Does Lorazepam Impair the Antidepressant Response to Nortriptyline and Psychotherapy?

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Background: This analysis sought to determine whether lorazepam influences time to response or rate of response in elderly depressed patients receiving nortriptyline and psychotherapy and to examine clinical and polysomnographic correlates of lorazepam treatment.

Method: Patients with recurrent major depressive disorder (N = 119; mean ± SD age = 68.0 ± 6.1 years; diagnosis defined by Research Diagnostic Criteria) received acute treatment with nortriptyline and interpersonal psychotherapy. Thirty-five patients received open-label adjunctive lorazepam for anxiety or insomnia symptoms (LZ+) and 84 did not. Statistical analyses were conducted between the LZ+ group and a group of 35 patients who received no lorazepam (LZ–) and were matched for anxiety level. Patients had polysomnographic studies prior to treatment and after remission of depressive symptoms.

Results: The LZ+ group reported more anxiety on the Brief Symptom Inventory ($p = .04$) compared with the remaining 84 patients. The LZ+ group had a greater proportion of endogenous depression subtype than the anxiety-matched LZ– group, in addition to more abnormal EEG sleep (higher percentage of REM sleep, shorter REM latency, lower delta sleep ratio). Mean time to initial antidepressant response was no different between groups. However, a significantly greater proportion of LZ+ than LZ– patients responded to acute treatment (91.4% vs. 71.4%; $p < .03$).

Conclusion: Adjunctive lorazepam does not slow the antidepressant response to combined antidepressant/psychotherapy treatment in elderly depressed patients, and it is associated with a greater likelihood of antidepressant response. A greater percentage of patients treated with lorazepam have endogenous depression subtype and abnormal sleep findings (EEG) than those who are not treated with lorazepam. Adjunctive lorazepam is useful for treating anxiety in elderly depressed patients.

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Elderly patients with depression are as likely as middle-aged patients to respond to combined treatment with pharmacotherapy and psychotherapy, although they respond more slowly.[1] The delay in clinical response, even with combined treatment, remains one of the most difficult problems in the treatment of late-life depression. Elderly treatment responders and nonresponders can be distinguished as early as the fourth week of combined therapy,[2] but the median time to a meaningful clinical response, defined as a score ≤ 10 on the Hamilton Rating Scale for Depression (HAM-D), is 12–13 weeks.[3] Clinical factors that presage a slow response or a lower overall rate of response include anxiety symptoms or disorders,[4,5] sleep disturbance,[6] longer episode duration,[7] personality pathology,[2] and the presence of severe life events during the 6-month period before the index episode.[8] These observations raise the possibility that treating comorbid anxiety and insomnia symptoms with adjunctive benzodiazepines may actually hasten the antidepressant response or improve the total rate of response in elderly depressed patients.

Two concerns arise with this approach.[9] First is the persistent concern that benzodiazepines may actually exacerbate depression. Early clinical observations of depression developing in patients treated with diazepam[10] were supported by further observational studies demonstrating the occurrence of major depression in patients treated with lorazepam and alprazolam for panic disorder.[11,12] Prescription-event monitoring of > 10,000 patients treated with alprazolam revealed drowsiness and depression to be the most commonly reported neuropsychiatric events.[13] On the other hand, the high rate of comorbid major depression in patients with panic disorder—nearly 70% in some studies[14,15]—calls into question a causal relationship. Furthermore, several studies

have demonstrated the efficacy of the triazolobenzodiazepine alprazolam for the treatment of moderate depression in outpatients.[16,17] Comparisons of tricyclic/benzodiazepine combinations to tricyclic antidepressants alone have not demonstrated lower response rates for the combination,[17–19] and the addition of benzodiazepines to ongoing antidepressant treatment does not appear to increase depressive symptoms.[20–22]

A second issue is whether benzodiazepines administered concurrently with antidepressants slow the antidepressant response. Again, data do not tend to support this concern. Fawcett and colleagues[17] found no significant difference in the time course of response between patients treated with desipramine or a desipramine-alprazolam combination; patients treated with alprazolam alone showed larger reductions in symptoms early in the course of treatment. Two studies found a slightly faster antidepressant response in patients treated with an amitriptyline-chlordiazepoxide combination compared with amitriptyline alone.[19,23]

