Effectiveness of Benzodiazepine Receptor Agonists in the Treatment of Insomnia: An Examination of Response and Remission Rates

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Study objectives: To examine the real-world effectiveness of benzodiazepine receptor agonists (BzRAs) by quantifying response and remission rates in a clinical sample receiving chronic BzRA treatment for insomnia.

Methods: Participants were outpatients (*N* = 193; 72% female; 55.2 ± 11.1 year) who had an insomnia diagnosis per medical records, and who were taking a therapeutic dose of BzRA for their insomnia. Endpoints were nocturnal sleep disturbance and Insomnia Severity Index (ISI) scores. A reduction meeting the criterion for the minimally important difference in ISI scores (change ≥ 6) constituted "response"; "remission" was inferred when symptoms fell below the clinical cutoff (ISI < 11).

Results: Most participants (71%) used BzRAs at least 5 nights per week. Mean ISI scores were significantly lower (*t* = 22.31; *p* < .01) while on BzRAs than when untreated, but remained in the clinical range (mean = 11.0; standard deviation = 5.7). Although 76.7% responded to treatment, only 47.7% remitted. The majority (68.9%) of participants had a sleep-onset latency > 30 minutes and/or wake-time after sleep onset > 60 minutes while on BzRAs. After controlling for gender and insomnia severity when untreated, odds of insomnia persistence despite BzRA use were 2 times higher in patients with comorbid medical [odds ratio (OR) = 2.39; 95% confidence interval (CI) = 1.20% to 4.77%; *p* < .05] and psychiatric disorders (OR = 2.24; 95% CI = 1.21% to 4.13%; *p* < .05).

Conclusions: This is the first study to distinguish between response and remission in insomnia patients taking BzRAs. Findings suggest that while many insomnia patients respond to chronic BzRA treatment, most do not remit. Remission rates are particularly low for comorbid insomnia, the most prevalent phenotype of the disorder.

Keywords: Benzodiazepine receptor agonists, insomnia, remission, minimally important difference, comorbidity.

Statement of Significance

Use of benzodiazepine receptor agonists (BzRAs) in insomnia treatment is widespread. However, as their evidence base is composed entirely of efficacy trials, the critical question of whether these drugs are effective in clinical settings is unclear. Efficacy trials focus on treatment response, as indexed by reductions in the sample mean on specific sleep disturbance parameters. By contrast, the proportion of patients who remit from insomnia disorder is seldom assessed. The present study indicates that large proportions of insomnia patients fail to remit despite almost nightly BzRA use, with higher rates in those with medical/psychiatric comorbidities. Incomplete remission may be a risk factor for not just relapse, but sustained risk for other insomnia-related morbidities.

INTRODUCTION

Benzodiazepine receptors agonists (BzRAs) are the most commonly prescribed of the US Food and Drug Administration (FDA) medications indicated for insomnia.[1] However, nearly all the empirical support for these agents derives from efficacy trials, with limited research on effectiveness in clinical samples. Efficacy trials suffer from 2 systematic limitations. First, the primary endpoints in the vast majority of efficacy trials are improvements in the sample mean on nocturnal sleep disturbance measures.[2] Their focus is on evaluating a minimally important difference (MID) in specific nocturnal symptoms, which is more an index of treatment *response* than of *remission* per se. A second shortcoming of most efficacy trials is that they exclude patients suffering from the most prevalent phenotype of the disorder, i.e., insomnia comorbid with medical and psychiatric disorders.[3–5] As such, efficacy in a controlled trial may not translate to effectiveness in clinical practice. A recent report[6] identified a series of sleep clinic patients with persistent insomnia symptoms despite chronic nightly use of prescription sleep-aids, of which BzRAs were the most commonly used and accounted for two-thirds of all sleep-aids. However, as only nonremitters were included in this study, rates of remission (and nonremission) from insomnia disorder among BzRA users in clinical settings is currently unknown. What is the scope of this problem? Further, it is also unclear which, if any, specific patient characteristics may compromise the effectiveness of BzRA treatment. As always, the more pertinent question is not whether a particular treatment works, but for whom it is an appropriate therapeutic option.

While acute and transient nocturnal sleep disturbances, including increased sleep-onset latency (SOL) and wake-time after initial sleep onset (WASO), are ubiquitous, 6% to 10% of the population meets diagnostic criteria for insomnia disorder.[7] An important distinction is that insomnia is a not just a nocturnal disorder but one involving concurrent daytime impairments, with growing evidence of elevated arousal throughout the 24-hour day.[8–10] Yet, the endpoints in most BzRA efficacy trials are specific nocturnal sleep disturbance parameters. Even in pharmacological trials evaluating long-term BzRA use, efficacy probes still target sleep onset/maintenance measures. For instance, in one of the longest clinical trials of an FDA-approved BzRA sleep aid,[11] efficacy was assessed for 2 consecutive nights at the 1-month and 8-month marks following randomization. However, the endpoints were sleep disturbance on those particular nights, and not insomnia remission at the end of treatment. With respect to the assessment of daytime function, the goal in efficacy trials is not to evaluate improvements in insomnia-related daytime impairment, but to rule out the residual sedative effects of the sleep aid.[2] Thus, most BzRA trials assess treatment response in terms of improved nocturnal sleep and residual drug effects, neither of which adequately captures insomnia remission.

