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Review Article

Abuses and Misuses of Benzodiazepines and Antidepressents; A Review

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Abstract

Although benzodiazepines and antidepressants are valuable in the treatment of anxiety and depression disorders, they have some potential for abuse and may cause dependence or addiction. It is important to distinguish between addiction to and normal physical dependence on benzodiazepines and antidepressants. Intentional abusers of benzodiazepines usually have other substance abuse problems. Benzodiazepines are usually a secondary drug of abuse used mainly to augment the high received from another drug or to offset the adverse effects of other drugs. Few cases of addiction arise from legitimate use of benzodiazepines and antidepressant. Pharmacologic dependence, a predictable and natural adaptation of a body system long accustomed to the presence of a drug, may occur in patients taking therapeutic doses of benzodiazepines and antidepressant. However, this dependence, which generally manifests itself in withdrawal symptoms upon the abrupt discontinuation of the medication, may be controlled and ended through dose tapering, medication switching, and/or medication augmentation.

Keywords: Benzodiazepines; Antidepressants; Misuses; Abuses

Benzodiazepine Abuses and Misuses

When a person takes a legal prescription medication for a purpose other than the reason it was prescribed, or when that person takes a drug not prescribed to him or her, that is misuse of a drug. Misuse can include taking a drug in a manner or at a dose that was not recommended by a health care professional. Benzodiazepines act primarily on the gamma-amino butyric acid (GABA) receptors and, through this molecular interaction, increase levels of inhibitory brain signaling-depressing the central nervous system and resulting in sedation and feelings of elaxation [1]. Benzodiazepines and related drugs are usually effective when first prescribed and nearly all the disadvantages and problems come from long-term use. People of all ages and both genders use and misuse benzodiazepines for many different reasons and there is much common use and treatment for long term use but there are some specific problems in specific groups including: patients with a mental health problem the "therapeutic dose" users and people who tend to use high-doses may use illicit benzodiazepines and other illicit drugs and/or alcohol are seeking pleasure. When taken orally they can be exhaled and/or injected. Benzodiazepine use leads to higher rates of risk behavior and social dysfunction, and problems may lead to fatal overdose. Benzodiazepines are also known as tranquilizers [1]. Similar names include valium and Xanax. They are some of the most commonly prescribed medications in the world. They have high potential for drug abuse and addiction. A woman who takes benzodiazepines during pregnancy risks having her baby develop a cleft in the mouth, withdrawal symptoms and floppy infant syndrome, a condition in which the baby lacks muscle tone and does not develop normally.

Lorazepam

lorazepam is classified as a benzodiazepine medication used primarily for short-term treatment of anxiety and seizure activity. It is sometimes used to manage intractable insomnia, and as a sedative for hospitalized or aggressive patients [2]. The drug works to slow down the central nervous system of the person using it by boosting the effects of a neurotransmitter called GABA--lowering signs of physical tension and psychological anxiety. Generally when used as directed by a physician, it is safe and effective. However, when misused or taken recreationally it can be addictive and dangerous. lorazepam initially produces the following short-term effects such as Reduced sense of physical and psychological anxiety, worry and tension, Increased feelings of euphoria, Drowsiness

Alprazolam

The high potency and short onset of action of alprazolam makes it a preferred drug for abuse. Alprazolam is the most commonly reported benzodiazepine among injecting drug users who report

injection of benzodiazepines [3]. Alprazolam is more subject to non-medical use compared with other benzodiazepines, and causes a disproportionally high level of serious harm than other benzodiazepines. Harms related to alprazolam include severe ischemic limb damage and disability associated with injecting alprazolam, memory blanks acutely and over days, dis inhibited and aggressive behavior and death when used concurrently with opioids [2]. Alprazolam is often sought to enhance the high of injected opiates and to upgrade the 'come down' from amphetamine use or symptoms of opiate withdrawal. Patients describe risky behaviors while under the influence of alprazolam that include driving, assaults, drug use, other criminal behaviors or waking up after a period of amnesia and being frightened by what might have happened to them or what they might have done. Alprazolam is readily available and relatively cheap.

