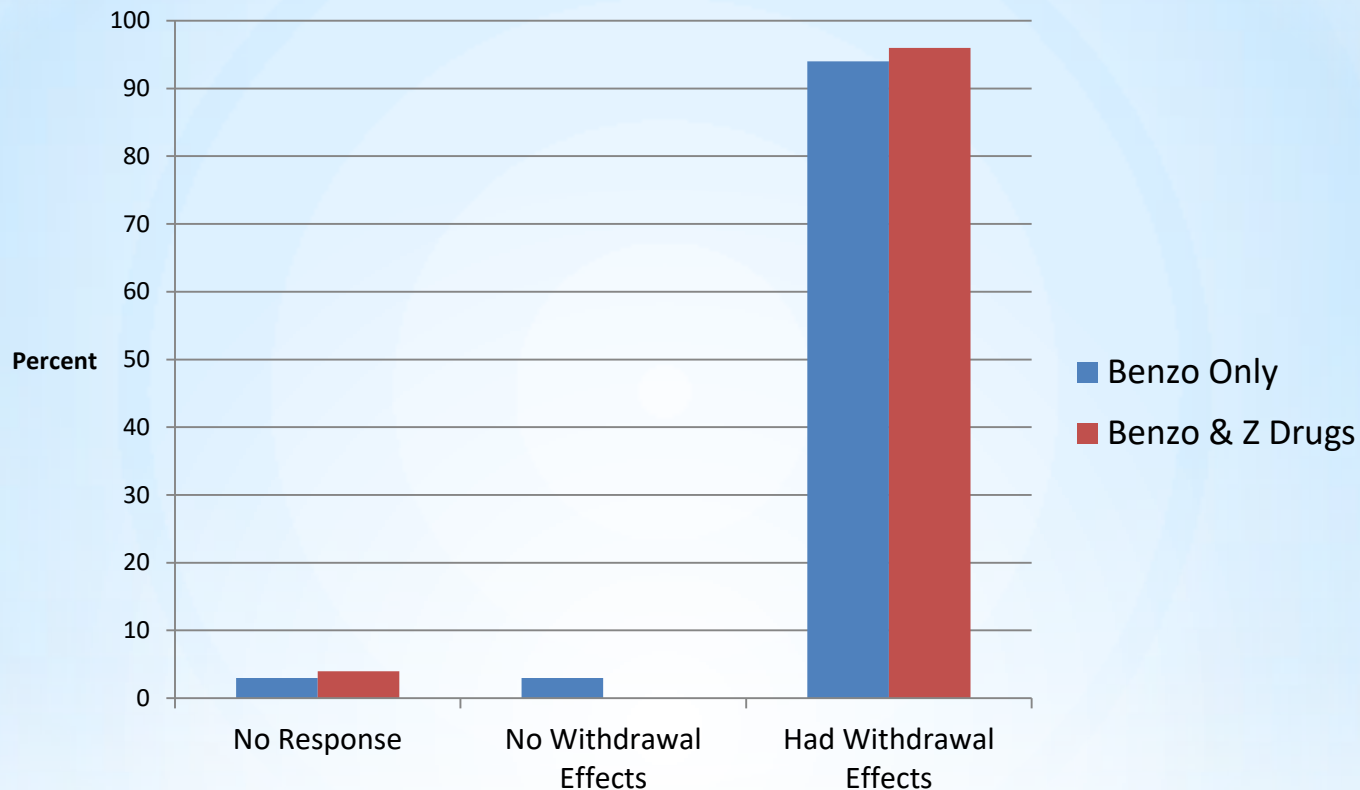
Data and results are all based on Pittman and Youngs (2013)

