A Post Hoc Analysis of the Effect of Nightly Administration of Eszopiclone and a Selective Serotonin Reuptake Inhibitor in Patients With Insomnia and Anxious Depression

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Objective: Patients with major depressive disorder (MDD) and significant anxiety are less responsive to antidepressants than those without anxiety. In this post hoc analysis of patients with insomnia and comorbid anxious depression, eszopiclone cotherapy with a selective serotonin reuptake inhibitor (SSRI) was compared with placebo cotherapy.

Method: Data were pooled from 2 randomized, double-blind, 8-week trials. One trial (conducted from January 2004 to October 2004) included patients with *DSM-IV* insomnia and comorbid MDD treated with fluoxetine concurrently with eszopiclone 3 mg/d or placebo. The other trial (conducted from July 2005 to April 2006) included patients with *DSM-IV-TR* insomnia and comorbid generalized anxiety disorder treated with escitalopram concurrently with eszopiclone 3 mg/d or placebo. Anxious depression was defined as a baseline 17-item Hamilton Depression Rating Scale (HDRS-17) score ≥ 14 (excluding insomnia items) and an anxiety/somatization factor score ≥ 7. Treatment group differences were determined for mean changes in HDRS-17 scores (with and without insomnia items), HDRS anxiety/somatization scores, and response and remission rates. Severity of insomnia was assessed by the Insomnia Severity Index (ISI).

Results: In the combined dataset, 347 of 1,136 patients (30.5%) had insomnia and comorbid anxious depression. Significant improvements in insomnia were observed for eszopiclone cotherapy relative to placebo cotherapy (mean change from baseline on the ISI: −11.0 vs −7.8, respectively; $P < .001$). There were greater reductions in HDRS-17 scores at week 8 following cotherapy with eszopiclone compared with placebo when the insomnia items were included (mean change: −14.1 vs −11.2, respectively; $P < .01$) or excluded (−10.6 vs −8.9; $P < .01$), but not for anxiety/somatization (−4.3 vs −4.1; $P = .23$). Response rates were greater for eszopiclone cotherapy than for placebo cotherapy (55.6% vs 42.0%, respectively; $P = .01$; 50.0% vs 44.4% when insomnia items were removed; $P = .3$). Remission rates were not significantly different (32.6% vs 27.2%, respectively; $P = .28$).

Conclusions: In this post hoc analysis of patients with insomnia and comorbid anxious depression derived from 2 trials, 8 weeks of eszopiclone therapy coadministered with an SSRI resulted in significantly greater improvements in insomnia, significantly greater reductions in HDRS-17 total score, and significantly greater HDRS-17 response rates compared with placebo coadministration. There were no significant differences in response rates (when insomnia items were excluded) and remission rates, as well as in anxiety/somatization scores. Further research is warranted to determine whether these modest antidepressant effects can be replicated, and anxiolytic effects demonstrated, when evaluated in a prospective manner.

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Anxiety and nervousness are established common symptoms among patients with major depressive disorder (MDD).[1] Anxious depression, defined as MDD with high levels of anxiety symptoms, has been found to be associated with greater severity of illness and functional impairment,[2] greater chronicity,[3] and an increased risk of suicidality.[4] Although the *DSM-IV* classification does not include a depressive subtype of anxious depression, there is now emerging evidence from the literature[5] that this may indeed be a valid diagnostic subtype.

Recently, 2 separate analyses[5,6] of primary and specialty care patients with MDD participated in the multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) project. In the trials, 44%–46% of the 3,851 depressed outpatients qualified for the designation of anxious depression, defined as a baseline Hamilton Depression Rating Scale anxiety/somatization factor score of 7 or greater.[5,6] In both studies, patients with anxious MDD were significantly more likely to be unemployed, less educated, and more severely depressed, and significantly more patients endorsed symptoms related to anxiety disorders, as well as items concerning melancholic/endogenous depression features. These findings were true even after adjustment for severity of depression.