In the relatively few BzRA trials which have examined remission using empirically validated outcomes, insomnia remission

rates are modest (46% to 55%) relative to placebo (20% to 40%).[12,13] An important question therefore arises: are remission rates even lower in clinical settings where most patients present with comorbid disease? Psychiatric/medical disorders are comorbid with insomnia in 70% to 86% of cases,[14–16] and have been proposed as an important factor in the effectiveness of prescription sleep-aids.[6] The exclusion of patients with medical and psychiatric disorders in efficacy trials has been criticized for this reason since as early as 1989.[3–5] In its prescribing information (label) for 2 common BzRAs, the FDA notes that nonremission from insomnia while taking these medications may reflect a comorbid condition warranting assessment.[17,18] However, efforts to examine the efficacy of BzRAs in treating insomnia comorbid with another disorder have only begun recently. Efficacy data for BzRAs are currently available for insomnia comorbid with major depressive disorder (MDD),[19–21] generalized anxiety disorders (GAD),[22–24] rheumatoid arthritis,[25,26] menopause,[27,28] and chronic back pain.[29] There is still considerable disparity between the small number of disorders studied in these trials and those that accompany insomnia in clinical settings.[3]

Effectiveness studies in clinical samples can complement efficacy trials by addressing some of these limitations and providing essential real-world data on treatment outcomes. However, nearly all BzRA research beyond efficacy trials has focused on epidemiological questions: trends in the prescribing habits of physicians, the prevalence of use in the general population, and the association between chronic use and adverse consequences.[30–36] Only 2 prior studies have examined effectiveness.[37,38] Neither study distinguished between sleep complaints and insomnia disorder and, as such, response to treatment and remission from the disorder could not be extricated. Vital information on the dose and pattern of prescription sleep aid use was missing from both studies. Additionally, important characteristics such as comorbid psychiatric/medical illness, were unavailable. To address these gaps in the literature, the present study assessed outcomes of BzRA treatment in a clinical sample of insomniacs. Information on dosage and frequency of BzRA use was collected, and only patients who reported therapeutic dosages and "indicated use" for insomnia were retained. As an insomnia disorder diagnosis is symptom based, patient-reported outcomes offer the most valid metric for gauging treatment effectiveness and were hence the primary endpoints in this study. Treatment "response" was determined per empirically validated criteria for the MID in symptomatology,[39] and remission was operationalized as a reduction in symptoms to subclinical levels.[40]

METHODS

Setting and Participants
Participants were recruited from a central repository which included electronic medical records of all patient encounters within the Henry Ford Health System. Over 3 million patient encounters are added to this repository each year, and the patient sample reflects the gender, race, and ethnic composition of Southeastern Michigan. Outpatients from this database were invited to participate via email if: (1) they had received an insomnia diagnosis in the past 2 years; (2) were prescribed a BzRA medication for insomnia (see Measures section for a list

of eligible medications); and (3) had received at least one refill of this BzRA. This email invitation included the web address (URL) for a screening questionnaire which assessed additional inclusion/exclusion criteria (Figure 1). Inclusion criteria were: age 20 years or more; exclusion criteria were: other sleep disorders, including sleep apnea, restless legs syndrome, narcolepsy; age older than 70 years; night, evening, rotating shift-work, on-call work-schedule (Table 1). This electronic screening questionnaire was administered using Qualtrics, an internet-based software suite developed by Qualtrics Inc. (Provo, UT). Eligible participants were automatically directed to the full survey, which was also completed via Qualtrics. The institutional review board at the Henry Ford Health System approved this protocol. Demographic characteristics of excluded cases (n = 107) did not diverge significantly from the final sample: (age: 53.1 ± 11.2 year; 71.2% female). Levels of medical/psychiatric comorbidities were also comparable (depression: 39.4%; anxiety: 29.8%; hypertension: 46.2%; high cholesterol: 39.4%).