Diazepam

Diazepam is primarily used to treat anxiety, panic attacks, insomnia, seizures, restless legs syndrome, and alcohol withdrawal. Even though it is used to treat many different ailments, it is still quite addictive [4]. It is a sedative and muscle relaxant that affects the central nervous system, and it is a benzodiazepine depressant similar to Xanax. Diazepam is a popular drug that is highly prescribed. The nature of Valium being readily accessible helps promote a Valium addiction. A person who is recreationally abusing diazepam is trying to attain an intense euphoric reaction to the drug, also known as getting "high". Once an addiction to diazepam is developed, the side effects can be very difficult to tolerate. Some of the symptoms experienced include dry retching, psychosis, slurred speech, panic attacks, hallucinations, increased risk of suicide, aggression and impaired coordination. Diazepam is often abused by merely swallowing several pills, but it can also be taken intravenously [5]. Repeatedly, diazepam is abused with alcohol and a number of other drugs. This increases the likelihood of developing a Valium addiction as well as an addiction to other drugs or alcohol. Some of the more common drugs types used in combination are amphetamines (Adderall, Dexedrine), other depressants (Marijuana, Alcohol), opiates (Heroin, Morphine), and hallucinogens (LSD, Angel Dust) [6]. Fatal respiratory depression (unable to perform the needed oxygen and carbon dioxide exchange) can easily happen when a combination of Valium and other depressants are mixed together. diazepam is sold to over 500 countries and is marketed under the names of Apozepam, Calmosedan, Benzopin, Anxionil, Calmigen, Bialzepam, Betapam, Azepam, Azedipamin, Calmpose, Apollonset, Antenex, Alboral, and Aneurol

Triazolam

Triazolam is a potent benzodiazepine, and some people can form an addiction to it in as little as two weeks. Even people taking with a prescription have become dependent on the drug. The presence of withdrawal symptoms when quitting Halcion is a major indicator of an addiction. People addicted to triazolam also feel helpless and unable to function without the drug [7]. Triazolam produces a gentle, calming effect. It slows brain activity to a point where worries seem to slip away, enhancing the user's mood. At higher doses, triazolam produces a euphoric high. But once an addiction forms, it can seem impossible to do anything without the drug. People who already have a strong addiction to other benzo may turn to triazolam because of its potency and rapid onset effects compared to similar drugs. Some trizolam users have reported having hallucinations from taking the drug, and have continued abusing it to achieve those effects. All the benzodiazepine has been abused shown in the table. Those which enter the brain rapidly such as diazepam are preferred to those which are absorbed more slowly such as oxazepam. Diazepam, nitrazepam and flurazepam are the most commonly abused benzodiazepine in the line with the increase in temazepam prescription and possibly because of the availability of easily injectable forms of temazepam from capsules and jellies and eggs [8]. Potent benzodiazepines such as triazolam, alprazolam and lorazepam have achieved popularity among benzodiazepine abusers [9] (Table 1).

Table 1: Triazolam.

Generic Name	Brand Name	Potency
Alprazolam	Xanax	0.5
Bromazepam	Lexotan	5
Chlordiazepoxide	Librium	25
Diazepam	Valium	10
Flurazepam	Dalmane	15-30
Lorazepam	Ativan	1
Medazepam	Nobrium	10
Oxazepam	Serenid	20
Temazepam	Normison, Euhypnos	20
Triazolam	Halcion	0.5

Health risks and social consequences

Some hazards associated with high dose benzodiazepines abuse that is shown in the table below the risks associated with them have been underestimated. Benzodiazepines are believed to be safe in over dose when the drug is taken alone. And the fetal outcome from over dosage is mostly with flurazepam and temazepam than with other benzodiazepines. Misuse and abuses of benzodiazepines also adds to the respiratory depression which is cause by other drugs. Benzodiazepines use increases the risk of road traffic accidents epically when driving under the influences of higher doses. Mental disturbances caused by benzodiazepines include black outs and memory loss, aggression, associated with obsession. The loss of the judgment and amnesia caused by the benzodiazepines may be related with high risk sexual behavior including casual sexual contacts and unprotected sexual activity which appears to be a particular feature of temazepam abusers. Mental impairment including scarcities in learning and memory. Regular use of benzodiazepines especially in high doses readily leads to physical dependence. The withdrawal symptoms on sudden cessation are shown in the Table 2 below.

