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Review Article

Anxiety Disorders: Use of Benzodiazepines Maximizing the Benefits and Minimizing the Risks

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Abstract

Anxiety disorders are the most prevalent mental health conditions. Although they are less visible than schizophrenia, depression, and bipolar disorder, they can be just as disabling. The diagnoses of anxiety disorders are being continuously revised. Both dimensional and structural diagnoses have been used in clinical treatment and research, and both methods have been proposed for the new classification in the *Diagnostic and Statistical Manual of Mental Disorders IV (DSM-5).* However, each of these approaches has limitations. More recently, the emphasis in diagnosis has focused on neuroimaging and genetic research. This approach is based partly on the need for a more comprehensive understanding of how biology, stress, and genetics interact to shape the symptoms of anxiety.

Anxiety disorders can be effectively treated with psychopharmacological and cognitive–behavioral interventions. These interventions have different symptom targets; thus, logical combinations of these strategies need to be further studied in order to improve future outcomes. New developments are forthcoming in the field of alternative strategies for managing anxiety and for treatment-resistant cases. Additional treatment enhancements should include the development of algorithms that can be easily used in primary care and with greater focus on managing functional impairment in patients with anxiety.

Keywords

Pharmacotherapy, Anxiety disorders, Benzodiazepines.

Introduction

Anxiety disorders are among the most prevalent and disabling psychiatric disorders in the United States. Approximately one in four adults will suffer from an anxiety disorder at some point in their lives. Patients with anxiety disorders experience substantial physical and emotional discomfort and have elevated rates of substance use and medical illnesses. Co-occurring anxiety disorders in the context of other psychiatric disorders, for example major depressive disorder (MDD) or bipolar disorder, are associated with a more chronic and treatment refectory course and these patients are at an elevated risk for suicide. The combination of high prevalence and high functional disability associated with anxiety disorders leads to a particularly high economic and social cost.

The core feature of anxiety disorders is excessive fear and anxiety and related behavioral disturbances. The diagnostic schema for anxiety disorders in the United States was revised with the publication of the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) .The DSM-V recognizes the following anxiety disorders: separation anxiety disorder, selective mutism, specific phobia (SP), social anxiety disorder (SAD), panic disorder, agoraphobia, generalized anxiety disorder (GAD), substance/medication-induced anxiety disorder and anxiety disorder due to another medication condition. There are two residual categories for presentations that do not fit any of the preceding categories: other specific anxiety disorder and unspecified anxiety disorder. Separation anxiety disorder and selective mutism are expressed primarily in childhood and will not be discussed here further. In DSM-V, agoraphobia has been added as a new diagnosis and posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) have been moved elsewhere in the diagnostic schema.

PTSD is a disorder of excessive fear and anxiety and is appropriately retained in considerations of the biology and treatment of anxiety disorders. OCD may be distinctive compared to the anxiety disorders and PTSD in terms of clinical presentation, biology and treatment.

As a group, anxiety disorders represent a heterogeneous group of illnesses that have excessive fear and anxiety as their core phenomenology. Psychiatry has struggled to determine the appropriate nosological classification of these disorders and the newest version of the DSM presents yet another configuration, as noted above. The changing diagnostic landscape and uncertain boundaries between anxiety disorders create challenges for drug development, compounding other hurdles noted above. In response to these challenges, some major pharmaceutical companies have either substantially reduced their investment in CNS research or else eliminated their CNS programs altogether. This concerning development compels changes in the approach to anxiety drug development by academia and industry.

Numerous treatment guidelines recommend that long-term use of benzodiazepines (BZD) should be avoided primarily due to development of tolerance and a risk for BZD dependence. Despite this, long-term BZD use remains a controversial subject in clinical patient care with "for and against" debates. However, there is no explicit understanding of what is meant by long-term BZD use in real world. The aim of this study was to assess different definitions, usage patterns, prevalence and other characteristics of long-term BZD use based on published register-based studies. Synthesis of these characteristics is essential to derive a meaningful definition of long-term BZD.