Previous research[7] has also shown that individuals with anxious depression (ie, experiencing MDD with high levels of anxiety symptoms) have a delayed response to treatment and are less likely to respond to antidepressants than those without a strong component of anxiety. This finding was seen in almost all the studies,[8–10] including levels 1 and 2 of STAR*D,[11] regardless of the type of antidepressant treatment used. The association between anxious depression and poorer response to antidepressant treatment may account

for the results of a study[12] showing that the concomitant use of anxiolytics or hypnotics was a significant predictor of treatment resistance in older adults with depression. These findings clearly suggest that anxious depression is a form of difficult-to-treat mood disorder, and the poorer outcome with all treatment arms at level 2 of STAR*D, including the anxiolytic buspirone augmentation of citalopram,[11] implies that multiple common antidepressant treatments, including augmentation strategies, may not fare as well in this population.

With respect to sleep disturbances, patients with anxious depression often report difficulties sleeping. In fact, in the entire STAR*D sample (n = 3,787),[5,6] patients with anxious depression had rates of early insomnia, midinsomnia, and late insomnia of 81%, 88%, and 65%, respectively, which were significantly higher (in the nonadjusted comparisons) than the rates in patients with nonanxious depression (58%, 74%, and 43%, respectively).

There is extensive literature that suggests genetic and phenotypic overlap between MDD and generalized anxiety disorder (GAD).[13] For this reason, one would expect that, in both populations, anxious-depressive cohorts would be highly represented. Although the results of the studies in MDD[14] and GAD[15] have been reported separately, we felt this was an opportunity to examine the population with greater conceptual overlap between the two, ie, those with anxious depression.

METHOD

Individual patient data were pooled from 2 randomized, double-blind, placebo-controlled clinical trials. One trial[14] was conducted from January 2004 to October 2004 in patients with insomnia and comorbid MDD (clinicaltrials.gov Identifier: NCT00368030), and the other trial[15] was conducted from July 2005 to April 2006 in patients with insomnia and comorbid GAD (clinicaltrials.gov Identifier: NCT00235508). Patients in these trials were randomly assigned to receive either eszopiclone 3 mg/d plus a selective serotonin reuptake inhibitor (SSRI) or placebo plus an SSRI nightly for 8 weeks. The SSRIs administered were fluoxetine hydrochloride (starting dose, 20 mg/d; dose range, 20–40 mg/d) in the comorbid MDD trial and escitalopram oxalate (10 mg/d) in the comorbid GAD trial. The 8-week treatment period was followed by a 2-week single-blind placebo run-out period (and continued SSRI treatment) to assess rebound insomnia. Detailed descriptions of the methodologies of these 2 trials have been reported previously.[14,15]

Study Parameters

In brief, the patient population studied in the comorbid MDD trial consisted of men and women between 21 and 64 years of age (inclusive) who met *DSM-IV* criteria for insomnia and comorbid MDD. Patients in the comorbid MDD trial were required to have scores ≥ 14 (excluding the 3 insomnia-related items) on the 17-item Hamilton Depression Rating Scale (HDRS-17).[16] In the comorbid GAD trial, men and women between 18 and 64 years of age (inclusive) met *DSM-IV-TR* criteria for GAD and for insomnia associated with GAD. Comorbid GAD patients also had Hospital Anxiety and Depression Scale[17] scores ≥ 10 on the anxiety subscale; Clinical Global Impressions-Severity of Illness scale scores ≥ 4; Hamilton Anxiety Rating Scale[18] scores ≥ 20, with a score of at least 2 on items 1 and 2 (anxious mood and tension); and Montgomery-Asberg Depression Rating Scale[19] scores < 20. In both studies, patients also reported total sleep time ≤ 6.5 hours and sleep latency ≥ 30 minutes (and in the comorbid MDD trial, wake time after sleep onset ≥ 45 minutes) per night at least 3 times per week during the preceding month.

Both studies utilized the Insomnia Severity Index (ISI)[20] during the treatment period. The ISI is composed of 7 items assessing the severity of sleep onset and sleep-maintenance difficulties, satisfaction with current sleep patterns, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. Each item is rated on a scale from 0 to 4, and the total score ranges from 0 to 28 (total scores of 0–7 = clinically nonsignificant insomnia; 8–14 = subthreshold insomnia; 15–21 = moderate insomnia; and 22–28 = severe insomnia).

In the comorbid MDD study, the HDRS-17 was completed at baseline and at weeks 4 and 8. In the comorbid GAD study, the HDRS-17 was completed at baseline and at weeks 1, 2, 4, 6, 8, and 10.