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Table 2: Health risks and social consequences.

General	Complications of IV Use
Fatalities due to over dosage (particularly in combination with opioids)	thrombophlebitis
Violence and criminal behavior	Pulmonary micro embolism
Fetal and neonatal risks if taken in pregnancy	Gangrene requiring amputation
Dependence	Hepatitis B, C
Withdrawal seizers	HIV infection
Blackout and memory loss	Deep and superficial abscesses

Many of the risks for injecting benzodiazepines users are common to self-injectors of all types of drugs in the table. It has been claimed that the use of the temazepam is especially associated with the practice of sharing injecting equipment's thus increasing the risk of HIV infection and hepatitis. In addition benzodiazepines particularly temazepam obtained from the capsules tablets and elixirs are extremely irritating and likely to cause tissue damage. Doctors may prescribe a benzodiazepine for the following proper medical conditions such as Anxiety, insomnia, alcohol withdrawal, seizer's control, muscle relaxation, inducing amnesia for uncomfortable procedures, given before any surgery, panic attacks, and stress reactions. Benzodiazepine act on central nervous system which produce sedation, relaxation and lower down the anxiety level. More than 2,000 different benzodiazepines have been produced, from which only 15 are currently FDA-approved in the United States. They are usually classified upon their effect timing.

a. Ultra-short acting- Midazolam (versed), Triazolam (halcion)

b. Short-acting- Alprazlam (Xanax), Lorazepam (Ativan)

c. Long-acting- Chlordiazepoxide (Librium), diazepam (valium)

Benzodiazepines are commonly abused due to toxic effects that they produce and also to their prevalent availability. They can be chronically abused or as seen more commonly in hospital emergency departments purposely or accidentally taken in overdose. In some cases death and serious illness result from benzodiazepine abuse alone however they are normally taken with either alcohol or other medications. Benzodiazepines and alcohol combine can be dangerous and even lethal. Benzodiazepines also used as a "date rape" drug because they can even abolish functions that normally allow a person to resist or even want to resist sexual violence or physical attack [10]. Now the exposure and persuasion of people involved in this has increased intensely. The drug is usually added to alcohol containing drinks or even soft drinks in powder or liquid forms and can be hard to taste. Some people may have genetic fondness to become addicted to drugs and environmental factor also play role in addiction. Some of the more common environmental impacts are low socio economic status, unemployment, and peer pressure depression.

Benzodiazepine abuse symptoms

a. At regular and normal doses benzodiazepine relieves anxiety depression and enhances euphoric condition. People using benzodiazepine may feel sleepy and shaky and also have intense and disturbing dreams. Two of the main effects of abuse are development of tolerance and addiction. The side effects occur only due to long term usage with increased doses and the side effect due to over dosage or in the case of addiction include: Drowsiness, confusion, dizziness, blurred vision, weakness, slurred speech, lack of coordination, difficulty in breathing, coma [11].

b. Due to addiction chronic drug abuse include change in the mentally and physically appearance and their behavior which effect the relationships and their work performance. In children signs occur include abrupt change in their moods and their less attention and performance in school [12]. Chronic abuse of benzodiazepines can lead to the following symptoms that mimic many of the indications for using them in the first place:

c. Anxiety, insomnia, anorexia, headache, weakness

d. Benzodiazepines can lead to physical and psychological dependence which can result in withdrawal symptoms and even seizures when they are stopped abruptly. The symptoms of withdrawal can be similar like anxiety. Symptoms usually develop at 3-4 days from last use, they can also appear earlier with shorter-acting varieties [13].

