Journal of Affective Disorders 128 (2011) 305–308

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Efficacy and safety of nonbenzodiazepine hypnotics for chronic insomnia in patients with bipolar disorder

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ARTICLE INFO

Article history:
Received 27 May 2010
Accepted 17 July 2010
Available online 11 August 2010

Keywords:
Bipolar disorder
Insomnia
Hypnotic

ABSTRACT

Background: Insomnia in patients with bipolar disorder (BD) can cause distress, daytime dysfunction, cognitive impairment, worsening of hypomanic/manic symptoms and increased suicide risk. Physicians often prescribe hypnotics for BD patients with insomnia although no hypnotic has a specific FDA indication for this use. In this study, the patterns of use, efficacy and safety of five nonbenzodiazepine hypnotics (NBZHs) were assessed in a large group of outpatients with BD.

Method: A chart review was performed for all older adolescents and adult BD outpatients in a private outpatient clinic. Clinical data was collected for any patient who had ever been prescribed a NBZH for insomnia and included successful current use, past unsuccessful treatments, side effects, duration of use, concurrent psychiatric medications, and absence or presence of untoward events often associated with chronic use of hypnotics.

Results: A significant number of BD patients take NBZHs as needed or on a daily basis. Four NBZHs had adequate success rates; ramelteon was limited in efficacy. Some patients experienced satisfactory results from a NBZH after unsuccessful trials with one or more other NBZHs. About half of the current NBZH users are taking them on a daily long-term basis, and none of these patients have experienced unacceptable untoward events. About three quarters of the chronic NBZH users are taking antimanic medications concurrently, and less than half of the chronic users are taking antidepressants.

Limitations: The results may not be generalizable to other BD populations. A control group was not included in the design. Chronic users of NBZHs were not asked to discontinue their NBZH in order to confirm indication for long-term use.

Conclusions: Most NBZHs can be effective and safe agents for selected BD outpatients with episodic or chronic insomnia. Failure to respond to one or more NBZH does not preclude a satisfactory response to a different NBZH. Some BD patients who take maintenance antimanic agents also require NBZH treatment. Overactivation from antidepressant treatment does not contribute to chronic NBZH use in most BD patients.

1. Introduction

A recent NIH conference on the manifestations and management of chronic insomnia in adults concluded that "chronic insomnia is a major public health problem affecting millions of individuals, and that little is known about the mechanisms, causes, clinical course, comorbidities and

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doi:10.1016/j.jad.2010.07.018

consequences of chronic insomnia." Moreover, the same panel was concerned about the lack of research data on the long-term use of medication treatment for chronic insomnia (National Institutes of Health state of the science conference statement, 2005).

Chronic insomnia is a prevalent problem in patients with bipolar disorder (BD) (Harvey, 2008). Recent studies indicate that BD patients can experience chronic insomnia even when their daytime mood symptoms are under control between affective episodes (Harvey et al., 2005). Successful treatment of chronic insomnia for any patient is important because persistent insomnia can cause considerable subjective distress, metabolic disorders, impairment in cognition and daytime dysfunction. Moreover, results from a recently published study indicate that chronic insomnia may be associated with a reduction of gray matter in the left orbitofrontal cortex (Altena et al., 2010). The control of chronic insomnia in patients with BD is now considered a therapeutic priority because chronic insomnia can cause or exacerbate manic-related symptoms in bipolar patients (Colombo et al., 1999; Wehr et al., 1987, Wehr et al., 1982) and can also increase the risk of suicide (Wojnar et al., 2009).

Many physicians who treat BD prescribe hypnotics for selected patients on both a short and long-term basis despite the lack of clinical trials supporting this intervention in BD patients (Plante and Winkelman, 2008). Moreover, there is no specific FDA indication for the use of any hypnotic in the treatment of insomnia associated with BD.

Benzodiazepines have been the most commonly prescribed hypnotics in general until the recent introduction of several nonbenzodiazepine hypnotics (NBZHs), beginning with zolpidem in 1993. NBZHs are promoted as having several advantages over the benzodiazepines (Schatzberg and Nemeroff, 2009). Several studies have addressed the safety and efficacy of NBZHs for patients with chronic primary insomnia (Schatzberg and Nemeroff, 2009). However, no studies have addressed patterns of use, safety and efficacy of NBZHs specifically for insomnia in BD patients, especially the extended daily use for chronic insomnia in this patient population (Plante and Winkelman, 2008). In this preliminary study, not subsidized by the pharmaceutical industry, the patterns of use, efficacy and safety of NBZHs were addressed in a large group of BD outpatients.

2. Methods

A review was performed on all the treatment charts of all older adolescent (ages 15–17) and adult outpatients with any type of DSM-IV-TR BD diagnosis (American Psychiatric Association, 2000) currently treated in a private practice staffed by two board certified psychiatrists (CBS and LCS), each with 30 years of clinical experience, who specialize in the treatment of BD. Patients were considered a candidate for a hypnotic if they were experiencing a sleep disturbance characterized by difficulty initiating sleep, difficulty maintaining sleep, early morning awakening or nonrestorative sleep; and if the sleep disturbance was causing clinically significant distress or impairment in social, occupational or other important areas of functioning. This definition of insomnia meets the DSM-IV-TR criteria for a Sleep Disorder Related to Another Mental Disorder (American Psychiatric Association, 2000).

