Withdrawal Symptoms Among Chronic Users of Oral Benzodiazepines for Anxiety Disorders

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ABSTRACT

Introduction: Anxiety disorders are among the most prevalent mental disorders in the general population. Benzodiazepines have been used extensively for the treatment of anxiety and related disorders.

Aim of the Study: To describe the characteristics of patients with anxiety disorders, who use oral BDZ for a long period of time (more than 2 years) and to identify the withdrawal symptoms they experience and the most annoying withdrawal symptom which may play a key role in hindering the discontinuation of the drug and delaying abstinence.

Subjects and Methods: 423 BDZ users (for more than 2 years) suffering from anxiety disorders were subjected to Psychiatric history and examination, they were diagnosed according to DSM-IV diagnostic criteria, using SCID-I. Patients were asked to fill in a designed questionnaire about the symptoms they suffered from after decreasing the doses of BDZ and then they were asked to specify the most subjectively annoying withdrawal symptom.

Results: The study revealed age, gender and specific diagnoses of this sample of patients suffering from different types of anxiety disorders and using BDZ for more than 2 years and correlation was done with the type of BDZ, the duration of its use and the most subjectively annoying withdrawal symptom.

Conclusion: The demographic and clinical characteristics, the type of BDZ and the duration of its use could significantly affect the perception of the patient about withdrawal symptoms and subsequently his ability to discontinue BDZ.

Key words: Withdrawal Symptoms; Benzodiazepines; Anxiety Disorders.

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INTRODUCTION

Hysterectomy Anxiety disorders are among the most prevalent mental disorders in the general population. Nearly 30 million persons are affected in the United States, with women affected nearly twice as frequently as men. Anxiety disorders are often chronic and resistant to treatment. Anxiety disorders can be viewed as a family of related but distinct mental disorders, which include the following as classified in the text revision of the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR):

1. Panic Disorder with or without agoraphobia.
2. Agoraphobia with or without panic disorder.
3. Specific phobia.
4. Social Phobia.
5. Obsessive-compulsive disorder (OCD).
6. posttraumatic stress disorder (PTSD).
7. Acute stress disorder.
8. Generalized anxiety disorder[1].

Beginning with chlordiazepoxide in 1960, benzodiazepines have been used extensively for the treatment of anxiety and related disorders. Eight benzodiazepine derivatives have been approved by the Food and Drug Administration for this purpose (Chlordiazepoxide, Diazepam, Clorazepate, Prazepam, Halazepam, Alprazolam, Lorazepam, Oxazepam). Another benzodiazepine, clonazepam, is also prescribed for this purpose but is labeled as an anticonvulsant[2].

Since the early 1960s benzodiazepines have become widely available, reaching prescription peaks in the 1970s[3]. Subsequently more and more data were reported indicating the disadvantages of long-term benzodiazepine use, such as the risk of dependence, a higher risk of accidents and falls and cognitive disturbances[4]. In the past few years the prevalence rate of benzodiazepine consumption in most European countries is estimated to be stable or slightly decreasing[5], but remains at levels varying between 2% -3% of the

general population[6]. Although long-term therapeutic use of benzodiazepines is controversial, limited evidence suggests long-term efficacy in specific diagnostic groups such as panic disorder and social phobia[7,8]. The prevalence of these disorders among people who are long-term benzodiazepine users is relatively low[9].

In many studies, a high proportion of benzodiazepine recipients used these medications for long-term treatment, defined as ≥60 days of use or as receiving benzodiazepines at each of several waves in a multiyear panel study[10,11].

Numerous patients think that chronic use of BDZ is not hazardous, while a lot of health professionals believe that chronic use of BDZ is synonymous to BDZ addiction. So where do chronic BDZ users stand, are they addicts or patients on continuation or maintenance therapy?

Initiation and Maintenance of Treatment:

Approaches to initiating benzodiazepine therapy are based largely on clinical experience. Therapy is initiated with a low dose that is based on the patient's age, sex, body size and medication history and the dose is increased every few days until therapeutic benefit is achieved or side effects supervene. When side effects are encountered, further increases in the dose should be delayed or the dose should be reduced. Many patients who have drowsiness or other sedative effects soon after the initiation of therapy report that these symptoms diminish with continued therapy. This diminution is attributable to adaptation or tolerance. In the majority of patients, a daily dose can be found that results in substantial clinical improvement with few or no sedative side effects[2]. The literature includes conflicting reports about the risks arising from long-term benzodiazepine use. Long-term users can develop withdrawal symptoms if benzodiazepines are tapered rapidly or discontinued abruptly[12].