Measures

Insomnia
Eligible participants rated insomnia severity using the Insomnia Severity Index (ISI).[41] The ISI is a 7-item self-report questionnaire, which has been validated for detecting the caseness of insomnia disorder, quantifying severity, and assessing treatment response.[39,40] Participants completed 2 separate versions of the ISI: one referencing the period when they were untreated, and the other targeting the period when they were on BzRAs for their insomnia. The latter began with the following prompt: "Please rate the severity of your insomnia symptoms while taking [endorsed BzRA]". By contrast, the ISI for the untreated period included the following prompt: "Please rate the severity of your insomnia symptoms while NOT taking any insomnia medication". The same strategy was used to assess levels of sleep disturbance, i.e., SOL and WASO.
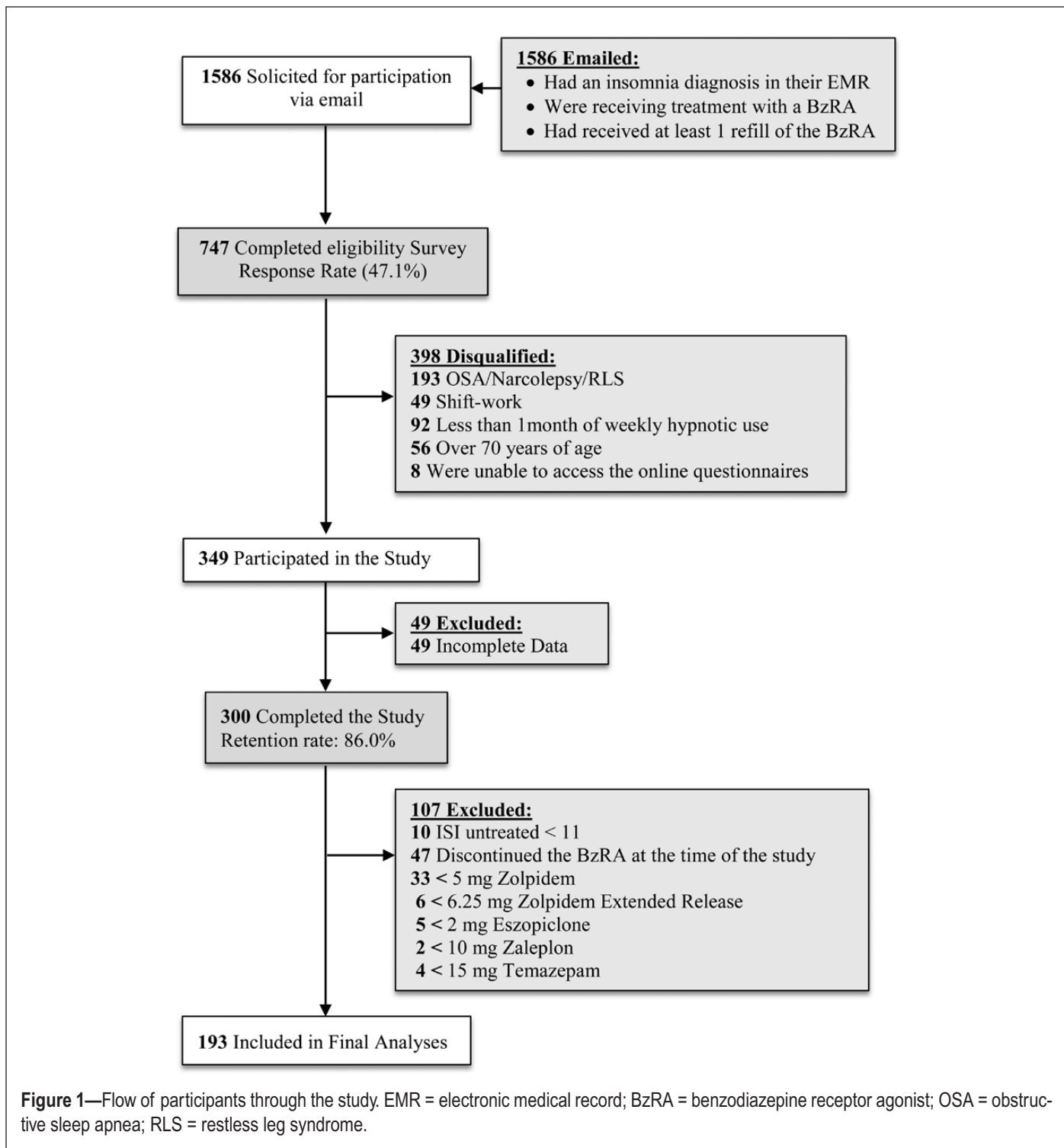
BzRA Use
Participants reported the specific BzRA they were taking for the insomnia, as well as the dosage and frequency of use. They also listed all other medications they were taking (Supplemental Material).

Response and Remission
The MID cutoff (ISI reduction ≥ 6) to operationalize treatment response was based on prior research on the ISI as an index of therapeutic change. Yang and colleagues[39] found that a 6-point reduction in ISI scores was reflective of clinically significant improvements in health-related outcomes, such as fatigue, daytime functioning, and quality of life. With respect to remission, a cutoff of 11 on the ISI shows the highest sensitivity and specificity in detecting caseness of insomnia disorder in clinical samples.[40] As such, participants who scored below 11 while taking BzRAs were considered remitted.