The presence of rebound insomnia was assessed for the eszopiclone group by examining patient-reported sleep latency, wake time after sleep onset, and total sleep time relative to baseline on each posttreatment night during the 2-week single-blind placebo run-out period.

In the current analysis, patients from the 2 trials were designated as having anxious depression if their baseline HDRS-17 scores were 14 or greater, after subtracting the 3 insomnia-related items, and their baseline HDRS anxiety/somatization factor scores were 7 or greater. The anxiety/somatization factor, derived from the factor analysis by Cleary and Guy[21] of the original HDRS-17, includes the following 6 items: psychic anxiety, somatic anxiety, gastrointestinal somatic symptoms, general somatic symptoms, hypochondriasis, and insight.

All patients in the original studies gave written informed consent, and the institutional review boards at each study site approved the protocols.

Statistical Methods

All statistical testing was 2-sided and was conducted at the 5% significance level. A last-observation-carried-forward method was utilized to handle missing data. Differences between the groups were evaluated for the following endpoints at week 4 and week 8 of the treatment period (the common time points for assessments): mean change from baseline in HDRS-17 total scores, mean change from baseline in HDRS-17 scores excluding the 3 insomnia-related items, mean change from baseline in HDRS anxiety/somatization

Table 1. Baseline Demographic and Disease Characteristics by Treatment Group

Characteristic	Eszopiclone + SSRI, N = 178	Placebo + SSRI, N = 169	*P* Value[a]
Age, mean ± SD, y	41.6 ± 10.7	39.8 ± 10.7	.0225
Female sex, n (%)	121 (68.0)	118 (69.8)	.9411
White race, n (%)	116 (65.2)	102 (60.4)	.3537
ISI total score, mean ± SD	20.5 ± 4.2	20.2 ± 4.1	.7505
HDRS-17 total score, mean ± SD	24.6 ± 3.5	23.7 ± 3.6	.0568
HDRS-17 score excluding insomnia, mean ± SD	19.2 ± 3.2	18.6 ± 3.1	.0716
HDRS anxiety/somatization, mean ± SD	8.2 ± 1.3	8.2 ± 1.2	.8130

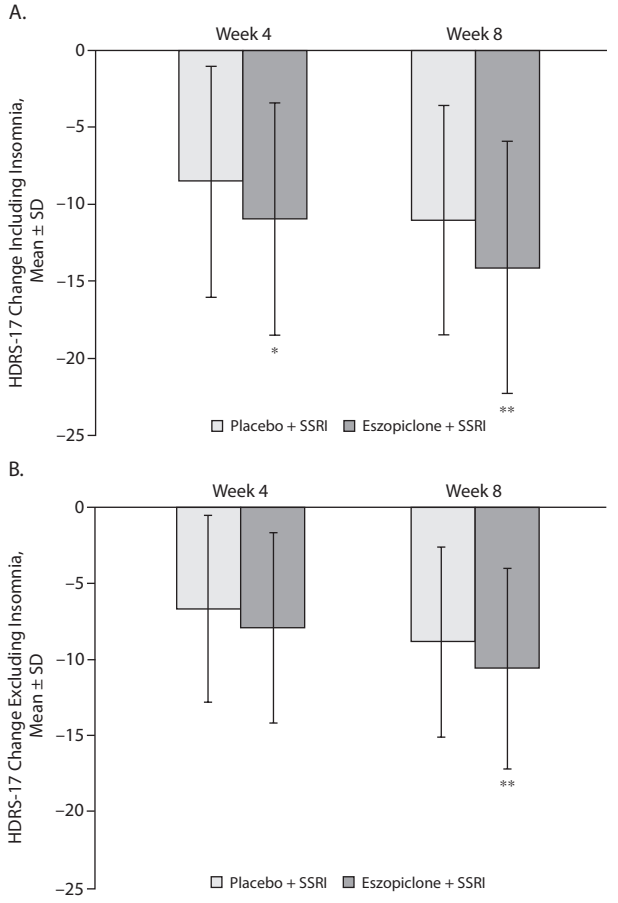
[a]Continuous variables were analyzed using an analysis of variance model with treatment and pooled site as fixed effects. Categorical variables were analyzed using the Cochran-Mantel-Haenszel test for general association, controlling for pooled site.
Abbreviations: HDRS = Hamilton Depression Rating Scale, ISI = Insomnia Severity Index, SSRI = selective serotonin reuptake inhibitor.