Withdrawal Status



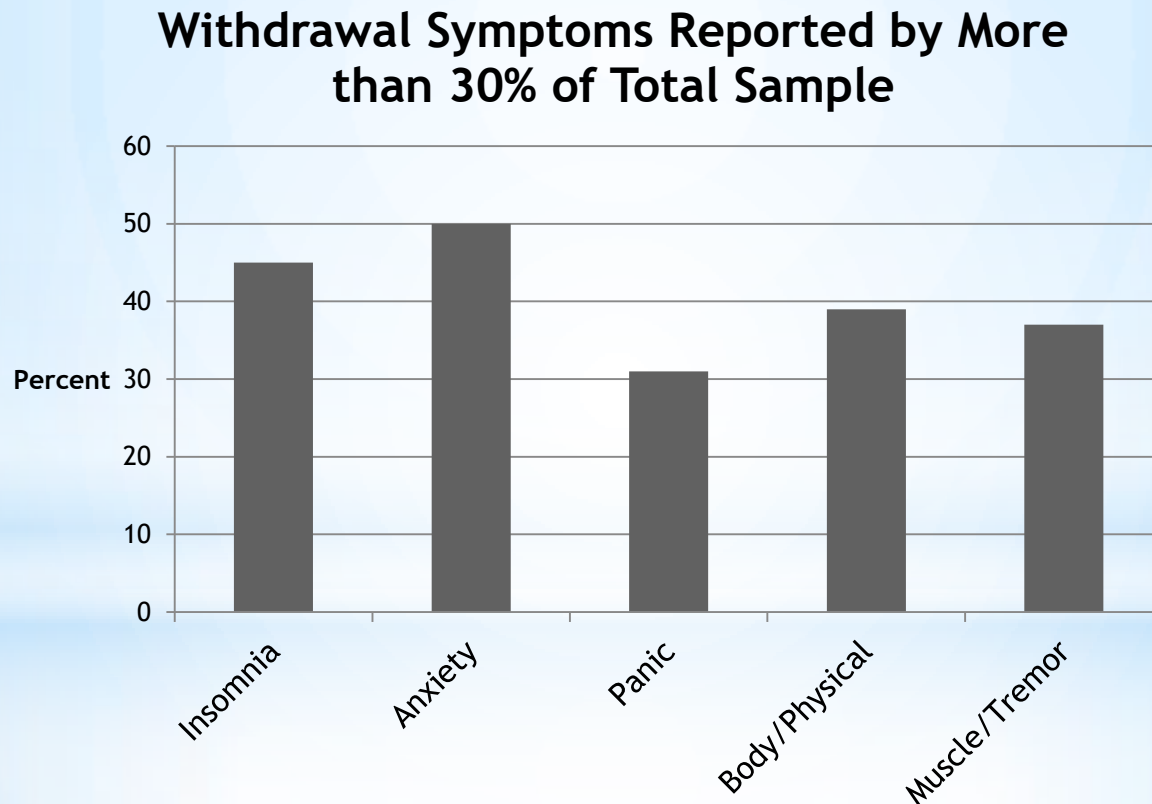
- Of 493 participants, 29% were in the process of completing the withdrawal process, 9% had previously tried but did not successfully withdraw, and 59% had successfully withdrawn. Only 2% had not (yet) attempted withdrawal (Pittman & Youngs, 2013).
- The BenzoBuddies site is clearly a resource for those engaged in the withdrawal process.
- Why were the 59% still active on the site?