Data Analysis
Statistical analyses were conducted using IBM SPSS Statistics, version 23 (Armonk, NY).[42] McNemar χ^2 tests were conducted to examine whether the proportion of participants with

Figure 1—Flow of participants through the study. EMR = electronic medical record; BzRA = benzodiazepine receptor agonist; OSA = obstructive sleep apnea; RLS = restless leg syndrome.

difficulties initiating sleep or maintaining sleep were significantly different on BzRAs compared to when untreated; this strategy accounts for repeated measures and the binary nature of outcomes. Similarly, a paired-samples t test was used to examine whether ISI score was significantly different while taking BzRAs compared to when untreated. Univariate between-group comparisons (e.g., participants with comorbid medical/psychiatric disorders vs. those without comorbidities) were done using independent samples t tests (continuous outcomes) and Pearson χ^2 tests of independence (dichotomous outcomes) as appropriate. For more complex between-group models involving multiple covariates and dichotomous outcomes (remitters vs. nonremitters), logistic regression analyses were used. Covariates for logistic regression models were selected per hypotheses and/or if they were related to the outcome variable in univariate analyses at a significance level of $p < .20$.[43]

RESULTS
A small proportion of respondents (16.7%) reported using less than the minimal therapeutic dose of the endorsed BzRA

Table 1—Distribution of BzRA Use (*n* = 193).

Agent[a]	Trade name	Minimal therapeutic dose	Prevalence *n* (%)
Zolpidem	Ambien	5 mg	138 (71.5)
Temazepam	Restoril	15 mg	22 (11.4)
Eszopiclone	Lunesta	2 mg	13 (6.7)
Zolpidem ext. release	Ambien CR	6.25 mg	12 (6.2)
Zolpidem oral spray	Zolpimist	5 mg	2 (1.0)
Zolpidem sublingual	Intermezzo	1.75 mg	2 (1.0)
Flurazepam	Dalmane	15 mg	1 (0.5)
Triazolam	Halcion	0.125 mg	2 (1.0)
Zaleplon	Sonata	10 mg	1 (0.5)

BzRA = benzodiazepine receptor agonist; mg = milligrams.
[a]The following BzRAs were assessed, but not endorsed by any participants: Doral (Quazepam); Edluar (Sublingual Zolpidem); Prosom (Estazolam).

Table 2—Sample Characteristics, Stratified by Insomnia Response/Remission While Taking BzRAs.

	Full sample	Nonresponders	Responders	Nonremitters	Remitters
	n = 193	*n* = 45	*n* = 148	*n* = 101	n = 92
	%	%	%	%	%
	100	23.3	76.7	52.3	47.7
Gender (women)	72.0	55.6	77.0	66.3	78.3
Race (white)	77.2	68.9	79.7	75.2	79.3
Smoker (yes)	10.4	6.7	11.5	9.9	10.9
Psyc. comorbidity	50.3	51.1	50.0	59.4	40.2
Med. comorbidity	73.6	86.7	69.9	81.2	65.2
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age (years)	55.2 (11.1)	56.5 (10.5)	54.8 (11.3)	55.2 (10.2)	55.1 (12.2)
Alc. drinks/week	1.4 (2.2)	1.2 (1.9)	1.4 (2.2)	1.4 (2.2)	1.4 (2.2)
ISI untreated	21.1 (4.3)	19.2 (4.7)	21.7 (4.0)	21.6 (3.9)	20.5 (4.7)
ISI while on BzRAs	11.0 (5.7)	16.6 (5.0)	9.2 (4.7)	15.3 (3.9)	6.2 (2.9)
Frequency of BzRA use (days/week)	5.6 (2.0)	5.0 (2.2)	5.8 (1.9)	5.5 (2.0)	5.7 (2.9)

BzRA = benzodiazepine receptor agonist; Cig. = cigarettes; ISI = insomnia severity index; *M* = mean; Med. = medical; Psyc. = psychiatric; *SD* = standard deviation.