Other Consequences

a. Excessive work or school absences.

b. Poor occupational or academic performance.

c. Familial problems, such as child neglect or divorce.

d. Neglect of hobbies and activities that were once enjoyable.

e. Loss of close friends due to Benz abuse.

f. Increased risk of injury or fatality due to accidents.

g. Increased risk of poly substance abuse (the abuse of more than one substance).

h. Increased risk of overdose due to poly substance abuse

Benzodiazepine misuse in opioid users

High risk opioids users typically misuse benzodiazepine to self-medication to increase the effect of opioids. Users self-medicate to treat psychiatric disorders and negative emotional such as anxiety and insomnia ant to alleviate withdrawal symptoms or the adverse effects of the drugs like alcohol or cocaine [14]. Benzodiazepine can also prolong the intensity and duration of the effects of the other illicit drugs. Benzodiazepine can also prolong the intensity and duration of the effect of opioids especially when injected. Patients in opioids substitution treatment with methodane for example may misuse benzodiazepine to increase the effects of their opioids medication reports suggests this practice may be correlated with

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an under dosing of the substitution treatment which results in the reemergence of the withdrawal symptoms. Benzodiazepine are generally taken orally snorted and by intravenous injection among high risk opioids user [15]. Benzodiazepine with a more rapid onset of action such as diazepam, alprazolam or lorazepam appear to be more frequently used by opioids abusers than those with a slower onset such as oxazolam or parazepam. Users obtain benzodiazepines from different sources including diversion of prescriptions such as doctor shopping the illicit market and the internet. Combined use of opoids and benzodiazepine is a significant issue among those receiving treatment [16].

Misuse and Abuse of Antidepressants

Many of the individuals who are being prescribed antidepressants don't usually misuse medication. But many classes of antidepressants have potential for medication abuse especially in individuals with another history of substance abuse is at higher risk of medication (antidepressant) abuse. As soon as any substance misuse is detected the patient should be referred to addiction specialist so that an effective treatment plan can be detected and implemented.

According to large scale survey of epidemiology antidepressant is not included in category of substance of abuse. But there is small literature, that is growing, that is reporting antidepressant abuse. The most diverse class of antidepressant is MAOIs that is being abused. Majority cases of MAOIs misuse is in 1960-1990. Some anti depressant that are abused are as follows:

Bupropion

This antidepressant acts by inhibiting dopamine and norepinephrine reuptake as a result there is increasing concentration of these two neurotransmitters intra-synaptically [17]. Bupropion has some activity on nucleus accumbens (a part of brain responsible for developing addiction). Bupropion is FDA approved drug for treating disorders like depression, nicotine addiction, and seasonal effective disorder. It is also used "off label" for sexual dysfunction, obesity, bipolar depression, hyperactivity disorder [18]. Bupropion has very low potential for drug abuse. Hiliard et al has stated that bupropion has replaced drugs with decreased availability like benzodiazepines and stimulants in correctional facilities as a result it is abused in these facilities. Bupropion abusers have cocaine or stimulant like effects (euphoria and sensation of feeling high) [19]. Reports have shown that athletes also misuse bupropion for euophoric and motivational effect [20]. Up till 2003 bupropion was on world's anti-doping agency list of prohibited substances. Occasional routes for drug abuse are oral, nasal for bupropion. Nasopharynx is highly vascularized route for excellent drug absorption directly in to blood stream by passing first pass metabolism. The only case of I/V abuse of bupropion was reported by Bari beau and Araki. A 29 year old woman abuses bupropion by injecting 100-200mg daily by dissolving 300mg tablet in water thus having euphoria and stimulant like effect. During abstinence experiences low mood and irritability [21].