Reported Withdrawal Effects for Each Group



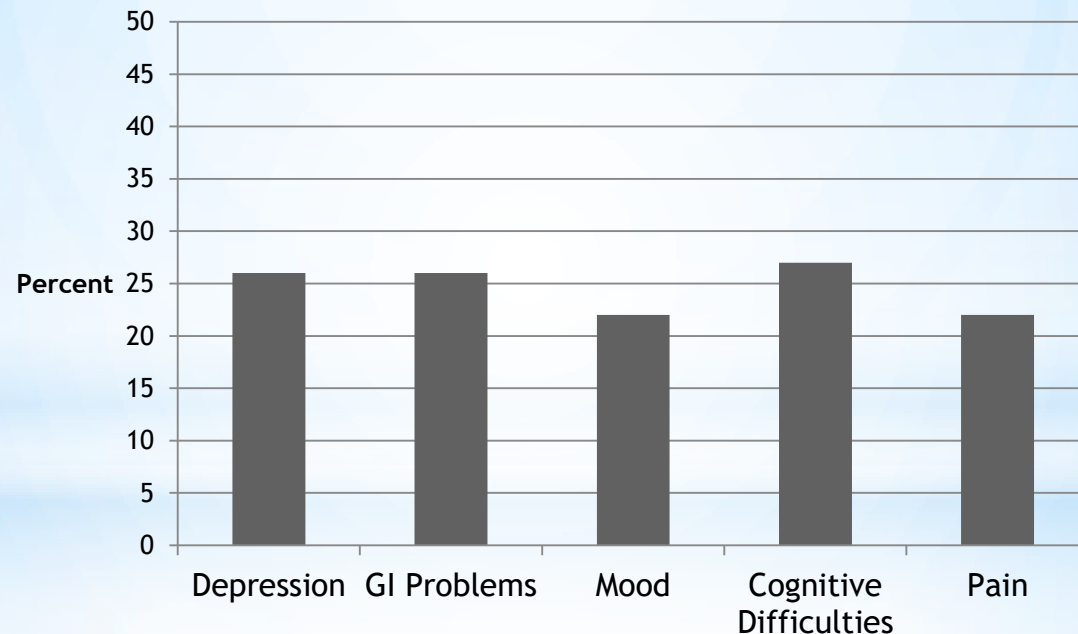
- Of the 493 participants, about 30% had not completed withdrawal.
- Of those who had completed withdrawal (345 in total), 96% reported their withdrawal symptoms continued after discontinuation (Pittman & Youngs, 2013).
- Only 4% reported that they were symptom free after withdrawal.

What are the withdrawal symptoms reported by those individuals on this site? In this descriptive study, participants were asked an open-ended question about their withdrawal symptoms, and their responses were categorized. This allowed us to identify symptoms we might not have anticipated. The most common symptoms are below. (Pittman & Youngs, 2013)



A second set of commonly reported symptoms are identified below. These varied symptoms illustrate why it may be difficult for a patient or a physician to recognize the symptoms as an indication of benzodiazepine withdrawal (Pittman & Youngs, 2013).

Withdrawal Symptoms Reported by More than 20% of Total Sample



Length of Withdrawal Symptoms After Discontinuation

- Of those who had completed withdrawal, the average length of withdrawal symptoms reported by those 156 participants (53% of total) whose symptoms had subsided was Fourteen Months.
- Of those who had completed withdrawal, 139 (47%) were continuing to have withdrawal symptoms, and therefore could not identify when withdrawal symptoms subsided (Pittman & Youngs, 2013).
- Why would withdrawal last so long?
- Benzodiazepines result in lasting changes in the brain and body. The inhibition they produce affects the neurological network throughout the body when they are used daily (Rivas-Vasquez, 2003).
- The inhibition affects the brain and body's ability to transfer and process information so that cells begin to recalibrate in order to overcome the inhibition. These changes are difficult to correct.

Should We Worry about Benzos?

Occasional use of benzodiazepines is not as likely to lead to problems

Even with occasional use, risks exist including

- * Impaired cognitive functioning and memory (Madhusoodanan & Bogunovic, 2004)
- * Impairment of driving or balance (with increased risk for falls) has been identified, especially among the elderly (Smink et al., 2010; Wagner et al., 2004)
- * When combined with alcohol or opioids, benzos can be life-threatening

With extended use, which can occur after 3 or 4 weeks, benzos result in dependence that is rarely detected quickly, and that can lead to severe discontinuation and withdrawal symptoms.

It is essential that prescribers understand the potential dangers when they prescribe benzodiazepines.

When Accidental Dependency Develops: What are the Options?