The duration of benzodiazepine treatment should be tailored to the character of the underlying illness. Patients with intermittent symptoms or symptoms that are triggered by identifiable anxiety-provoking situations are candidates for intermittent therapy. Those with persistent unremitting symptoms may require more continuous treatment[13], but the appropriate duration of therapy for such patients has not been clearly established.

Substance Dependence:

The revised 3rd edition DSM-III-R and ICD-10 formulations for substance abuse and dependence defined substance dependence as follows: "A syndrome manifested by a behavioral pattern in which the use of a given psychoactive drug, or class of drugs, is given a much higher priority than other behaviors that once had higher value".

That central notion is continued in DSM-IV, which states: "The essential feature of dependence is a cluster of cognitive, behavioral and physiological symptoms indicating that the individual continues substance use despite significant substance-related problems".

The central notion in ICD-10 is virtually the same: "A cluster of behavioral, cognitive and physiological phenomena that develop after repeated substance use and typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance and sometimes a physical withdrawal state".

The above definitions in addition to DSM-IV-TR criteria for substance dependence[1] prove that Chronic use of a substance does not fulfill the criteria of substance dependence.

Benzodiazepine withdrawal syndrome:

Benzodiazepine withdrawal syndrome is the cluster of symptoms which appear when a person who has taken benzodiazepines long term and has developed benzodiazepine dependence stops taking benzodiazepine drug(s) or reduces the dosage too rapidly[14]. Chronic exposure to benzodiazepines causes physical adaptations in the brain to counteract the drug's effects. This is known as a tolerance and physical dependence. When the drug is removed or dosage reduced in an individual physically dependent on benzodiazepines, numerous withdrawal symptoms (both physical and psychological) may appear and will remain present until the body reverses the physical dependence by making adaptions to the drug-free environment and thus returning the brain to normal function[15].

Generally the higher the dose (dosage size), the longer a benzodiazepine is used (length of use), the more rapidly a benzodiazepine is discontinued (rate of tapering), the more likely severe withdrawal symptoms will occur. However, severe withdrawal symptoms can still occur during gradual dose reduction or from relatively low doses[16].

GABA is the second most common neurotransmitter in the CNS (after glutamate)[17] and the most abundant inhibitory neurotransmitter; roughly 1/4 to 1/3 of synapses use GABA. The use of benzodiazepines has an effect on almost every aspect of brain and body function, either directly or indirectly. Benzodiazepines cause a decrease in nor-epinephrine, serotonin, acetylcholine and dopamine. These neurotransmitters are needed for normal memory, mood, muscle tone and coordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control.

With chronic benzodiazepine use, tolerance develops rapidly to most of its effects, so that when benzodiazepines are withdrawn, various neurotransmitter systems go into overdrive due to the lack of inhibitory GABA-ergic activity. Withdrawal symptoms then emerge as a result and persist until the nervous system physically reverses the adaptions (physical dependence) which have occurred in the CNS.

Withdrawal symptoms typically consist of a mirror image of the drug's effects: sedative effects and suppression of REM and SWS stages of sleep can be replaced by insomnia, nightmares and hypnogogic hallucinations; its anti-anxiety effects are replaced with anxiety and panic; muscle relaxant effects are replaced with muscular spasms or cramps; and anticonvulsant effects with seizures, especially in cold turkey or overly-rapid withdrawal[18].

SUBJECTS AND METHODS

Thirty Aim of the study: To describe the characteristics of patients with anxiety disorders, who use oral BDZ for a long period of time (more than 2 years) and to identify the withdrawal symptoms they experience and the most annoying withdrawal symptom which may play a key role in hindering the discontinuation of the drug and delaying abstinence.

We considered patients to have used benzodiazepines as outpatients if they filled a prescription for any of the following medications on an outpatient basis: alprazolam, bromazepam, clonazepam, diazepam, lorazepam, We noted whether benzodiazepines were prescribed on an "as needed" (p.r.n.) Basis or as regular doses.

An operational definition to the chronic BDZ user was done: "These are patients who were complaining of anxiety symptoms, were prescribed BDZ in a clinical setting as a treatment for their anxiety disorder and who continued on BDZ intake for duration exceeding the longest recommended duration of treatment for any of the different subtypes of anxiety disorders".

