REVIEW ARTICLE

The use of benzodiazepines in bipolar disorders

Yassine Otheman[1*], Mohammed Kadiri[2], Jamal Mehsanni[2], Mohammed Zakaria Bichra[2]

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INTRODUCTION: Benzodiazepines are widely prescribed for patients with bipolar disorders, especially in episodes of mood disturbances. However, comorbid anxiety, sleep problems and substance abuse are frequent in these patients, and may lead to more prescription of benzodiazepines in inter-critic period.

DISCUSSION: While acute anxiety/sleep problems and substance withdrawal syndromes are potential indications for short-term benzodiazepines use, the long-term use may aggravate the outcome of bipolar disorders, clinically and functionally, and lead to poor prognosis in general. The lack of studies about the management strategies, in patients coming with bipolar disorders and one of these particular situations, is the reason why the use of benzodiazepines may still be a solution for many practitioners, but that must be done with a lot of caution. This situation highlights the need to explore more deeply this important question.

CONCLUSION: Although benzodiazepines have many benefits for patients with bipolar disorders, their use must be very cautious, because of the associated risk of misuse and other possible consequences, especially in some particular clinical situations. Concerns remain about efficacious alternatives to manage comorbid anxiety, sleep disturbances and substance use disorders. Despite the clinical importance of that issue, there is a lack of randomized studies. Due to ethical reasons, this situation highlights the need to explore more deeply this question, by naturalistic studies and neurobiological research, to better understand the role of BZD and GABAergic mechanisms in the pathophysiology of BD, anxiety and sleep disturbances.

Key Words: *Benzodiazepines; Bipolar disorders; Anxiety; Sleep disturbances; Substance abuse*

BENZODIAZEPINES

Benzodiazepines (BZD) are one of the most prescribed pharmacological agents in the world (1,2), despite the risks of dependence, abuse and other concerns (3). They are widely prescribed for patients with mental disorders such as schizophrenia, major depressive disorder, opioids detoxification, anxiety disorders and bipolar disorders (BD) (4,5).

Because of the high prevalence of anxiety and insomnia in patients with BD, benzodiazepines are commonly used by these patients (6,7), prevalence of BZD use among bipolar patients is varying from 58% to 75% (5,8).

Prescribing BZD in patients with BD must be weighed depending on the clinical presentation, and individual story of substance abuse. The variety of mood state and the frequency of comorbidity in BD, especially with anxiety disorders, sleep disturbances and substance abuse, make it difficult to have a unique strategy of BZD prescription. In this article, after a brief presentation of BZD and BD, we will address different situations where BZD may be used in bipolar patients and the problems they may pose.

Benzodiazepines are psychoactive drugs that were discovered accidentally by Leo Sternbach in 1955. They were first greeted by practitioners and patients, and were among the most prescribed drugs in the 1970s. This popularity has since been slowed down by many shortcomings, like abuse, dependence and cognitive impairment (9).

The mechanism of action of BZD is based on the enhancement of GABA (gamma-amino-butyric acid) at the GABAA receptor. GABA is the major inhibitory neurotransmitter in the central nervous system. BZD have many properties: anticonvulsant, hypnotic, muscle relaxant, amnesic and anxiolytic. However, they are more used by physicians to reduce anxiety and insomnia (3).

Benzodiazepines are indicated for short-term treatment of severe anxiety, occurring alone or in association with insomnia or short term organic or psychiatric disorders; while only severe or disabling insomnia should be treated by BZD for a short period (3,10). Many side effects may occur with BZD, especially paradoxical excitement that may have possible legal implications due to aggressive impulses or hostility (3).

Discontinuation maybe accompanied by a withdrawal syndrome that can include a rebound of anxiety and insomnia, with a prolonged sleep onset, nightmares, irritability and muscle spasms. These symptoms are usually reversible in few days, but the patient often resumes medication and becomes dependent to it (11,12).

Moreover, BZD are widely misused, especially in the context of recreational or addictive behaviors (13). There is also a lot of evidences, suggesting cognitive impairment in the long term users of BZD (14,15), and an exacerbation of cognitive dysfunction in patients with bipolar disorders who have BZD dependence (16,17). Recent data show that even low usage of BZD was associated with increased risk of mortality (18,19).