- Few physicians or psychiatrists recognize symptoms of benzodiazepine tolerance.
 - They often mimic symptoms of anxiety disorders.
 - They comprise a cluster of divergent symptoms.
- Very few physicians or psychiatrists have the knowledge or experience to help a person successfully withdraw from benzodiazepines.
- Withdrawal can take an *extended* period of time that many physicians are not prepared for.
- Detox clinics are not suitable for the long period of time required. Rapid withdrawal requires adjunctive medications due to the risks for seizures and even death.
- All this means that options are extremely limited.

Reduce Use of Benzodiazepines...

- Prescribing benzodiazepines is not a benign intervention.
- Benzodiazepine dependence occurs relatively easily, without notice, and is at the least potentially life-altering and at the worst potentially life-threatening

Warning signs that PRESCRIBING benzodiazepines will be detrimental

- Prescribing benzos to individuals with addiction history or problems
- Prescribing benzos when opioids, narcotics, barbiturates, or alcohol are also being used
- Prescribing benzos to assist with chronic sleep difficulties
- Prescribing benzos for a long-term disorder or condition
- Prescribing benzos to someone whose anxiety is likely to have a chronic course, including those coping with depression, bereavement, or a stressful life situation
- Prescribing daily use of benzos beyond 3 weeks

Addiction vs. Dependence

- * Note: Addiction is not always the problem. Patients can become dependent on the drug without being addicted.
- * Dependence occurs because the brain and body adapts physiologically to chronic exposure to a drug. This physiological dependence is often a part of addiction, but they are not equivalent.
- * Addiction involves additional changes to brain circuitry and is distinguished by compulsive drug seeking and continued use despite negative consequences.
- * We need to be aware of and sensitive to situations that lead to dependence
- * We also need to spot the early signs of dependence

How to Spot Dependence

Warnings Signs of Benzodiazepine Dependence

- * Daily benzodiazepine use beyond 3 weeks
- * Patients complaining that meds are no longer effective, that anxiety or sleep problems are increasing
- * Patients using, requesting, or “needing” a higher dosage
- * Patients showing signs of misuse of the medication
- * Patients showing mild withdrawal symptoms like anxiety, headaches, blurred vision, confusion, forgetfulness, irritability, body aches and pains, difficulty falling asleep

Examining Current Use...

From 1993 to 2014, visits to a physician in which benzodiazepines were prescribed with opioids increased significantly, from an average of 9.8 visits per 10,000 visits to 62.5 per 10,000 visits, over a 600% increase! (Hirschtritt, Delucchi, & Olfson, 2018).

The group that was most likely to be prescribed benzodiazepines along with opioids were in the age range of 50 to 64, white, insured individuals who were seeing their primary care physician.

Benzodiazepines are typically prescribed in response to complaints of anxiety or sleep difficulties, and this is especially frustrating because more effective methods treatment are available...

For managing anxiety, psychotherapy (especially cognitive-behavioral approaches) and alternative medications (typically SSRIs) are readily available and recommended (Baldwin et al., 2005). For sleep difficulties, cognitive-behavioral interventions are also found to be superior and more lasting than use of medications in general (Maust et al., 2016) .

An Increase in Overdose Deaths

As use has gone up, we see a corresponding increase in the presence of benzodiazepines in opioid overdose deaths from 18% of opiate overdose deaths in 2004 to 31% in 2011 (as cited in Guidelines from the Commonwealth of Pennsylvania.)

Hirschtritt et al. (2018) cite a variety of sources documenting overdose. High dose opioid users who were also prescribed benzos were nearly 10 times more likely to die from overdose. In the VA, among those prescribed opioids, nearly half of overdose deaths occurred when patients were concurrently prescribed benzos.

When factors that contribute to opioid overdose are examined, benzodiazepines are clearly a concern. Benzos had been prescribed during the 180 days before an overdose in 49% of nonfatal overdoses and 19% of fatal overdoses in Olfson et al.'s (2018) study, but they note other studies find risks of fatal overdose around 30%. The risk that benzos potentiate opioid-induced respiratory suppression was proposed.