Table 2. Insomnia Severity Index and 17-Item Hamilton Depression Rating Scale (HDRS-17) Scores at Weeks 4 and 8 by Treatment Group

Measure	Eszopiclone + SSRI, N = 178	Placebo + SSRI, N = 169	*P* Value[a]
Insomnia Severity Index total score, mean ± SD			
Week 4	10.8 ± 7.1	13.3 ± 6.7	.0002
Week 8	9.6 ± 7.1	12.4 ± 7.1	< .0001
HDRS-17 score, mean ± SD			
Week 4	13.6 ± 7.1	15.0 ± 7.5	.0101
Week 8	10.4 ± 7.2	12.3 ± 7.4	.0004
HDRS-17 score excluding sleep items, mean ± SD			
Week 4	11.1 ± 5.9	11.8 ± 6.3	.0762
Week 8	8.6 ± 5.9	9.5 ± 6.2	.0095
HDRS anxiety/somatization factor score, mean ± SD			
Week 4	4.9 ± 2.8	5.2 ± 2.9	.5170
Week 8	3.9 ± 2.8	4.1 ± 2.7	.2270

[a]Pairwise comparison of placebo mean with eszopiclone mean using an analysis of covariance model with treatment and site as fixed effects and baseline as the covariate.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 1. Change From Baseline to Weeks 4 and 8 for HDRS-17 Total Score by Treatment Group, (A) Including and (B) Excluding Insomnia Items



*P = .01, **P < .01.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

factor scores, and mean change from baseline in patient-reported sleep (as assessed by the ISI), as well as response rates (≥ 50% reduction from baseline in HDRS-17 total scores, with and without the insomnia items) and remission rates (HDRS-17 total scores ≤ 7).

The differences in mean change from baseline between the treatment groups were compared using an analysis of covariance model with treatment and site as fixed effects and baseline as the covariate. Differences between the treatment groups in response and remission rates were compared using the Cochrane-Mantel-Haenszel test of general association with no stratification factors. No formal multiplicity adjustment was made.

RESULTS

Of the 1,136 patients randomly assigned in the 2 parent trials, 347 (30.5%) met the criteria for anxious depression (93 patients [26.8%] from the comorbid GAD trial and 254 patients [73.2%] from the comorbid MDD trial). Baseline demographic and disease characteristics of the pooled sample are reported for both treatment groups in Table 1. Except for age (mean ± SD of 41.6 ± 10.7 years in the eszopiclone + SSRI group and 39.8 ± 10.7 years in the placebo + SSRI group), there were no statistically significant differences between the treatment groups for the other demographic characteristics or baseline disease state.

Significantly greater mean ± SD improvements from baseline in ISI total scores were observed for the eszopiclone + SSRI group when compared with the placebo + SSRI group, both at week 4 (−9.7 ± 6.7 vs −6.9 ± 6.7, respectively; P < .001) and at week 8 (−10.9 ± 6.8 vs −7.8 ± 7.2, respectively; P < .0001) (Table 2).

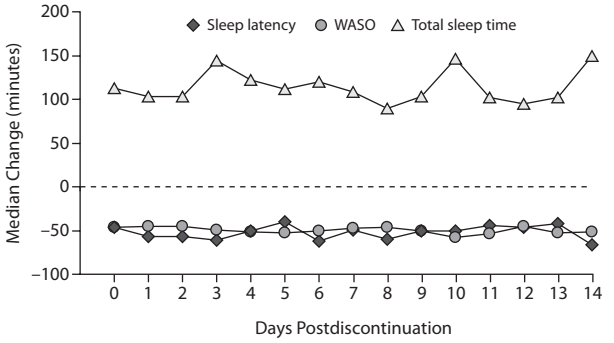
The reductions from baseline in mean ± SD HDRS-17 total scores were significantly greater following coadministration of eszopiclone and SSRI compared with placebo and SSRI at week 4 (−10.9 ± 7.6 vs −8.5 ± 7.4, respectively; P = .01) and at week 8 (−14.1 ± 8.1 vs −11.2 ± 7.5, respectively; P < .01) (Figure 1A). When the insomnia items were excluded, the relative decreases from baseline in HDRS-17 scores between the treatment groups at week 4 were not