Each of the following hypnotics was considered a NBZH: zolpidem (Ambien®), zolpidem CR (Ambien CR®), eszopiclone (Lunesta®), zaleplon (Sonata®) and ramelteon (Rozerem®). The NBZHs were prescribed based on typical clinical variables: characteristics of the sleep disturbance, previous successful trial of a NBZH, failure to respond to other families of hypnotics, duration of hypnotic use, history of substance abuse, cost, insurance coverage, patient preference, and NBZH availability on the market at the time of treatment.

Clinical data were collected from 1993 (date of introduction of the first NBZH, zolpidem, in the United States) to the present time for any patient who had ever been prescribed a NBZH for insomnia and included demographic information: successful current use, past unsuccessful treatments, side effects, untoward events often associated with benzodiazepine hypnotics such as fractures from falls, motor vehicle accidents, current abuse/misuse of their NBZH and tolerance. Treatment with a NBZH was considered successful if the patient reported a sufficient global benefit for insomnia as defined by a score of 1 or 2 ("much improved" or "very much improved") on the Clinical Global Impression Scale-Bipolar Version (GCI-BP) (Spearing et al., 1997), if the patient expressed a desire to continue the NBZH, and if the treating doctor concluded that the benefits of continued treatment with the NBZH outweighed the risks.

Treatment with the NBZH was considered unsuccessful if the NBZH had to be discontinued because of lack of effectiveness, unacceptable side effects or evidence of abuse or misuse of the NBZH. In this study, we used the DSM-IV-TR criteria for Substance Abuse to define NBZH abuse (American Psychiatric Association, 2000). A patient was considered a NBZH misuser if any of the following characteristics were met: 1) the patient took more than the prescribed dose without the support of the treating physician, 2) the patient reported that the NBZH prescription was lost or stolen on more than one occasion, 3) the patient required early refills of a NBZH prescription on more than one occasion, 4) another physician confirmed that the patient sought or received a NBZH prescription while being treated with NBZHs by the investigators, 5) a significant other reported inappropriate or excessive use of a NBZH by the patient, and 6) the patient himself reported inappropriate or excessive use of the NBZH. Chronic use was defined as 1 month or longer of daily use of a prescribed NBZH based upon patient report and confirmation by prescription refill history. Additional variables noted for chronic NBZH users included duration of use, concurrent psychiatric medications, and history of any substance abuse as defined by DSM-IV-TR (APA, 2000).

3. Results

Data was collected from a total of 361 consecutive BD patients; two hundred fifty (69%) were female. One hundred and seventy-three (48%) of the 361 total had taken at least one NBZH. Of these 173 patients, 87 (49%) are currently taking a NBZH. Of the current NBZH users, 47 (55%) are taking them as needed and 40 (46%) are taking them chronically. The distribution of the combined current chronic and as needed NBZH use is zolpidem: 50 (59%), zolpidem CR: 9

(11%), eszopiclone: 17 (20%), zaleplon: 7 (8%) and ramelteon: 3 (4%).

The treatment success rate for all past trials of each NBZH was zolpidem: 87/145 (60%), zolpidem CR: 15/26 (58%), eszopiclone: 34/74 (46%), zaleplon: 12/33 (36%) and ramelteon: 4/27 (15%). The most common causes of treatment failure for all of the NBZHs were lack of efficacy (44%) and intolerable side effects (26%). The most common side effects which resulted in discontinuation of each NBZH are listed in Table 1 and for all NBZHs combined are listed in Table 2. Twenty-nine (34%) of the current NBZH users did not respond to one previous NBZH trial, 16 (19%) failed two previous NBZH trials, and two (2%) were not successful with three previous NBZH trials.

The NBZHs taken by the 40 current chronic daily users include zolpidem (18), eszopiclone (13), zolpidem CR (5), ramelteon (3) and zaleplon (1). The average duration of use for the chronic users is 30 months ± 30 SD (range 1 to 132 months). Twenty-eight (74%) of the chronic users are also taking maintenance antimanic medications (lithium, valproic acid, carbamazepine, and antipsychotics), and 17 (45%) are taking maintenance antidepressants (medications which have FDA approval for an acute major depressive episode or lamotrigine). Seven (18%) of the chronic users have a prior history of substance abuse. Only one of the chronic users was taking over the maximum recommended dose (15 mg of zolpidem), and this dose was with the concurrence of the treating psychiatrist. None of the chronic users reported any of the following known negative consequences of long-term use of hypnotics: misuse/abuse, tolerance, fractures from a fall, motor vehicle accidents or parasomnias.

Table 1
Most common side effects which resulted in discontinuation, by NBZH.