(Figure 1). These cases were stricken from analyses. Another 47 participants (15.7%) had discontinued BzRA use at the time of the study. The most commonly cited reasons for ceasing use were side effects (40.4%) and lack of efficacy (27.7%); none of these participants attributed BzRA discontinuation to a resolution of sleep problems. Finally, ISI scores while untreated were lower than the clinical cutoff (<11) for only 10 participants (3.3%), who were also excluded from analyses.[1]

Sample Characteristics
Demographic characteristics of the final sample appear in Table 2. Participants were predominantly middle-aged (55.2 ± 11.1 year) and "white" (77.2%), though some demographic diversity was observed (African American: 12.4%; more than 1 race: 4.1%; Asian: 2.6%). Women were over-represented (72.0%), as expected per the gender disparity in the prevalence of insomnia.[44] Of the overall sample, 11.4% reported no psychiatric or medical comorbidity. About half (50.3%) of the sample presented with psychiatric comorbidities, of which depression (39.4%) and anxiety (31.1%) were the most common. Hypertension was the most prevalent medical comorbidity (48.7%), followed by high cholesterol (42.0%) and chronic pain (39.9%). Overall, 73.6% of the sample presented with some form of medical comorbidity. The proportion of smokers was 10.8%, and mean alcohol use was 1.4 beverages per week. As for concomitant medications (Supplement),

lisinopril (14.3%) and simvastatin (10.8%) were the most common. About a third (27.7%) of the sample was on antidepressants, of which sertraline (7.9%) and bupropion (5.4%) were the most widely used. Anxiolytic use was reported by 13.8% of the sample; alprazolam (6.4%) was the most common, followed by lorazepam (3.4%).

BzRA Use

Zolpidem was the most frequently used BzRA, endorsed by 71.5% of the sample. Temazepam and eszopiclone were endorsed by 11.4% and 6.7%, respectively, and were the second and third most commonly used BzRAs. Dose distribution of zolpidem was fairly even: 45.7% took the 5 mg dose, 49.3% were on 10 mg. Most eszopiclone users (61.5%) were on the 3 mg dose, whereas the 30 mg dose (40.4%) was the most common among temazepam users. Frequency of BzRA use was high (mean (M) = 5.6 day/weeks; standard deviation (SD) = 2.0), with a median of 7 days per week. The majority (71%) of the sample reported using BzRAs at least 5 days per week. Frequency of use did not vary significantly across BzRAs. Roughly half the sample (51.2%) had tried 2 or more prescription medications for their insomnia in the past.

Nocturnal Sleep Disturbance

As Figure 2 shows, nearly all participants reported elevated SOL and WASO[45] while untreated. Overall proportions of participants endorsing these sleep disturbances while taking BzRAs were significantly lower than while untreated (all p values < .001; Table 3). However, a large majority (68.9%) reported SOL >30 minutes and/or WASO >60 minutes while taking BzRAs.
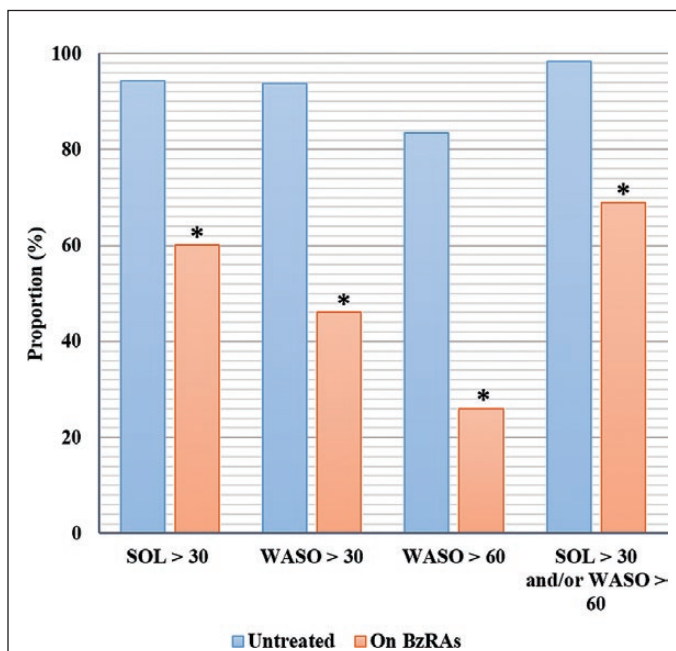
Figure 2—Sleep disturbances while on BzRAs. BzRA = benzodiazepine receptor agonist; SOL = sleep onset latency; WASO = wake-time after sleep onset; *all McNemar's chi-square tests were significant at p < .001.

ISI Scores While Untreated

Participants reported high ISI scores while untreated (M = 21.1; SD = 4.3; median = 21; Table 4). An independent samples t test comparing men and women on mean ISI scores (men: M = 19.4; SD = 4.0; women: M = 21.7; SD = 4.3) was statistically significant (t = 3.52; p < .05). Between-group comparisons of participants with psychiatric comorbidities (M = 21.9; SD = 4.2) and those without (M = 20.2; SD = 4.3) also yielded a statistically significant difference (t = 2.73; p < .05). Participants with medical comorbidities (M = 21.2; SD = 4.4) and those without (M = 20.7; SD = 4.2) did not differ (t = 0.75; p = .45).