A Pattern in Overdose Deaths

In a study of over 20,000 Medicare recipients (average age = 66) who were concurrent users of benzos and opioids in the U.S., 68% of them had more than 180 days of overlapping supplies of both medications (Hernandez, He, & Brooks, 2018).

The highest risk of overdose occurred in the first months of concurrent use, with the hazard ratio for days 1 to 90 being 5.05 for overdose with concurrent use, compared to a hazard ratio of 1.87 for days 91 to 180 (Hernandez et al., 2018). This means 5 times as many people are overdosing in the first 90 days if they are prescribed both medications.

This study also indicated that white, disabled, Medicare beneficiaries are most likely to use opioids and benzodiazepines currently, and that individuals with depression and/or anxiety were more likely to be concurrent users of benzos and opioids.

Depression or anxiety can be effectively treated without benzos...

Not the First Line Treatment!

- * The most effective treatments for anxiety disorders, as well as anxiety-based disorders such as PTSD and OCD, are evidence-based psychotherapies, especially cognitive behavioral therapies (CBT) (Spiegel & Bruce, 1997).
- * Due to their side effects, psychotropic medications are not routinely recommended as a first line treatment (Baldwin et al., 2014), but they are often prescribed by primary care physicians in response to patient complaints of anxiety.
- * Improvements in referring patients for psychotherapy prior to the initiation of psychopharmacological treatment could be beneficial.
- * If medication is being considered, SSRIs and SNRIs are preferred over, and have been demonstrated to be more effective than, benzodiazepines (Baldwin et al., 2014).
- * In fact, the VA/DoD Practice Guidelines for the Management of PTSD recommend against routine use of benzodiazepines, based on both the unproven efficacy of the medications in treatment and their known risk for dependency and abuse.

Risks for Overdose?

A recent study attempted to identify important factors that increase an individual's risk to overdose, and once again benzos came up.

Olfson, Wall, Wang, Crystal, and Blanco (2018) recently conducted a study focused on 1) identifying individuals who had experienced a nonfatal overdose, and 2) following up to discover whether they had experienced subsequent overdoses and what factors contributed.

They found that benzodiazepines were an important factor.

Controlling for age, sex, ethnicity and region, they found the risk for fatal overdose was significantly greater for those who had been prescribed benzodiazepines in the six months before their first overdose.

This indicates that benzodiazepine prescription is likely playing a role in increasing the risks for drug dependence and overdose.

Who is Using? Older Adults

- * Studies indicate that benzodiazepine use increases with age, as does long term use.
- * Olfson, King, & Schoenau (2015) found that individuals aged 65 to 80 had the highest rates of benzodiazepine use
- * A concern because American Geriatric Society Expert Panel (2012) recommended against benzodiazepine use in older adults

<u>Age</u>	<u>% Using Benzodiazepines</u>
18-35	2.6%
36-50	5.4%
51-64	7.4%
65-80	8.7%

<u>Age</u>	<u>% With Long Term Use of BZs</u>
18-35	14.7%
36-50	22.4%
51-64	28.0%
65-80	31.4%

- * Psychiatrists were less likely to prescribe benzos long term, and were more likely to prescribe less as age of patient increased
- * Most of increase in long term benzo use with age is due to primary care physicians (Olfson et al., 2015)
- * The study also found that women are almost twice as likely to be using benzodiazepines as men.

Who is Using? Teens

- * While the greatest use is among the elderly, they aren't the only group at risk.
- * Some areas in the U.S. have seen a sharp increase in the use of benzodiazepines, particularly Xanax, among teens.
- * Dr. Sharon Levy, director of adolescent addiction treatment at Boston Children's Hospital conducted a study for the National Institute of Drug Abuse reports that while much substance use among teens is going down, the number of teens hooked on Xanax is increasing (Vestal, 2018).
- * High school children are often exposed to the medications as something that a parent or grandparent uses, and don't recognize that they can develop dependence or put their own health and safety at risk.
- * Many teens come in taking daily doses, or routinely combining the medication with opioids or alcohol

Risks for Overdose?