Issues regarding adjunctive treatment with benzodiazepines have not been addressed in elderly depressed patients. Such issues are particularly salient in this group, because the elderly may have greater sensitivity to both anxiety or insomnia symptoms, as well as the potential adverse effects of sedative medications. In this study, we addressed the following specific questions: (1) Do elderly depressed patients who receive adjunctive benzodiazepine treatment differ in terms of clinical or polysomnographic measures from those who do not receive such treatment? (2) Does adjunctive treatment with benzodiazepines slow the time to remission in elderly depressed patients who are also treated with nortriptyline and psychotherapy? (3) Does adjunctive lorazepam decrease the overall rate of treatment response?

METHOD

Subjects

Subjects included 119 elderly patients diagnosed with recurrent unipolar nonpsychotic major depressive disorder, as determined by the Schedule for Affective Disorders and Schizophrenia[24] and Research Diagnostic Criteria.[25] The mean ± SD age was 68.0 ± 6.1 years, and the sample included 33 men and 86 women. Patients were required to have a score ≥ 17 on the 17-item HAM-D[26] at study entry. Patients with unstable medical conditions, medications that could cause depression, or comorbid psychiatric conditions (other than secondary anxiety disorders) were excluded from participation. Patients were characterized in terms of demographics and depression episode features. In addition, we characterized patients' clinical status using the following instruments: HAM-D, Beck Depression Inventory (BDI),[27] Asberg Rating Scale for Side Effects,[28] anxiety scale from the Brief Symptom Inventory (BSI),[29] Personality Assessment Form (PAF),[30] Global Assessment Scale (GAS),[31] Beck Hopelessness Scale,[32] Cumulative Illness Rating Scale (CIRS),[33] and the Pittsburgh Sleep Quality Index (PSQI).[34] Demographic and clinical characteristics of patients are shown in Table 1. All patients signed informed consent for participation in this study, which was approved by the University of Pittsburgh Biomedical Institutional Review Board.

Treatment Procedures

Patients were enrolled in a research study of maintenance treatments in late-life depression.[3] The first phase of this study, which is the focus of this report, consists of open clinical treatment with nortriptyline (with a target steady-state blood level of 80–120 ng/mL) and weekly interpersonal psychotherapy (IPT).[35,36] Patients continue with the acute-phase treatment until clinical response occurs, defined as a score ≤ 10 on the HAM-D for 3 consecutive weeks. They then enter a continuation phase, with nortriptyline continued and IPT sessions once every 2 weeks for 16 weeks. Remission was defined as a HAM-D score ≤ 10 at the end of the continuation phase together with a serum nortriptyline level in the therapeutic range. Following this, patients enter a transition phase prior to random, double-blind assignment to nortriptyline or placebo and IPT or clinic management for maintenance therapy.

During the acute phase, treating psychiatrists were also permitted to prescribe lorazepam 0.5 to 2.0 mg q.d. or b.i.d. as an adjunctive medication for anxiety or insomnia. Treatment with lorazepam was conducted openly, rather than through random assignment. The decision to start lorazepam was based on the treating psychiatrist's judgment, not a specified level of severity on rating scales. Lorazepam was permitted for the duration of acute and continuation therapy. A total of 35 patients received adjunctive lorazepam (LZ+ group). Of the 35 LZ+ patients, 15 received lorazepam for anxiety symptoms, 8 for insomnia symptoms, and 12 for a combination of anxiety and insomnia symptoms. The mean ± SD time between the start of acute treatment with nortriptyline/IPT and the start of lorazepam treatment was 6.0 ± 8.9 weeks (median = 3 weeks; range, 0–41). The mean lorazepam dose was 1.4 ± 0.9 mg (median = 1; range, 0.25–3.5), and the mean duration of adjunctive treatment was 18 weeks (median = 20; range, 1–54).