Responders and Remitters

A paired-samples t test showed that ISI scores while on BzRAs were significantly lower than while untreated (t = 21.31; p < .01), but still remained in the clinically significant range (M = 11.0; SD = 5.7; median = 11). A high percentage (76.7%) of participants showed a therapeutic response to BzRAs. However, only 47.7% of the sample achieved remission (59.5% of responders). To examine whether response and remission rates varied as a function of BzRA dose, the sample was divided into 2 groups (high vs. low dose of the respective BzRA). Dose was unrelated to response (χ^2 = .04; p = .83) or remission rates (χ^2 = .26; p = .61).

Chi-square tests of independence showed that participants with medical comorbidities had significantly lower response (72.5% vs. 88.2%) and remission rates (42.3% vs. 62.7%) than did those without medical illness (all p values < .05; Figure 3). Participants with comorbid psychopathology had significantly lower remission rates (38.1% vs. 57.1%) than those without, but response rates did not differ between these groups (Table 5). To further explore these findings, we examined response and remission rates, controlling for untreated ISI scores and pertinent covariates (p <.20 in univariate analyses).

First, we fit a logistic regression model with treatment response as the dependent variable (0 = responder; 1 = nonresponder). Gender, psychiatric comorbidity, medical comorbidity, and ISI scores while untreated served as the independent variables (IVs). A test of the model with all predictors against a constant-only model was statistically significant (χ^2 = 22.83; p < .01), indicating that this model reliably distinguished between responders and nonresponders. The Hosmer–Lemeshow test showed that the model fit the data well (χ^2 = 6.65; p = .58). Odds of responding were significantly lower among participants with medical comorbidities (Table 6). Stated another way, participants with medical comorbidities were significantly more likely to not respond [odds ratio (OR) = 3.24; p < .05].

We fit a similar logistic regression model with remission status as the outcome (0 = remission; 1 = nonremission, i.e., insomnia persistence); again, the IVs were gender, psychiatric comorbidities, medical comorbidities, and ISI scores while untreated. A test of this model with all predictors against a constant-only model was statistically significant (χ^2 = 21.32; p < .01), and fit the data well (Hosmer–Lemeshow test: χ^2 = 6.89; p = .55). Psychiatric comorbidity (OR = 2.24; p < .05) and medical comorbidity (OR = 2.39; p < .05) were each associated with significantly higher odds of insomnia persistence.

Table 3—Sleep Disturbance While on BzRAs.

	Untreated (%)	On BzRAs (%)	McNemar's χ^2
SOL > 30 m.	94.3	60.1	63.64; $p < .001$
WASO > 30 m.	93.8	46.1	88.48; $p < .001$
WASO > 60 m.	83.4	25.9	109.21; $p < .001$
SOL > 30 m. and/or WASO > 60 m.	98.4	68.9	55.02; $p < .001$

BzRA = benzodiazepine receptor agonist; m = minutes; SOL = sleep onset latency; WASO = wake-time after sleep onset.

Table 4—Group Differences in ISI Scores While Untreated.

	ISI scores while untreated	Independent samples t test
	$M \pm SD$ (n)	
Gender		
Men	19.4 ± 4.0 (54)	3.52; $p < .05$
Women	21.7 ± 4.2 (139)	
Race[a]		
White	21.2 ± 4.2 (149)	0.90; $p = .37$
African American	20.3 ± 4.9 (24)	
Smoker		
Yes	21.2 ± 4.9 (20)	0.08; $p = .94$
No	21.1 ± 4.3 (173)	
Medical comorbidity		
Without	20.7 ± 4.2 (51)	0.75; $p = .45$
With	21.2 ± 4.4 (142)	
Psychiatric comorbidity		
Without	20.2 ± 4.3 (96)	2.73; $p < .05$
With	21.9 ± 4.2 (97)	

ISI = insomnia severity index; M = mean; n = sample size; SD = standard deviation.
[a]Results are presented for the 2 most commonly endorsed categories of the Race variable ("White" and "African American") as there were two few cases of other race categories for meaningful comparisons.

DISCUSSION

The present study examined whether outpatient insomniacs responded to chronic BzRA treatment with meaningful improvements, and more importantly, if such changes were accompanied by a remission of insomnia disorder. As clinicians rely on patient reports to diagnose insomnia, we focused on patient-reported outcomes; more objective assessment techniques, such as polysomnography, are not indicated for diagnosing insomnia and are rarely utilized in clinical practice.[46] Results showed that treatment response was high. For most patients (76%), treatment-related changes in symptoms were above the threshold for a MID (ISI change ≥ 6).[39] Proportions of participants reporting sleep disturbance above conventional quantitative cutoffs[45,47] were also significantly lower while taking BzRAs. Insomnia

remission rate (47.7%), however, was less promising, with over half the sample reporting clinically significant insomnia levels (ISI ≥ 11)[40] despite almost nightly BzRA use. Remission rates were even lower in patients with medical comorbidities (42%) and those with comorbid psychopathology (38%). This finding is particularly noteworthy as 88.6% of insomniacs in the present study presented with some psychiatric/medical comorbidity; prior studies suggest a similar prevalence (86%) of comorbid disease in insomniacs.[16] Overall, this study points out that BzRAs are not fully effective in large numbers of patients. Prior data on the wide-scale effectiveness of these sleep-aids likely capture treatment response and not remission.[37,38]