It seems clear that prescription of benzodiazepines is likely playing a role in increasing the risks for drug dependence and overdose.

Most physicians do not view continuous use of benzodiazepines as a public health concern (Cook et al., 2007)

Many physicians believe (erroneously) that these medications are effective treatments for anxiety and insomnia. They are NOT the first line treatment, and they do not have long term effectiveness.

Physicians may know to consider risk of substance abuse, but they do not consider risk of dependence or concurrent use of other substances

Unless more attention is devoted to reducing long term use of benzodiazepines, especially by older adults, risks of these medications are likely to increase over the next decade

Multifaceted clinical interventions that incorporate patient education, psychotherapy, and regular medication review are needed

What's the Problem Here?

- Patients come in with a complaint of anxiety and/or worry
- Physicians want to help, and have an inexpensive medication at hand that seems effective.
- Patients experience relief from the medication, and often are satisfied with this intervention.
- Who is going to see this as a problem?
- As the medication continues to be prescribed, if daily use continues longer than 3 weeks, the need for the medication should be reviewed, because dependence can develop.
- But this check is rarely done, and many patients begin to rely on daily use of benzodiazepines.
- The first indication of a problem is increased anxiety, difficulty sleeping, or a vague set of symptoms, but problems are not likely to be seen as connected to the benzodiazepines.
- Often a higher dose of benzodiazepines is prescribed, and the patient reports improvement.
- But this pattern continues until we have a benzodiazepine dependency problem, and a higher risk of overdose--- even though the meds were taken as prescribed.

Back to the Forgotten Group...

- The BenzoBuddies sample may not be representative of all benzodiazepine users, but they are an important indication that we are not serving all anxiety and insomnia sufferers well.
- Important Questions:
 - Does the frequent prescription of benzodiazepines in this country need to be re-evaluated?
 - Do we have a responsibility to insure that clients have informed consent to be placed on benzodiazepines for longer than four weeks?
 - When benzodiazepines are offered for specific disorder that we know may have a chronic course (e.g., Insomnia, Generalized Anxiety Disorder, Panic Disorder, OCD, or PTSD) are we creating an unnecessary risk of dependence when other treatments are more effective in the long term?
 - Are we offering sufficient services for those who have become dependent on benzodiazepines?

What can we do to help?

- Revised guidelines released by the Centers for Disease Control and Prevention (CDC) (Dowell et al., 2016) for prescribing opioid analgesics for chronic pain recommend that “clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently”
- Before prescribing benzodiazepines for sleeping difficulties or anxiety/stress issues, consider more effective treatments
 - ❑ Psychotherapy is more beneficial in treating anxiety/stress and sleep issues
 - ❑ SSRIs and SNRIs are more effective for anxiety than benzos
 - ❑ Cognitive Behavioral Therapy has demonstrated effectiveness for treatment of anxiety disorders
 - ❑ CBT-I (Cognitive Behavioral Therapy for Insomnia) has been demonstrated to be more effective in long term than medications
- If benzodiazepines are prescribed, the risks of daily use for an extended period need to be explained to patients
- Our patients need to be given clear (written?) information about potential risks of benzodiazepines, including the risks of tolerance and dependence before they agree to take them.

What can we do to help?

- Keep in mind how quickly benzodiazepines pose a risk-- dependency can develop by ***4 weeks*** and overdoses typically occur in the ***first 90 days*** of prescription.
- When daily use continues longer than 3 weeks, the need for the medication should be reviewed, because dependence can develop as early as 4 weeks.
- Alternative treatments should be considered, including other pharmacological treatments.
- The impact of benzodiazepine use on other treatment strategies should be considered, because they have been shown to interfere with other more effective treatments like CBT.

If dependency develops,

- Clients attempting benzodiazepine cessation should be educated, and given medical and psychological support throughout the process (Parr et al., 2008).
- CBT should be considered because it has been shown to facilitate benzodiazepine cessation more effectively than nonspecific supportive therapy, although both provided benefits (Gosselin et al., 2006)

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