NBZH	Side effect	# of patients who discontinued due to the side effect	% patients who discontinued due to side effects of each NBZH
Ambien	Daytime sedation	9	6.2%
	Headache	4	2.8%
	Parasomnia	2	1.4%
	Depression	2	1.4%
	Nausea	1	0.7%
	Cognitive impairment	1	0.7%
Ambien CR	Daytime sedation	4	15.4%
	Headache	1	3.8%
Lunesta	Bitter taste	10	13.5%
	Daytime sedation	8	10.8%
	Headache	2	2.7%
	Moodiness	1	1.4%
	Nightmares	1	1.4%
	Cognitive impairment	1	1.4%
	Anxiety	1	1.4%
Sonata	Daytime sedation	1	3.0%
	Nightmares	1	3.0%
Rozerem	Daytime sedation	4	14.8%
	Cognitive impairment	1	3.7%
	Other	4	14.8%

Table 2
Most common side effects which resulted in discontinuation, all NBZH.

Side effect	# of patients who discontinued due to the side effect	% of all NBZH users who discontinued due to the side effect
Daytime sedation	26	15.0%
Bitter taste	10	5.8%
Headache	7	4.0%
Cognitive impairment	3	1.7%

4. Discussion

The results of this preliminary study provide several important findings regarding the use of NBZHs for insomnia in outpatients with BD. About one half of the subjects have been prescribed a NBZH, indicating that NBZHs are frequently indicated for this patient population in a clinical treatment setting. Zolpidem, zolpidem CR and eszopiclone were relatively efficacious for both as needed and chronic use (46% to 60%). Zaleplon was effective for as needed use in a few patients (36%), but there was insufficient data to assess its efficacy for chronic use. Although ramelteon was effective for chronic use in a few patients, it had a lower overall success rate (15%) compared to the other four NBZH medications.

The NBZHs were generally well tolerated, although 26% of the patients experienced side effects resulting in a failed NBZH trial. None of these patients required active medical treatment, medical hospitalization or referral to a medical emergency room as an intervention for the unacceptable side effect.

Almost half (47%) of patients currently receiving a NBZH are taking them daily on a chronic basis. These chronic NBZH users have not experienced any of the serious problems that have been associated with chronic benzodiazepine hypnotic use. About three quarters of the chronic NBZH users are taking at least one antimanic agent concurrently, indicating that the use of maintenance antimanic medications does not always produce adequate control of insomnia. Conversely, less than half (45%) of the chronic daily users of NBZHs are taking an antidepressant or lamotrigine, which suggests that insomnia due to overactivation from antidepressants is not the cause of chronic NBZH use in the majority of BD patients with insomnia. Lastly, none of the patients misused or abused NBZHs, even those patients with a previous history of substance abuse.

There are two possible theories to explain the lack of efficacy of ramelteon compared to the response to the other NBZHs in this patient population. Ramelteon is the only NBZH in this group with a different mechanism of action (Kato et al., 2005). Furthermore, it does not have sedating properties, and many BD patients suffering from persistent insomnia do not have the patience to wait for a delayed hypnotic effect.

A possible factor to explain the uneven distribution of use of the different NBZHs in our patient population could be the duration of time of each NBZH on the market. For example, zolpidem has been available since 1993, and zolpidem CR,

eszopiclone and ramelteon have been available only since 2005.

This study has several limitations. The subject patients have been treated in only one outpatient clinic and by only two psychiatrists. The practice of prescribing hypnotics in general and NBZHs in particular for BD probably varies among different individual psychiatrists and in different outpatient settings. Our patients were not compared to a control group of patients taking other types of hypnotics or a placebo. The patients who use NBZHs chronically were not asked to discontinue them for the purpose of this study to determine if chronic use was still indicated at the time of the collection of the data. It should be noted, however, that it is the practice of the treating psychiatrists who conducted this study to encourage their patients who use any hypnotic chronically to make periodic attempts to taper and discontinue the hypnotic in order to confirm that chronic use is still indicated. Standard insomnia rating instruments were not utilized in this study because baseline ratings for many of the subjects who began receiving NBZHs in the remote past could not be obtained.

Despite the limitations of this study, the results are significant for several reasons. This is the first known study to address the pattern of use, efficacy and safety of NBZHs for insomnia in a large number of patients with BD. Our data suggest that most NBZHs can be an effective and safe pharmacological intervention for the many BD patients who suffer from insomnia. Moreover, NBZHs can be considered a useful maintenance medication for some BD patients who experience chronic insomnia. Ramelteon may not be an effective hypnotic for insomnia associated with BD. Our data also indicate that failure to respond to one or more NBZHs does not preclude a trial with another NBZHs. Lastly, NBZH can be a useful option to treat insomnia for BD patients for whom benzodiazepine hypnotics are contraindicated. Additional research, including controlled prospective studies, by other investigators in different clinical settings are required to determine if the data from this study are generalizable.

Role of funding source

No grants, individual or industry support were provided to any of the authors related to this study.

Conflict of interest

All authors declare that they have no actual or potential conflicts of interest.

Acknowledgement

No acknowledgements.

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