BzRA Treatment for Comorbid Insomnia

Insomnia patients rarely present without some form of medical/psychiatric comorbidity,[48] a clinical reality which calls into question the common practice of excluding medical/psychiatric illness from efficacy trials. In the only prior study of patients whose insomnia was resistant to treatment with prescription sleep-aids including BzRAs, levels of comorbid psychopathology were high.[6] However, this study lacked a comparator group of treatment responders, rendering it difficult to implicate comorbid psychopathology in treatment-resistance. Another report presented post hoc analyses of BzRA treatment from 5 different efficacy trials, including patients with "primary" insomnia and those with insomnia comorbid with depression, GAD, menopause, and arthritis.[49] Outcome effect sizes were the largest for primary insomnia and the smallest for insomnia comorbid with GAD/MDD. However, these analyses were restricted to a single-dose of a single-agent. Our findings support the hypothesis that comorbid conditions undermine the effectiveness of other, commonly prescribed BzRAs. The important question therefore is what drives this effect?

Insomnia severity is an unlikely candidate. Two prior studies[4,5] compared insomniacs who participated in efficacy trials with insomniacs who presented to sleep clinics. Though comorbid disease was more common in the latter, the two groups did not differ on the severity of any sleep disturbance parameter. This finding was replicated in our study. Notably, differences in ISI scores while untreated between patients with and without comorbid psychopathology were statistically significant. However, scores in both groups were elevated, and the difference was small and unremarkable by any clinical standards. ISI scores while untreated in insomniacs with and without medical comorbidities were also comparable (Table 4).
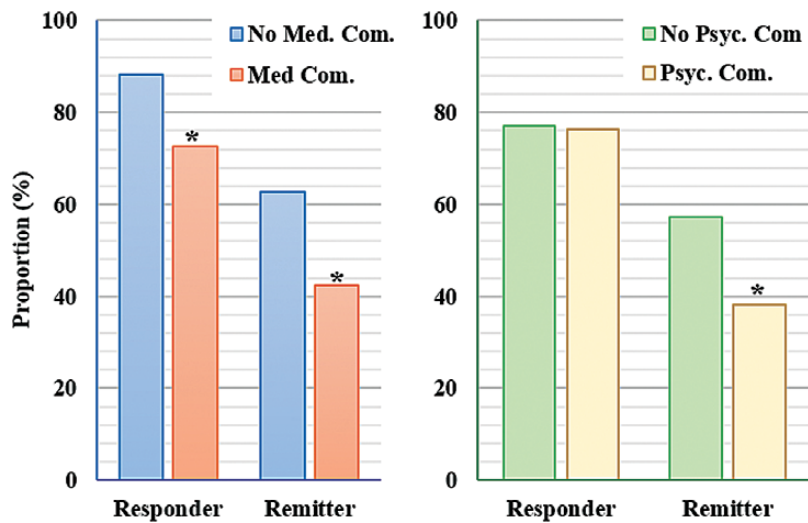
Figure 3—Response and remission rates, stratified by medical/psychiatric comorbidity. Med = medical; Pscy = psychiatric; Com = comorbidity. *$p < .05$.

Table 5—Response and Remission Rates Stratified by Medical/Psychiatric Comorbidity.

	Response rate %	Pearson's χ²	Remission rate %	Pearson's χ²
Med. Com.		5.17; $p < .05$		6.32; $p < .05$
Without	88.2		62.7	
With	72.5		42.3	
Psyc. Com.		0.17; $p = .90$		7.09; $p < .05$
Without	77.1		57.3	
With	76.3		38.1	

Com = comorbidity; Med = medical; Psyc = Psychiatric.

Another possibility is that adjunctive treatment of comorbidities is a factor in the effectiveness of BzRAs. As we lacked detailed information on the dosage and use-frequency of non-sleep medications, we were unable to examine the potential sleep/daytime effects of other agents. Interestingly, treatment response to antidepressant medications when combined with a BzRA for insomnia has been tested against monotherapy with antidepressants (i.e., antidepressant + BzRA vs. antidepressant + placebo).[19,20] However, there are no studies on the hypnotic effects of BzRAs as a function of adjunctive therapy for a comorbid condition (BzRA + other agent vs. BzRA + placebo). Such studies are needed to examine the effectiveness of BzRAs in the majority of insomnia patients, who are likely receiving treatment for comorbid medical/psychiatric disorders.