Table 3. Most Frequently Reported Adverse Events by Treatment Group[a]

Adverse Event	Eszopiclone + SSRI, N = 178, n (%)	Placebo + SSRI, N = 169, n (%)
Any adverse event	143 (80.3)	127 (75.1)
Unpleasant taste	47 (26.4)	3 (1.8)
Nausea	28 (15.7)	34 (20.1)
Headache	25 (14.0)	27 (16.0)
Dry mouth	21 (11.8)	14 (8.3)
Somnolence	20 (11.2)	20 (11.8)
Dizziness	20 (11.2)	8 (4.7)
Nervousness	17 (9.6)	8 (4.7)
Diarrhea	17 (9.6)	11 (6.5)
Infection	14 (7.9)	15 (8.9)
Dyspepsia	13 (7.3)	8 (4.7)
Pharyngitis	12 (6.7)	5 (3.0)
Asthenia	11 (6.2)	12 (7.1)
Anorexia	11 (6.2)	12 (7.1)
Pain	10 (5.6)	12 (7.1)
Impotence[b]	3 (5.3)	2 (3.9)
Accidental injury	8 (4.5)	12 (7.1)
Back pain	8 (4.5)	9 (5.3)
Myalgia	8 (4.5)	9 (5.3)
Abdominal pain	7 (3.9)	11 (6.5)

[a]Greater than or equal to 5% in any treatment group.
[b]Men only (n = 57 in the eszopiclone + SSRI group; n = 51 in the placebo + SSRI group).
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 2. Median Change From Baseline for Rebound Insomnia Items During the 2-Week Single-Blind Run-Out Period for the Eszopiclone Group[a,b]



[a]Day 0 represents the change from baseline during the last week of treatment.
[b]*P* values for all sleep measures on each postdiscontinuation day were < .0001 (Wilcoxon signed rank test, which assessed whether the distribution of changes from baseline was centered on zero).
Abbreviation: WASO = wake time after sleep onset.

significantly different (−7.9 ± 6.4 vs −6.7 ± 6.2, respectively; *P* = .08), but significantly greater improvements were observed at week 8 following coadministration of SSRI and eszopiclone (−10.6 ± 6.7 vs −8.9 ± 6.3, respectively; *P* < .01) (Figure 1B). Mean ± SD changes from baseline in the anxiety/somatization factor scores were not significantly different at either time point (week 4: −3.3 ± 2.7 vs −3.0 ± 3.0, respectively; *P* = .52; and week 8: −4.3 ± 2.8 vs −4.1 ± 2.9, respectively; *P* = .23) (Table 2).

Response rates were significantly higher in anxious depressed patients in the eszopiclone + SSRI group compared with those in the placebo + SSRI group at the end of treatment (55.6% vs 42.0%, respectively; *P* = .01). However, when the insomnia items were removed, the difference between groups was not significant (50.0% vs 44.4%, respectively; *P* = .30). Additionally, remission rates did not differ significantly at either time point (week 4: 16.3% vs 16.6%, respectively; *P* = .94; and week 8: 32.6% vs 27.2%, respectively; *P* = .28).

The overall incidence of adverse events was 80.3% in the eszopiclone + SSRI group and 75.1% in the placebo + SSRI group. With the exception of unpleasant taste (26.4% in the eszopiclone + SSRI group and 1.8% in the placebo + SSRI group), the incidence of individual adverse events was similar in the 2 treatment groups (Table 3). In the majority of patients in the eszopiclone + SSRI group, unpleasant taste occurred during the first 2 weeks of treatment and resolved in most patients. No study discontinuations or dropouts resulted from this adverse event. There was no evidence of rebound insomnia following discontinuation of eszopiclone as measured by increased sleep latency and wake time after sleep onset, or decreased total sleep time, relative to baseline observations (Figure 2).