Sleep Studies

Three consecutive nights of EEG sleep studies were conducted at baseline (while patients were depressed and prior to treatment) and again 1 month into continuation treatment (while they were still taking nortriptyline ± lorazepam). The recording montage included one central EEG channel (C3 or C4 referenced to A1 + A2), two electro-oculogram (EOG) channels (referenced to A1 + A2), and a bipolar submental electromyogram

Table 1. Demographic and Clinical Data

Variable	No Lorazepam (Matched for Anxiety) N	Mean	SD	Lorazepam N	Mean	SD	Test Statistic (t or χ^2)	p Value
Demographics								
Age (y)	35	67.3	5.9	35	68.1	6.4	–0.56	.58
% Male	35	31.4		35	20.0		1.20	.27
% Black	35	2.9		35	11.4		1.94	.16
Education (y)	35	12.7	2.3	35	12.8	2.8	–0.14	.89
Baseline clinical measures								
Number of episodes[a]							0.04	.97
Age at onset (y)	35	49.5	11.8	35	47.0	17.9	0.68	.50
Duration current episode (wk)	35	27.7	28.6	35	21.4	22.7	1.07	.29
Endogenous (definite), %	35	48.6		35	71.4		3.81	.05
Lifetime Research Diagnostic Criteria anxiety disorder, %	35	14.3		35	20.0		0.40	.53
Rating scale scores								
Hamilton Rating Scale for Depression, 17-item (baseline)								
Total	35	19.4	4.8	35	18.4	5.0	0.82	.41
Anxiety items	35	4.3	1.4	35	4.0	2.1	0.87	.39
Sleep items (continuation)	35	3.4	1.7	35	3.5	1.7	–0.14	.89
Beck Depression Inventory	35	21.3	8.2	35	19.8	10.7	0.65	.52
Beck Hopelessness Scale	30	7.8	4.9	31	7.1	5.4	0.58	.56
Global Assessment Scale	35	58.6	6.6	35	57.5	5.3	0.81	.42
Asberg Rating Scale for Side Effects	33	12.8	5.1	35	12.1	6.4	0.56	.58
Brief Symptom Inventory-anxiety	35	1.5	1.0	35	1.5	1.0	–0.16	.87
Personality Assessment Form	32	19.0	3.4	35	18.7	4.0	0.38	.71
Pittsburgh Sleep Quality Index	24	10.2	4.3	22	11.7	4.1	–1.19	.24
Cumulative Illness Rating Scale								
Total	31	6.7	3.2	34	7.4	3.3	–0.83	.41
Count	31	4.5	2.1	34	4.7	1.6	–0.49	.63

[a]For the No Lorazepam group, the median number of episodes was 4 (range, 2–15); for the Lorazepam group, the median number was 4 (range, 2–28).

(EMG). High- and low-frequency filter settings for the EEG and EOG were 30 and 0.3 Hz, respectively, with a sensitivity of 7.5 μV/mm. Records were visually scored for traditional sleep stages and for estimates of phasic rapid eye movement (REM) activity during REM sleep. In addition, period-amplitude analysis of the EEG and automated detection of rapid eye movements were conducted as previously described.[37] The specific period-amplitude measure of delta EEG activity used in this analysis was the delta ratio. This is the ratio of 0.5- to 2.0-Hz EEG waveforms per minute in the first non–rapid eye movement (NREM) sleep period divided by 0.5- to 2.0-Hz EEG waveforms per minute in the second NREM period. The delta ratio has previously been found to correlate with time to recurrence in depressed patients during maintenance treatment.[38] EEG sleep results are presented as mean values for the second and third nights of study. Patients were also screened for the presence of sleep apnea and periodic limb movements during sleep on the first night of studies. Patients with > 10 apneas/hypopneas per hour of sleep or > 10 periodic limb movements with arousal per hour of sleep were excluded from the study.