The study was conducted in the psychiatric clinic of a private Saudi hospital, during one year period between September 2008 and September 2009. During the period of the study, 591 patients visited the Psychiatric clinic for BDZ prescriptions. They were educated about the study and an informed consent was obtained from those who accepted to participate. Seven patients refused to participate and 37 patients did not fulfill the criteria of chronic BDZ users (operational definition).

547 BDZ chronic users were subjected to psychiatric history and examination, SCID-I semi-structured interview and they were diagnosed according to DSM-IV diagnostic criteria. Patients having diagnoses other than anxiety disorders were excluded to avoid confounding results. They were: 38 patients diagnosed as depressive disorders, 28 patients diagnosed as bipolar disorders, 19 patients diagnosed as schizophrenia, 14 patients diagnosed as adjustment disorder with depressive symptoms, 10 patients diagnosed as dementia, 10 patients diagnosed as insomnia and 5 patients diagnosed as impulse control disorders. After exclusion of the previous groups of patients, 423 patients suffering from different subtypes of anxiety disorders were selected to be the subjects of the study.

They were prescribed pharmacotherapy for their psychiatric symptoms according to their diagnoses and they received sessions of supportive psychotherapy (ranging from 4-8 sessions according to their condition), Supportive therapy sessions were led by a licensed clinical psychologist. Before participating in this study, she had previously treated a minimum of four patients by using this treatment. A detailed manual outlining each session was utilized. Two physicians (a general practitioner and a psychiatrist) provided consultations for the medication tapering condition. A detailed psychiatric education related to anxiety disorders and BDZ chronic use was given to patients, during which they were advised to decrease the doses of BDZ very gradually (1/4 dose every 2-4 weeks). In the subsequent visits every subject filled in a designed questionnaire about possible withdrawal symptoms and was asked to specify the most annoying symptom.

This questionnaire was designed by the authors of this study using available information about reported withdrawal symptoms of BDZ use[19-30]. Symptoms were translated into Arabic language and was revised clinically for verification of patients understanding and accurate description.

RESULTS

Table Distribution of Anxiety disorders according to gender age and duration of BDZ use are represented in table (1, 2 and 3).

Table 1: Gender Distribution in different Categories of Anxiety Disorders

	Male N (%)	Female N (%)	Total
SAD	90 (82.6)	19 (17.4)	109 (25.8)
GAD	90 (72.0)	35 (28.0)	125 (29.6)
MAD	69 (65.7)	36 (34.3)	105 (24.8)
Panic Depression	22 (78.6)	6 (21.4)	28 (6.6)
Ad D Anx	5 (41.7)	7 (58.3)	12 (2.8)
Ad D Anx Dep	7 (43.8)	9 (56.3)	16 (3.8)
OCD	9 (47.4)	10 (52.6)	19 (4.5)
Sp Phobia	5 (100.0)	-	5 (1.2)
PTSD	3 (75.0)	1 (25.0)	4 (0.9)
Total	300 (70.9)	123 (29.1)	423 (100.0)

Table 2: Age Distribution in different Categories of Anxiety Disorders.

	Mean (SD)	Range
SAD	44.5 (12.1)	23 – 94
GAD	44.9 (11.3)	21 – 73
MAD	46.4 (12.7)	28 – 88
Panic Depression	43.6 (9.9)	26 – 67
Ad D Anx	41.6 (12.1)	22 – 68
Ad D Anx Dep	42.9 (9.8)	20 – 60
OCD	41.1 (18.6)	20 – 84
Sp Phobia	44.8 (6.7)	34 – 51
PTSD	41.2 (7.5)	31 – 49
Total	44.7 (12.1)	20 – 94

Table 3: Duration of BDZ Intake in different categories of Anxiety Disorders

	Median	IQR
SAD	51.0	36.5 – 80.0
GAD	54.0	36.5 – 89.0
MAD	52.0	41.0 – 104.5
Panic Depression	63.0	48.7 – 144.7
Ad D Anx	45.0	27.5 – 75.0
Ad D Anx Dep	51.0	30.0 – 76.2
OCD	58.0	29.0 – 92.0
Sp Phobia	48.0	29.5 – 80.5
PTSD	35.0	26.5 – 47.2
Total	51.0	37.0 – 89.0

Correlation between different factors and the discontinuation of BDZ use are represented in table (4 - 10).