DISCUSSION

In this post hoc analysis of a pooled sample derived from 2 distinct clinical trials, coadministration of eszopiclone and an SSRI was compared with SSRI monotherapy plus placebo in patients with insomnia and comorbid anxious depression. We found that the benefits conferred by the addition of eszopiclone previously reported in individuals with insomnia and comorbid MDD[14] or GAD[15] was also demonstrated in patients with insomnia and comorbid anxious depression. There were significantly greater reductions from baseline in mean HDRS-17 total scores observed following coadministration of eszopiclone and SSRI compared with placebo and SSRI at both week 4 and week 8. However, it should be noted that the severity of depression was not particularly high in these studies. When the insomnia items were excluded, the relative decreases from baseline in HDRS-17 scores remained significantly different for the eszopiclone + SSRI treatment group compared to the placebo + SSRI treatment group at week 8, although not at week 4. This finding suggests that benefits to depression per se occurred in a similar time course to that of antidepressant monotherapy.

Although prospective studies in large samples of patients with anxious depression are warranted, these findings may be suggestive of clinical usefulness of cotherapy with eszopiclone and SSRIs in patients with insomnia and comorbid anxious depression and may be explained by the pharmacologic effect of eszopiclone binding on specific γ-aminobutyric acid $(GABA)_A$ receptor subunits.

Eszopiclone interacts with a number of $GABA_A$ receptor subtypes and has shown a balanced selectivity for the α_1, α_2, α_3, and α_5 subtypes.[22–23] This characteristic differs from other hypnotics, such as zolpidem and zaleplon, which have principal selectivity for the α_1 subtype, and triazolam, which has selectivity for all the $GABA_A$ receptor subtypes.[22]

A review by Sieghart[24] suggests that sedative effects from sedative-hypnotic drugs are primarily associated with α_1 activity, whereas anxiolytic effects are associated with α_2 and α_3 activity. Thus, based on in vitro selectivity studies, eszopiclone may provide anxiolytic effects (via α_2 and α_3 activity) in addition to its other established effects. However, in this study, eszopiclone did not demonstrate a specific effect on the anxiety/somatization factor.

These findings are notable compared to the relatively poorer effectiveness of the anxiolytic buspirone augmentation at level 2 of STAR*D in anxious depression[11] and the failure of clonazepam to improve anxiety to a greater degree than placebo in resistant depression when coadministered with fluoxetine in MDD.[25] Selective serotonin reuptake inhibitor augmentation with atypical antipsychotic drugs such as quetiapine[26] and aripiprazole[27] have yielded greater improvements than placebo augmentation, but the tolerability issues of this class of drugs have limited their use as a first-line treatment.

That a medication with activity at multiple $GABA_A$ receptor subtypes may have antidepressant properties is consistent with the existing literature on the role of GABA in depression. Dysregulation of GABA neurotransmission has been implicated as an important biological factor in MDD. In animal models of depression, decreased GABA function and decreased $GABA_A$ receptor binding have been observed.[28] Earlier studies have shown decreased GABA levels in the cerebrospinal fluid of MDD patients compared with normal controls.[29] In addition, proton magnetic resonance spectroscopy (1H-MRS) studies[30] have shown reductions in occipital cortex GABA levels in unmedicated MDD patients compared with healthy volunteers. Two separate studies[31,32] reported significant increases in GABA levels in the occipital cortex of MDD patients after treatment with SSRIs[31] and after electroconvulsive therapy.[32] Selective serotonin reuptake inhibitors are also known to induce increases in brain allopregnanolone,[33] a neurosteroid with high affinity for $GABA_A$ receptors, which facilitates GABAergic actions. This is the mechanism by which Ketter and Wang[34] explain the SSRI role in increasing brain GABA levels. In addition, serotonergic cells of the dorsal raphe show selective α_3 expression.[35] Taken together, these findings are consistent with the hypothesis that the modest antidepressant activity of eszopiclone observed in our study might be related to its direct activity on several $GABA_A$ receptor subtypes.

Discontinuation of eszopiclone therapy in patients with comorbid psychiatric disease did not result in significant withdrawal or rebound insomnia or depression.[36] We had similar findings in this subset analysis. On the other hand, nightly treatment with eszopiclone for up to 8 weeks in patients with comorbid insomnia[14,15,37] and up to 12 months in patients with chronic insomnia did not result in tolerance to the hypnotic effect,[38] suggesting that eszopiclone could be used for a longer term in cases of insomnia and comorbid anxious depression. Further comparisons in this clinical population are needed between eszopiclone and other anxiolytics and hypnotics to better characterize eszopiclone's relative benefits.