Statistical Analyses

Descriptive statistics are shown as means with standard deviations, or medians with ranges. Data analysis proceeded in two stages. In the first stage, we examined the demographic and clinical characteristics of the 35 LZ+ and 84 remaining patients with t tests, nonparametric tests, and chi-square contingency tables to determine whether there were significant differences between these groups other than lorazepam treatment. Compared with the group of 84 patients, the LZ+ group had higher anxiety ratings on the BSI anxiety scale ($t = –2.1$, $p = .04$). The two groups did not differ significantly on demographic or other clinical variables (including number of depressive episodes, age at illness onset, duration of the index depressive episode, or proportion with endogenous depression subtype; proportion with lifetime RDC anxiety disorders; pretreatment HAM-D score, BDI score, Beck Hopelessness Scale score, or GAS; personality symptoms measured by the PAF; sleep quality measured by the PSQI; and chronic medical illness measured with the CIRS modified for geriatric use).

Anxiety symptoms can influence time to recovery from depression.[5] Therefore, we matched 35 patients who received no lorazepam (LZ–) to the LZ+ group on the basis of baseline BSI anxiety score, age, and sex. These matched groups of LZ+ and LZ– patients were then used for the second stage of data analysis in order to isolate findings attributable solely to lorazepam treatment (and not to coexisting anxiety). Clinical and polysomnographic

Table 2. Sleep Variables as Measured by EEG*

Variable	No Lorazepam (Matched for Anxiety) N	Mean	SD	Lorazepam N	Mean	SD	Test Statistic (t or χ^2)	p Value
Baseline (pretreatment)								
Total recording period (min)	24	455.8	64.4	22	461.8	40.9	–0.38	.71
Sleep latency (min)[a]	24	32.3	49.1	22	33.1	31.0	–0.77	.45
Sleep maintenance (%)[b]	24	84.8	9.4	22	82.0	9.8	–0.96	.34
Number of arousals	24	8.8	3.6	22	9.5	3.3	–0.65	.52
Time spent asleep (min)	24	361.6	83.6	22	350.6	50.5	0.54	.60
Stage 1 (%)[c]	24	7.0	5.5	22	6.0	2.9	0.42	.68
Stage 2 (%)[c]	24	61.3	7.6	22	59.2	8.7	0.87	.39
Delta (%)[c]	24	8.6	8.9	22	7.2	7.2	0.30	.77
REM (%)	24	23.1	4.7	22	27.6	7.3	–2.49	.02
REM latency (min)[c]	24	55.3	19.3	22	44.9	18.8	1.75	.09
REM density	24	1.7	0.5	22	1.6	0.5	0.26	.79
Delta sleep ratio[d]	24	1.3	0.4	22	1.2	0.4	0.91	.37
Continuation (on nortriptyline)								
Mean serum nortriptyline level	33	82.9	34.7	35	86.6	30.0	0.47	.64
Total recording period (min)	22	459.8	46.2	27	466.0	51.5	–0.44	.66
Sleep latency (min)[a]	22	25.4	22.8	27	30.3	23.7	–0.32	.75
Sleep maintenance (%)[b]	22	87.6	5.7	27	85.5	8.6	–0.65	.52
Number of arousals	22	12.5	3.6	27	11.3	3.6	1.13	.26
Time spent asleep (min)	22	379.8	33.0	27	371.5	48.7	0.67	.50
Stage 1 (%)[c]	22	7.1	2.9	27	8.2	4.8	–0.78	.44
Stage 2 (%)[c]	22	73.0	8.2	27	68.8	8.3	1.77	.08
Delta (%)[c]	22	6.0	7.4	27	4.8	5.2	0.35	.73
REM (%)	22	13.9	4.4	27	18.2	4.3	–3.52	.001
REM latency (min)[c]	22	111.2	50.1	27	78.4	30.6	2.70	.01
REM density	22	2.4	0.7	27	2.2	1.0	0.89	.38
Delta sleep ratio[d]	22	1.8	0.7	27	1.4	0.5	2.04	.05

*Abbreviations: NREM = non–rapid eye movement, REM = rapid eye movement. Means and standard deviations reported in their original units.
[a]Ln (x + 1) transformation used for analyses.
[b]Sleep maintenance = 100 × total sleep time/(total recording period – sleep latency) × Ln (100 – x + 1) transformation used for analyses.
[c]Square root of "x" ($\sqrt{x}$) used for analyses.
[d]Delta ratio = (delta EEG counts/min in NREM1)/(delta EEG counts/min in NREM2) × Ln (x + 0.1) transformation used for analyses.