Despite current guidelines, benzodiazepines are still considered by many clinicians to remain good treatment options, in both the acute and the chronic phase of the treatment of anxiety disorders, partially because of their rapid onset of action and their efficacy with a favourable side effect profile, and also because of the sometimes only incomplete therapeutic response and the emergence of side effects of alternative medications. Having experienced good initial symptom relief with benzodiazepine treatment, patients may also be reluctant to taper it down. Clinicians should, however, bear in mind the frequent physiological dependence associated with these substances, and suggest both pharmacological and psychological treatment alternatives before opting for a long-term benzodiazepine treatment, which may remain necessary in certain clinical conditions.

Benzodiazepines *v*. antidepressants for anxiety disorders

Separating short-term and long-term treatment of anxiety disorders is somewhat artificial. Most anxiety disorders have a chronic course and the initial choice of pharmacological agent is likely to determine treatment over the subsequent months or even years. Thus, it is important to ascertain when treatment with benzodiazepines is a reasonable initial strategy.

Mechanism of action, clinical effects and types of benzodiazepines

It is widely believed that benzodiazepines enhance the effects of the neurotransmitter gamma-aminobutyric acid (GABA). They do so through action at benzodiazepine receptors. Alleviation of fear is a result of GABA-induced inhibition of neuronal transmission that occurs in the amygdala, located in the brain stem, and thought to mediate brain circuits involved in the appraisal of threat and experience of fear.

Benzodiazepines produce a calming effect, decrease anxiety, relax tense muscles, alleviate symptoms of fear-related bodily arousal (e.g. heart racing, trembling), and promote sleep. It appears that soon after taking a benzodiazepine, many people experience a pleasant ‘glowing’ feeling and a sense of remoteness from or indifference to their worries or fears, but it is unclear whether these effects play a significant role in motivating people with anxiety disorders to continue taking benzodiazepines. Perhaps the key characteristic of benzodiazepines is that when dosed correctly, they calm and relax without causing drowsiness, and therefore do not interfere with routine, everyday activities and functioning.

However, classification on these grounds has several practical implications. Commonly used benzodiazepines

Short-acting

1. • Alprazolam
2. • Lorazepam

Intermediate-acting

1. • Oxazepam

Long-acting

1. • Diazepam
2. • Ethyl loflazepate
3. • Clorazepate
4. • Chlordiazepoxide
5. • Clonazepam

Issues in long-term benzodiazepine use

As a long-term treatment for anxiety disorders, benzodiazepines will be administered either as monotherapy or in combination with an anti-depressant. Benzodiazepines should be continued for at least 6–12 months after remission has been attained. To maximise treatment effects, patients need to be given accurate and unambiguous information about the benefits and risks of long-term benzodiazepine use.

Dependence, misuse and addiction

Dependence

Patients with anxiety disorders treated continuously with benzodiazepines for several weeks develop therapeutic or non-addictive dependence. This dependence is pharmacological (physical) in nature; it is a consequence of the physiological adaptation at the receptor level to the continuous use of benzodiazepines.

Misuse

Benzodiazepine misuse is a pattern of indiscriminate use with harmful behaviour (e.g. stealing to obtain the medication), often with a tendency to increase the dose. In the absence of a history of alcohol or other substance misuse or dependence, benzodiazepine misuse among patients with anxiety disorders is rare.

Addiction

Addiction encompasses an intense craving for and preoccupation with a substance, uncontrollable drug-seeking behaviour, tolerance, adverse health and/or social consequences, and occurrence of withdrawal symptoms on abrupt discontinuation of the substance.

Withdrawal symptoms and return of anxiety after cessation of benzodiazepines

Benzodiazepine withdrawal syndrome is often portrayed as dangerous and it is therefore dreaded by both patients and physicians. In fact, some patients continue taking benzodiazepines only to avoid withdrawal. This intensifies their fear that they will not be able to stop the medication and reinforces the notion that benzodiazepines are addictive.

Conclusions

Long-term BZD use is common and a clinical reality. Uniform definitions for "long-term", which is in line with population-based evidence, is needed to have more comparable results between studies. Our systematic review suggests that duration of BZD treatment over six months, the most common definition for long-term BZD use in the included studies. As also recommended previously, it is a useful starting point for further analyses on disadvantages but also potential advantages associated with long-term BZD use.

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