The primary limitation of this investigation is that it was completed post hoc and, therefore, was not included originally in the analytic plans of these 2 studies. These results can be used to generate testable hypotheses regarding the role of other combinations of targeted therapies in the treatment of anxious depression. Other limitations include the fact that all patients in the parent studies were required to have insomnia and either GAD or MDD. The parent studies were also not designed to be augmentation studies but were evaluations of the effect of cotherapy, as compared with monotherapy, on insomnia and comorbid depression or anxiety. For these reasons, no conclusions can be drawn about the effect of cotherapy in patients who do not have insomnia. In addition, there were no formal assessments of GAD in the MDD trial; therefore, one cannot establish the exact prevalence of MDD plus GAD in that particular trial. Based on STAR*D data,[11] however, it appears that anxious depression, defined as MDD and high levels of anxiety on the HDRS anxiety/somatization scale, has substantial overlap with MDD plus comorbid anxiety disorders. The parent studies did not specifically recruit individuals with anxious depression per se, and, therefore, the selection of subjects may not have been optimal for addressing the particular questions of this combined analysis. Nonetheless, this analysis is similar to other post hoc analyses of treatment studies, including STAR*D. Likewise, anxious depression is still not a recognized diagnosis, and continued characterization of, and professional consensus about, this subtype would eventually call for replication of these findings in patient samples specifically diagnosed with more rigorous criteria for anxious depression, if such criteria are developed. The parent studies used only 2 SSRIs, fluoxetine and escitalopram, both of which are known to have beneficial effects on anxiety; further investigation is therefore needed to determine whether these findings would extend to other antidepressants, particularly those such as bupropion, which are not known for their anxiolytic properties. Last, we did not use corrections for multiple comparisons as this was largely an exploratory analysis; further studies will be needed to validate these preliminary results.

In conclusion, on the basis of this post hoc analysis of pooled data from 2 clinical trials, we have shown that the coadministration of eszopiclone and 2 different SSRIs in patients with insomnia and comorbid anxious depression improved not only insomnia symptoms but also depressive severity and response rates as assessed by the HDRS-17. There were no significant differences in anxiety/somatization scores, response rates when insomnia items were excluded, or remission rates. The mechanism of action of eszopiclone (with direct activity on $GABA_A$ receptors) may provide insights into the rationale for the modest antidepressant effect noted. Further investigations in larger samples of patients with anxious depression are clearly needed.

Drug names: aripiprazole (Abilify), buspirone (BuSpar and others), citalopram (Celexa and others), clonazepam (Klonopin and others), escitalopram (Lexapro and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), quetiapine (Seroquel), triazolam (Halcion and others), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