Table 4: Different Withdrawal Symptoms in relation to BDZ Discontinuation.

	Continue	Discontinue	P value
Insomnia	94 (26.7)	6 (21.4)	0.005*
Irritability/Nervousness	52 (14.8)	4 (14.3)	0.023*
Dysphoria	30 (8.5)	6 (21.4)	NS
Apprehension to Stop	28 (8.0)	1 (3.6)	0.02*
Impulsivity	14 (4.0)	1 (3.6)	0.152 NS
Tachycardia	16 (4.5)	-	0.031*
Psychomotor Agitation	11 (3.1)	-	0.08 NS
Body Pains	11 (3.1)		NS
Headache	11 (3.1)	1 (3.6)	NS
Excessive Thinking	8 (2.3)	-	0.150 NS
IBS	10 (2.8)	1 (3.6)	NS
Tremors of the tongue, eye lid or hands	10 (2.8)	-	0.098 NS
Muscles Twitches	7 (2.0)	-	0.187 NS
Obsessive Symptoms	5 (1.4)	4 (14.3)	0.184 NS
Grand Mal Convulsions	10 (2.8)	-	0.098 NS
Dyspnea	8 (2.3)	1 (3.6)	NS
Malaise/Weakness	9 (2.6)	1 (3.6)	NS
Night Mares	6 (1.7)	1 (3.6)	NS
Paranoid Ideation	2 (0.6)	-	NS
Nausea/Vomiting	4 (1.1)	-	NS
Sweating	5 (1.4)	-	NS
Postural Hypotension	1 (0.3)	-	NS

Table 5: Gender Distribution of Anxiety Disorders Patients in relation to BDZ Discontinuation.

Gender: N (%)	Continue	Discontinue
Males	280 (93.3)	20 (6.7)
Females	105 (85.4)	18 (14.6)

% Are calculated from rows

Table 6: Average Age of Anxiety Disorders Patients in relation to BDZ Discontinuation.

	Continue	Discontinue
Mean (SD)	45.2 (12.1)	40.1 (10.4)
Range	21 – 94	20 – 67
P value	0.014*	

Table 7: Duration of BDZ use among those who discontinued compared to those who continued.

	Median	IQR
Discontinue (n=38)	51.0	37.0 – 88.5
Continue (n=385)	55.5	34.7 – 93.7
P value	NS	

Table 8: Occurrence of Withdrawal Symptoms in relation to BDZ Discontinuation.

Withdrawal Symptoms	Continue	Discontinue
Absent	33 (8.6)	10 (26.3)
Present	352 (91.4)	28 (73.7)
P value	0.002*	

Table 9: Discontinuation of BDZ according to use of another psychotropic.

	Continue	Discontinue
Alone	261 (95.6)	12 (4.4)
With other TTT	93 (82.3)	20 (17.7)
PRN	23 (82.1)	5 (17.9)
PRN With other TTT	6 (85.7)	1 (14.3)
P value	<0.001*	

Table 10: Discontinuation of BDZ Intake in relation to type of BDZ medication at first time intake.

	Continue	Discontinue
Alprazolam	159 (41.3)	17 (44.7)
Bromazepam	85 (22.1)	11 (28.9)
Diazepam	70 (18.2)	1 (2.6)
Clonazepam	62 (16.1)	6 (15.8)
Lorazepam	4 (1.0)	3 (7.9)
P value	0.007*	

DISCUSSION

In This study examined the use of benzodiazepines among patients diagnosed as having anxiety disorders, treated in a private psychiatric clinic. 423 patients who used oral BDZ for more than 24 months were examined by SCID-I and were diagnosed as having anxiety disorders: 25.8% of patients suffered from Social Anxiety Disorder, 29.6% had Generalized Anxiety Disorder, 24.8% were diagnosed as Mixed Anxiety Depression (Table 1)

Interestingly, males with SAD, GAD, MAD, Panic D, PTSD were more prone than females with the same diagnoses to use BDZ. While Females with OCD, Adjustment D with anxiety symptoms, were more commonly using BDZ.