LITERATURE REVIEW

Bipolar disorders

Bipolar disorders are common, chronic and of variable severity. They are characterized by recurrent episodes of mania with or without episodes of major depression (bipolar I disorder), or episodes of hypomania and major depression (bipolar II disorder) (20). The presence of at least four mood episodes that meet the criteria for manic, hypomanic, or major depressive episode, in the last year, define rapid cycling BD (20). The lifetime prevalence is 1% for bipolar I and 0.5 to 1.57% for bipolar II disorders (21,22). Bipolar disorders are highly linked to suicide, approximately 25 to 50% will attempt suicide at least once over their lifetime (23,24), with 10 to 20% completing suicide (23,25,26). They are also a disabling condition with loss of productivity, reduced occupational functioning and medical comorbidity leading to billions of dollars in healthcare costs (27-29).

The main treatment of these disorders are mood stabilizers, such as lithium, anticonvulsants, and antipsychotics, that should be continued indefinitely because of the risk of relapse (30,31). Other symptomatic medication, like BZD, maybe prescribed to deal with acute psychiatric disturbances. While psychotherapy is of an important contribution, especially by educating patients and their relatives about relapse, suicidal thoughts, and the necessity of early intervention to prevent complications (32,33).

However, even with important advances in research about BD, many patients remain symptomatic in inter-critic period (between the episodes), with social and functional impairments (34,35); and a lot of progress is expected to overcome these difficulties.

[1]*Assistant Professor of Psychiatry, Department of Psychiatry, Mohamed V Military Hospital, Rabat, Morocco;* [2]*Professor of Psychiatry, Department of Psychiatry, Mohamed V Military Hospital, Rabat, Morocco*

Correspondence: Dr. Yassine Otheman, Department of Psychiatry, Mohamed V Military Hospital, Rabat, Morocco. Tel: +212661056261, email: Dr.yassine.otheman@gmail.com

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Benzodiazepines in bipolar disorders

Benzodiazepines are frequently prescribed for patients with BD. The use of BZD as adjunctive treatment in depressive episodes is common, especially to reduce associated anxiety, insomnia, and risk of suicide during the first days of treatment (36,37). Benzodiazepines have also demonstrated efficacy for the acute management of mania (38,39) as adjuncts to mood stabilizers or antipsychotic drugs, to improve sleep and control anxiety, restlessness, agitation and aggressiveness (40,41). However, there is less evidence supporting their adjunctive use in other situations, and during longer-term treatment of patients with BD (42). Prescribing BZD is more frequent for patients with residual manic symptoms in bipolar I disorder, and BZD are usually used in difficult-to-treat, complex patients, with severe forms (42,43).

Few studies looked at the general effect of using BZD in patients with BD. Bipolar choice was a 6-month, randomized, multi-site comparison of a sample of 482 patients with bipolar I or II disorder. Authors found 138 (28.6%) BZD are users at baseline or follow-up. The researchers compared clinical measures, in BZD users and nonusers, including the Bipolar Inventory of Signs and Symptoms (BISS), Clinical Global Impressions-Bipolar scale (CGI-BP) and Clinical Global Impression Efficacy Index (CGI-EI). Although both groups demonstrated improvement, BZD users experienced significantly less improvement in BISS and CGI-BP scores than non-users did. Moreover, the outcome measure in patients with comorbid anxiety or substance use disorders was not affected by BZD use (44).

Another study on the effect of BZD on BD had demonstrated that Patients, whose state requires BZD, may be at particularly high risk for recurrence of a mood episode. The Benzodiazepine use was linked to greater hazard of recurrence that persisted after adjustment for potential confounding variables, like anxiety comorbidity, anxiety symptoms and residual mood symptoms. Authors concluded that the need for BZD treatment in these patients may simply be a marker for severe form of illness, rather than indicating an effect of benzodiazepines on the outcome (42). These findings highlight the fact that Practitioners use benzodiazepines to overcome the lack of alternatives in some difficult clinical situations.

DISCUSSION

Benzodiazepines in bipolar inter – Critic period

As we reported earlier, BZD are often used in the handling of acute period of mood episodes, and their use in other situations is not clearly established. In inter-critic period, the use of BZD is generally the same as in non-bipolar patients. However, anxiety, sleep disturbances and substance use problems, which are frequent in patients with BD, may pose some particular problems with the use of these molecules.

Anxiety

Anxiety is very common in BD, nearly one in two patients has an anxiety disorder in their lifetime (45), elevated rates of anxiety disorders were found in patients with BD (46), increasing adverse outcomes such as suicidal behavior, impaired functioning, substance and alcohol misuse (47,48).