MAOIs (Mono-amine oxidase inhibitors)

In late 1950 it was identified as effective antidepressant. The mechanism of action is inhibition monoamine oxidase A and B as a result prevents monoamine neurotransmitter breakdown and increase their availability [22]. Nor-epinephrine, epinephrine and serotonin are main substrates MAO-A. Benzylamine, Tyramineare substrate for MAO-B. MAOIs are selective for MAO-A, MAO-B or non-selective MAOIs usually are not considered to have abuse potential [23]. Number of reports of MAOIs misuse have shown that route of misuse is either not specified or oral. Mostly non-selective MAOIs phenelzine and tranylcypromine are mostly cited in literature. The pharmacological basis of misuse is not known but it is directly linked to similarity in structure with amphetamine but mechanism is unknown. Risks associated with MAOIs abuse are hypersensitivity, thrombocytopenia, Delirium etc [24].

Tricyclic antidepressants (TCA)

TCAs are widely used class of antidepressant. Their mechanism of action involves inhibition of reuptake of serotonin, nor-epinephrine. The most potent TCAs for serotonin transport blockage are tertiary TCA. Nor-epinephrine transport is blocked by secondary TCA [25]. Reports for the very first case for TCA was reported in 1970. Cohen et al surveyed 346 individuals who enrolled in methadone maintenance program and finds out that 25% took amitriptyline for achieving euphoria [26]. In many cases drug being abused is tertiary TCA which is usually taken orally [27]. It is reported by the individuals who are misusing TCA that they took large doses for high euphoria and pleasant feeling. TCA reports of abuse are also reported prisoners. Risks associated with misuse are delirium, confusion, seizures, orthostatic hypotension overdoses can cause death and main cause of death is cardiac arrhythmias [28].

Serotonin and nor-epinephrine reuptake inhibitors

SNRIs including desvenlafaxine, venlafaxine, duloxetine. Venlafaxine abuse can be studied in literature. A 38 years old individual with history of depression and amphetamine dependence was crushing and ingesting doses of duloxetine up to 40,50mg for achieving feeling of amphetamine like high [29]. Risks associated with venlafaxine abuse are chest pain in case of high dose, weight loss, tremors, muscle weakness, dizziness. Increased blood pressure is observed with venlafaxine abuse at therapeutic doses [30].

Selective serotonin reuptake inhibitor

SSRIs are most widely prescribed antidepressants. For anxiety and major depressive disorders they are first line of treatment. The mechanism of action is selective blockage of serotonin reuptake [31]. Although it is selective inhibitor of serotonin it still has effect on other neurotransmitter like dopamine and nor-epinephrine. Although it is widely prescribed it still has very few cases of abuse or misuse in literature. The route of abuse is oral mostly. A case of fluoxetine abuse described by Wilcox, by a woman experiencing anorexia nervosa. She took 120mg/day of fluoxetine for weight loss

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an appetite suppression. Another case of fluoxetine abuse was of a woman having history of poly-substance abuse, misusing fluoxetine by sucking very low dose through her mouth thus giving stimulant like effect. Paligaro and Paligaro reported a case of patient with history of cocaine or heroin abuse having fluoxetine abuse [32].

Tianeptine

Often included under classification of TCA but pharmacologically it is distinct. It's mechanism of action is not closely explained but most probably mechanism involves serotonin enhancement thus opposite to SSRI [33]. In rats it is shown that it increases extracellular concentration of dopamine in nucleus accumbens. Which play role in its abuse potential. Individuals who wants to have psychostimulant effect uses doses over 1000mg/day when usual maximum dose is 50mg/day. Route of abuse is not specified but usually it is oral [34].

Amineptine

It is an antidepressant classified as TCA but it is different due to 7-amino heptanoic acid chain it reduces dopamine selectivity in vitro and in vivo [33]. There are number of reports about amineptine abuse. Amineptine was removed from france and number of other countries because of concern about hepatotoxicity and abuse. Amineptine is never approved by FDA thus not available in USA [34].

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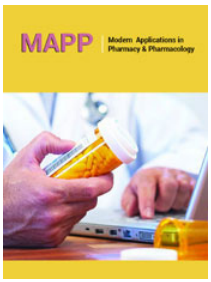

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