BDZ use to be common among all age groups ranging from early youth to elderly populations (Table 2). This finding is surprising, given that physicians must balance the risks and benefits of prescribing benzodiazepines and the risks appear to increase with the patient's age. It is possible that a higher percentage of older patients, compared to younger patients, have had exposure to benzodiazepines and that older

patients are thus more likely to request these medications. Older patients may also perceive greater benefit from benzodiazepine use or have more difficulty in discontinuing these medications once they have been started [10,31,32].

These patients have been taking BDZ without increasing the dose for more than 24 months. However when asked to decrease the dose on gradual basis aided by psychoeducation and supportive psychotherapy, they experienced a number of withdrawal symptoms as follows: Insomnia with 23.64% of patients, irritability with 13,24%, Dysphoria with 8.51%, apprehension to stop 6.86% (table 5). Withdrawal symptoms were least prominent in cases suffering from Specific phobia (60%), PTSD (75%) and Adjustment disorder with anxiety symptoms (75%)

Despite withdrawal symptoms, 42.1% of OCD patients, 18.8% of Adjustment Disorder with anxiety depression patients and 16.7% of Adjustment Disorder with anxiety patients, were able to discontinue BDZ doses within 3 months, with the aid of non BDZ psychiatric medications and supportive psychotherapy. However, some withdrawal symptoms (insomnia, irritability/nervousness, apprehension to stop and tachycardia) were significantly hindering the process of discontinuation (table 4) and the occurrence of withdrawal symptoms was a highly significant hindering factor to accomplishing abstinence from BDZ (table 8).

Studies on mice have found that discontinuation of benzodiazepines leads to decreased agonist affinity and increased inverse agonist affinity of the benzodiazepine receptors, essentially causing the receptors to reverse their natural function. This may explain at least in part the cause of the benzodiazepine withdrawal effects down regulation of other receptor subtypes[33]. Tolerance and the resultant withdrawal syndrome may be due to alterations in gene expression which results in long term changes in the function of the GABAergic neuronal system[34,35].

Female patients were more able to discontinue BDZ medications (table 5). The ability of the patient to discontinue BDZ treatment after prolonged use was also significantly affected by the patients' ages in favor of the youth (table 6), younger female patients were more flexible as regards the discontinuation strategies and supportive therapy sessions, they were also more understanding to the psychiatric education.

Interestingly, the use of another psychiatric treatment enhances the ability of the patient to discontinue the BDZ, as long as his symptoms of anxiety are controlled. Also the intermittent irregular (p.r.n.) Use of BDZ leads to easier discontinuation process (table 9)

Problems experienced by patients stopping long-term benzodiazepine use initiated the development of treatment strategies for discontinuing these drugs. A stepped care approach to address the problem of long-term use was proposed[36]. They advised starting with a minimal intervention and, if this failed, gradually intensifying treatment from supervised gradual withdrawal after patient assessment to specialized care including augmentation strategies[37].

The type of BDZ drug significantly affects the discontinuation rates (table 10) with Diazepam being the hardest to discontinue and Lorazepam being the easiest. Apparently the long half life of the drug makes it difficult to be discontinued, which is not the case with addictive drugs, because tolerance is faster and stronger with shorter acting drugs. Unexpectedly the duration of BDZ use was not statistically significant, so did not affect the discontinuation process. The duration of most controlled clinical trials of anxiolytic therapy was 4 weeks or less[38,39], so that efficacy beyond 4 weeks of therapy is less well established. Nonetheless, long-term (2-6 months) efficacy has been demonstrated for some benzodiazepines in a limited number of clinical trials[40-44].

Limitations:

This study had several limitations that must be considered in interpreting the results. It would be beneficial if we had more demographic data that may help in a full description of chronic BDZ users. The withdrawal symptoms would have been analyzed in a broader and more detailed study. It would be a more informative study if we could collect serum levels of BDZ drugs and relate them to withdrawal symptoms.

However, this study illustrated a neglected but quite important psychiatric problem still in the grey zone of the psychiatric classification. Nevertheless, given the numerous studies demonstrating adverse medical outcomes among long-term users of benzodiazepines, the high prevalence of benzodiazepine use in this sample remains a concern. Further research is needed on both the risks and benefits of this widespread practice. The question which remains without a definite answer is: Should the chronic use of BDZ become a psychiatric diagnosis as long as patients experience withdrawal symptoms on decreasing the dose and subsequently their functioning is affected? Or should it stay outside the scope of Psychiatric diagnosis as long as patients do not i and are stable on medications? Or there may be a third option?

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