Implications for Alternative Treatments

An important research priority in light of the large proportion of nonremitters in the present study is testing the effectiveness of non-BzRA agents in this population. Novel pharmacological agents with alternative mechanisms of action, including low-dose doxepin, a histamine antagonist, and suvorexant, a dual orexin receptor antagonist, have recently received FDA approval for insomnia treatment.[50–52] Off-label use of other agents, including sedative antidepressants, for insomnia is also common.[53] Overall, at least 11 different classes of medications are currently used in the treatment of insomnia in the United States.[54] However, the evidence base of dose-related risks and benefits for non-BzRA agents is considerably limited compared to that for BzRAs.[48] With a few exceptions, such as doxepin and ramelteon, Finally, although the availability of a wide array of pharmacological agents can help physicians tailor treatment per individual patient needs, pharmacotherapy in general may not be appropriate for all patients. Half the current sample had tried more than 2 different medications for their insomnia in the past, which suggests that multiple treatment attempts with different pharmacological agents is not uncommon in clinical practice. Continuing pharmacotherapy after multiple medications have proven ineffective is ill-advised.[53] Patients for whom a nonpharmacological alternative is more appropriate may benefit from cognitive-behavior therapy for insomnia, as empirical support for this modality is extensive.[55,56]

Table 6—Multivariate Models of Treatment Nonresponse and Insomnia Persistence.

	OR (95% CI) nonresponse	Wald's χ^2	OR (95% CI) insomnia persistence (nonremission)	Wald's χ^2
Med. Com.	3.24 (1.22–8.56)	5.66; $p < .05$	2.39 (1.20–4.77)	6.09; $p < .05$
Psyc. Com.	1.43 (0.69–2.98)	0.93; $p = .33$	2.24 (1.21–4.13)	6.61; $p < .05$
Overall model[a]: $\chi^2 = 22.83$; $p < .001$			Overall model[a]: $\chi^2 = 21.30$; $p < .001$	

CI = confidence interval; Com = comorbidity; Med = medical; OR = odds ratio; Psyc = psychiatric.
[a]Both logistic regression models controlled for gender and ISI scores while untreated.

Limitations and Future Directions

The primary limitation of this study is that insomnia symptoms "while untreated" were based on retrospective report. Future effectiveness studies can rule out this confound by using prospective designs. Another weakness of this study is that data on the duration of insomnia, an important covariate, were unavailable. Furthermore, as many insomniacs do not seek treatment, there is some risk of selective sampling in the present study.[57] Another factor limiting the generalizability of findings is that participants with primary sleep disorders, such as OSA, were excluded. We also note that this report addresses chronic BzRA use, as opposed to intermittent or short-term use. With respect to differences in the proportions of participants reporting sleep disturbance (e.g., SOL > 30, WASO > 60) while taking BzRAs, there is some risk of type 1 error due to multiple inference tests. Although significance tests were robust to family-wise alpha corrections, this adjustment strategy offers only a facile solution to the problem.[58] We argue that the interpretation of these data does not rest on "statistical significance." Instead, the practical value of these findings is in the identified proportions of patients reporting sleep disturbance despite BzRA use.

Effectiveness studies in clinical settings occupy the middle ground between randomized controlled pharmacological trials on one end and pharmacoepidemiological studies on the other. By definition, effectiveness studies lack the methodological precision of efficacy trials. As such, we were unable to address more nuanced outcomes, such as equipotency of different BzRAs or dose-responses curves, primarily due to the disproportionately high prevalence of zolpidem use in the present sample. Notably, this reflects nationwide increases in the prescription rates of non-benzodiazepine BzRAs for insomnia over the past 2 decades, and the nearly commensurate decrease in traditional benzodiazepine prescriptions during the same period.[59] While remaining consistent with epidemiological findings, this study has many additional strengths, including recruitment of actual insomnia patients, use of empirically validated instruments, and limiting BzRA cases to therapeutic dosages and indicated use for insomnia. As such, we avoided common pitfalls in pharmacoepidemiology, such as "confounding by indication" and poor characterization of insomnia.

The distinction between response and remission, while commonly addressed in outcome research for other disorders such as MDD,[19,60] has not been examined adequately in insomnia pharmacotherapy. Although BzRAs are the most widely used pharmacological agents in the treatment of insomnia, our findings point to an important limitation: while many patients improve, most do not remit. This is a significant health concern, as insomnia is a well-established risk factor for a number of disorders, including MDD and hypertension.[61–64] Do insomniacs who respond to treatment but fail to remit remain at increased risk for these morbidities? This is an important question for future research. There are a number of ongoing investigations on insomnia treatment as a preventive strategy against disorders such as MDD.[65,66] The distinction between treatment response and remission may be an important consideration in such prevention efforts.

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SUPPLEMENTARY MATERIAL

Supplementary Material is available at *Sleep* online.

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