measures were compared between groups by using t tests, nonparametric tests, and chi-square contingency tables. To compare time to remission in the two groups, we used Kaplan-Meier survival analysis with the log-rank test of equality. To identify the specific contribution of lorazepam and underlying symptoms to treatment response, we ran a Cox proportional hazards model on the matched groups of 35 LZ+ and 35 LZ– patients, examining lorazepam treatment, anxiety (from the BSI anxiety scale), sleep quality (from the global PSQI score), and percentage of REM sleep as covariates. Finally, the overall rate of initial treatment response and remission in the two groups was compared with a chi-square contingency table.

RESULTS

Clinical and Polysomnographic Features

The LZ+ and anxiety-matched LZ– groups did not differ on baseline clinical and demographic measures (Table 1) except for a greater percentage of patients with endogenous depression subtype in the LZ+ group (71.4% vs. 48.6% in the matched LZ– group; $\chi^2 = 3.8$, $p < .05$). Patients in the LZ+ and anxiety-matched LZ– groups did not differ in mean steady-state serum nortriptyline levels during continuation treatment (LZ+ = 86.6 ng/mL, LZ– = 82.9 ng/mL; t = –0.47, N.S.). Five (14%) of 35 patients in the LZ+ group dropped out of treatment in the acute or continuation phase, including one due to medical reasons, two due to noncompliance, and two due to refusal of further treatment. Seven (20%) of 35 patients in the anxiety-matched LZ– group dropped out of treatment in the acute or continuation phase, including four due to medical reasons, one due to noncompliance, one due to side effects, and one due to refusal of further treatment. This difference in dropout rate is not statistically significant ($\chi^2 = 0.40$, $p = .53$).

To determine whether LZ+ and LZ– groups differed neurobiologically, we compared EEG sleep characteristics both at baseline (before treatment) and at the end of continuation (during remission) (Table 2). The number of subjects in baseline EEG sleep analyses was reduced because some patients could not tolerate these procedures due to the severity of their illness, and the number at the end of continuation was reduced because of nonrespond-

ers and dropouts, who did not have repeat sleep studies. At each timepoint, LZ+ patients had a significantly higher percentage of REM sleep than anxiety-matched LZ– patients ($t = –2.5$, $p < .02$ at baseline; $t = –3.5$, $p < .001$ at continuation). In addition, LZ+ patients had significantly shorter REM latency ($t = 2.7$, $p < .01$) and a lower delta sleep ratio ($t = 2.0$, $p < .05$) than anxiety-matched LZ– patients at continuation. For each of these variables, the values were in the direction of greater abnormality in the LZ+ group compared with the anxiety-matched LZ– group.

Response Patterns

To determine whether the LZ+ and matched LZ– groups showed different patterns of treatment response, we performed ANOVAs with one between-group factor (LZ+ vs. LZ–), one repeated measure (baseline to remission), and three dependent variables (HAM-D, PSQI, and BSI anxiety scores). The groups showed no differential change in HAM-D, PSQI, or BSI anxiety scores from baseline to initial response, as indicated by the absence of significant group × time interaction effects on each measure. For each measure, treatment resulted in a significant reduction in symptoms, indicated by significant F values for the initial response-baseline repeated measure (HAM-D: $F = 95.70$, $df = 1,68$; $p < .0001$; PSQI: $F = 13.91$, $df = 1,53$; $p < .0005$; BSI: $F = 62.07$, $df = 1,68$; $p < .0001$). There were no significant main effects for group (LZ+ vs. LZ–) on HAM-D, PSQI, or BSI scores.