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REFERENCES

1. Fawcett J, Kravitz HM. Anxiety syndromes and their relationship to depressive illness. *J Clin Psychiatry*. 1983;44(8, pt 2):8–11.
2. Joffe RT, Bagby RM, Levitt A. Anxious and nonanxious depression. *Am J Psychiatry*. 1993;150(8):1257–1258.
3. Van Valkenburg C, Akiskal HS, Puzantian V, et al. Anxious depressions: Clinical, family history, and naturalistic outcome—comparisons with panic and major depressive disorders. *J Affect Disord*. 1984;6(1):67–82.
4. Tollefson GD, Holman SL, Sayler ME, et al. Fluoxetine, placebo, and tricyclic antidepressants in major depression with and without anxious features. *J Clin Psychiatry*. 1994;55(2):50–59.
5. Fava M, Alpert JE, Carmin CN, et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol Med*. 2004;34(7):1299–1308.
6. Fava M, Rush AJ, Alpert JE, et al. What clinical and symptom features and comorbid disorders characterize outpatients with anxious major depressive disorder: a replication and extension. *Can J Psychiatry*. 2006;51(13):823–835.
7. Clayton PJ, Grove WM, Coryell W, et al. Follow-up and family study of anxious depression. *Am J Psychiatry*. 1991;148(11):1512–1517.
8. Fava M, Uebelacker LA, Alpert JE, et al. Major depressive subtypes and treatment response. *Biol Psychiatry*. 1997;42(7):568–576.
9. Flint AJ, Rifat SL. Anxious depression in elderly patients: response to antidepressant treatment. *Am J Geriatr Psychiatry.* 1997;5(2):107–115.
10. Davidson JR, Meoni P, Haudiquet V, et al. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms. *Depress Anxiety.* 2002;16(1):4–13.
11. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008;165(3):342–351.
12. Bosworth HB, Hays JC, George LK, et al. Psychosocial and clinical predictors of unipolar depression outcome in older adults. *Int J Geriatr Psychiatry*. 2002;17(3):238–246.
13. Hettema JM. The nosologic relationship between generalized anxiety disorder and major depression. *Depress Anxiety*. 2008;25(4):300–316.
14. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry*. 2006;59(11):1052–1060.
15. Pollack M, Kinrys G, Krystal A, et al. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. *Arch Gen Psychiatry*. 2008;65(5):551–562.
16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
17. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand.* 1983;67(6):361–370.
18. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
19. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
20. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(4):297–307.
21. Cleary P, Guy W. Factor analysis of the Hamilton Depression Scale. *Drugs Exp Clin Res*. 1977;1:115–120.
22. Sanna E, Busonero F, Talani G, et al. Comparison of the effects of zaleplon, zolpidem, and triazolam at various $GABA_A$ receptor subtypes. *Eur J Pharmacol*. 2002;451(2):103–110.
23. Hanson SM, Morlock EV, Satyshur KA, et al. Structural requirements for eszopiclone and zolpidem binding to the γ-aminobutyric acid type-A ($GABA_A$) receptor are different. *J Med Chem.* 2008;51(22):7243–7252.
24. Sieghart W. Structure, pharmacology, and function of $GABA_A$ receptor subtypes. *Adv Pharmacol*. 2006;54:231–263.
25. Smith WT, Londborg PD, Glaudin V, et al; Summit Research Network. Is extended clonazepam cotherapy of fluoxetine effective for outpatients with major depression? *J Affect Disord*. 2002;70(3):251–259.
26. McIntyre A, Gendron A, McIntyre A. Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. *Depress Anxiety*. 2007;24(7):487–494.
27. Trivedi MH, Thase ME, Fava M, et al. Adjunctive aripiprazole in major depressive disorder: analysis of efficacy and safety in patients with anxious and atypical features. *J Clin Psychiatry*. 2008;69(12):1928–1936.
28. Sanacora G, Mason GF, Krystal JH. Impairment of GABAergic transmission in depression: new insights from neuroimaging studies. *Crit Rev Neurobiol*. 2000;14(1):23–45.
29. Gerner RH, Fairbanks L, Anderson GM, et al. CSF neurochemistry in depressed, manic, and schizophrenic patients compared with that of normal controls. *Am J Psychiatry*. 1984;141(12):1533–1540.
30. Sanacora G, Mason GF, Rothman DL, et al. Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 1999;56(11):1043–1047.
31. Sanacora G, Mason GF, Rothman DL, et al. Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *Am J Psychiatry*. 2002;159(4):663–665.
32. Sanacora G, Gueorguieva R, Epperson CN, et al. Subtype-specific

alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry*. 2004;61(7):705–713.
33. Uzunova V, Sheline Y, Davis JM, et al. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci U S A*. 1998;95(6):3239–3244.
34. Ketter TA, Wang PW. The emerging differential roles of GABAergic and antiglutamatergic agents in bipolar disorders. *J Clin Psychiatry*. 2003; 64(suppl 3):15–20.
35. Moragues N, Ciofi P, Tramu G, et al. Localisation of $GABA_A$ receptor ε-subunit in cholinergic and aminergic neurones and evidence for co-distribution with the θ-subunit in rat brain. *Neuroscience*. 2002; 111(3):657–669.
36. Krystal A, Fava M, Rubens R, et al. Evaluation of eszopiclone discontinuation after cotherapy with fluoxetine for insomnia with coexisting depression. *J Clin Sleep Med*. 2007;3(1):48–55.
37. Soares CN, Joffe H, Rubens R, et al. Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial. *Obstet Gynecol.* 2006;108(6):1402–1410.
38. Roth T, Walsh JK, Krystal A, et al. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Med*. 2005;6(6):487–495.