While using BZD to manage acute anxiety in patients with BD is accepted, their use is not recommended, as in general, to treat long-term anxiety. A major problem posed by the comorbidity of anxiety and BD is that antidepressants, used as core treatment for anxiety disorders, are known to induce manic switch and cycle acceleration in bipolar patients, especially if used without mood stabilizers (49). In fact, there are few options to treat established anxiety disorders in this case, with scarce research in this area (50). Some reports suggest the efficacy of the combination of olanzapine (Second generation antipsychotic) and fluoxetine (Selective serotonin reuptake inhibitor) (51), as well as quetiapine (atypical antipsychotic) (52,53), to reduce anxiety symptoms in bipolar patients. The limited proof for pharmacological treatment in this comorbidity has led to recommendations that psychotherapy, such as cognitive behavioral therapy, must be tried as first-line treatments (54). However, it has not been shown to be of major effect (53).

The management of anxiety symptoms in BD is not well studied (55), and more investigation is needed to adopt an optimal approach for this comorbidity.

Sleep disturbances

Bipolar disorders and sleep disturbances are strongly linked. Reduced need for sleep is the most frequent symptom of mania, while insomnia or hypersomnia are common during depression episodes. Sleep may also be disturbed in the inter-critic period, with implications in both prodromal and syndromal phases of BD (56). Insomnia is generally reported by 70% of BD patients (57,58).

Although depressive and manic episodes and inter-critic mood disturbances are thought to be linked to most of medical and social burden, recent evidences suggest that sleep disturbances play also a major role in these repercussions. In addition to being an important factor contributing to outbreak of BD (59), they are also responsible, at least in part, of functional and medical outcomes (60), especially by enhancing the risk for relapse and suicide attempts (61).

Sleep disturbances persist at high rates, despite adequate pharmacological and psychological interventions for BD (62).

The use of sedative antipsychotics, like chlorpromazine and levomepromazine, is frequent, but may lead to poorer functional improvement and to depressive mood (63,64). Benzodiazepines are not a good solution for persistent sleep problems; nevertheless, they are efficacious for acute sleep disturbances in all the phases: mania, depression and inter-critic period (62). In our practice, we have noticed that BZD may help to prevent relapse by handling acute sleep problems in stabilized bipolar patients, but studies are needed to confirm this clinical impression.

Psychological and lifestyle interventions may be preferred for their safety in term of side effects, for their durable action and the absence of abuse potential (62).

Substance abuse

Another situation, where BZD use may be problematic in BD, is substance abuse comorbidity. Bipolar disorders are associated with the highest rate of substance abuse among mood disorders (65). In patients with BD, substance use disorders are related to an increased risk of relapse, rapid cycling and other negative consequences, including increased symptom severity (66) and poor treatment compliance (67,68), resulting in poor prognosis, and higher rates of utilization of acute services, leading to more costly care (69).

Studies have found that alcohol use disorder is present in about half of patients with BD, while 41% of this population present any other substance use disorder (70,71). Concerning illegal drugs, cannabis is the most commonly used among patients with BD (72,73) estimates of use vary from 8% to 22%, and the life-time prevalence of its use is 30% to 64% (74). Both alcohol and cannabis are known for their sedative and anxiolytic effects, therefore, bipolar patients in manic and depressive period may use them as self-medication (75). Alcohol affects the GABA-benzodiazepine-chloride complex and has an agonist-like action (76).

Prescribing BZD in this population of patients, with bipolar and substance use disorders, must be done carefully, because of the high risk of misuse. On one hand, being addictive to a substance is a marker of susceptibility for other addictions, and in the other hand, the high prevalence of anxiety and sleep problems, that characterize people with substance use problems, may lead to long-term consumption of BZD (8,77).

The misuse of BZD, in combination with alcohol or other sedative substance, may create an additive effect, increasing central nervous system suppression, and causing physical and psychological repercussions (4,78-80). Avoiding the use of benzodiazepines (or other sedative-hypnotics) in patients with alcohol problems should prevent many potential complications (81).

CONCLUSION

Although benzodiazepines have many benefits for patients with bipolar disorders, their use must be very cautious, because of the associated risk of misuse and other possible consequences, especially in some particular clinical situations. Concerns remain about efficacious alternatives to manage comorbid anxiety, sleep disturbances and substance use disorders. Despite the clinical importance of that issue, there is a lack of randomized studies due to ethical reasons. This situation highlights the need to explore more deeply this question, by naturalistic studies and neurobiological research, to better understand the role of BZD and GABAergic mechanisms in the pathophysiology of BD, anxiety and sleep disturbances.

CONFLICT OF INTEREST

None.

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