Time to response. Survival analysis using the Kaplan-Meier log-rank test of equality showed no significant difference in time to response for the LZ+ and anxiety-matched LZ– groups (median in LZ+ group = 9.9 weeks; median in LZ– = 11.4 weeks; log-rank $\chi^2 = 0.09$, $p < .77$). To test whether anxiety symptoms, subjective sleep quality, or lorazepam treatment influences the time to initial response, we ran a Cox proportional hazards model to simultaneously evaluate the effects of these three variables on treatment response. In this analysis, only baseline PSQI score was a significant covariate of time to response (Wald's $\chi^2 = 5.34$, $p < .02$, risk ratio = 0.914); worse sleep quality was associated with prolonged time to response. Anxiety symptoms, lorazepam treatment, and percentage of REM sleep were not retained in the model as significant covariates (Wald's $\chi^2 < 0.36$, $p > .55$ for each).

Rate of response. Finally, we examined the effect of lorazepam on the overall rate of treatment response. A significantly greater proportion of LZ+ patients responded to acute treatment, i.e., had three consecutive HAM-D scores ≤ 10, compared with anxiety-matched LZ– patients (32/35 vs. 25/35; $\chi^2 = 4.63$, $p = .03$). The proportion who achieved full remission, i.e., HAM-D score maintained at ≤ 10 until the end of continuation treatment, was not significantly different between groups (29/35 in LZ+ and 25/35 in LZ– groups; $\chi^2 = 1.30$, $p = .26$).

DISCUSSION

Elderly depressed patients who received adjunctive treatment with lorazepam in addition to combined nortriptyline/psychotherapy had more self-reported symptoms of anxiety than patients who received no lorazepam. When groups were matched for baseline anxiety level, a greater proportion of those receiving lorazepam had endogenous depression subtype. Those receiving lorazepam also had more abnormal EEG sleep, both before and during treatment. There was no differential treatment response with regard to the level of depressive or anxiety symptoms nor any difference in the time to remission of depressive symptoms between LZ+ and LZ– groups. However, the proportion of patients who responded to acute treatment was significantly greater in the LZ+ group than in the LZ– group matched for baseline anxiety. Lorazepam does not impair the antidepressant response to medication/psychotherapy treatment, and it improves the likelihood of initial treatment response among anxious elderly depressed patients who have greater neurobiological abnormality (indicated by polysomnography).

Although the current study did not include a random, placebo-controlled, double-blind design, the original LZ+ and LZ– groups had remarkably similar clinical characteristics. In fact, the only differences between groups was for the target symptoms of anxiety. Factors associated with slower or less robust treatment response in other studies, such as personality traits,[8] episode duration,[39] race,[40] and cognitive impairment,[40] do not explain treatment differences in the LZ+ and LZ– groups.

EEG sleep differences between groups included a higher REM sleep percentage, lower REM latency, and a lower delta ratio in the LZ+ group. All of these findings indicate more abnormal sleep in the LZ+ than the LZ– group. Sleep differences between groups were more evident during continuation treatment (in the presence of the REM-suppressing drugs nortriptyline and lorazepam) than at baseline. This observation further supports the notion of increased "REM pressure" in the LZ+ group. The constellation of abnormal sleep measures in the LZ+ group can be interpreted as indicators of more severe depressive illness. Although this dimension of severity is not reflected in total HAM-D score, it is consistent with the greater proportion of endogenous depression subtype among LZ+ patients. Because the LZ+ and LZ– groups had equivalent levels of baseline anxiety and insomnia, it is reasonable to speculate that the treating psychiatrists' decision to prescribe lorazepam was actually prompted by subtle clinical indicators of more severe depression in the LZ+ group. Stated differently, psychiatrists' treatment decisions may have been based on clinical correlates of increased REM "pressure," which are not reflected in most ratings of anxiety, insomnia, and depression symptoms.

Adjunctive lorazepam was not associated with a delay in the remission of depressive symptoms after controlling for baseline anxiety. Previous studies also support this conclusion. When benzodiazepines have been started concurrently with antidepressants in randomized, placebo-controlled studies, combined treatment results in no difference or a more rapid response compared with antidepressants alone.[17,19,23]

The overall rate of initial treatment response was significantly greater in the LZ+ group compared with the anxiety-matched subgroup of LZ– patients. Not only does lorazepam *not* reduce the likelihood of responding to nortriptyline/psychotherapy treatment, it may actually *improve* acute treatment adherence, which may in turn lead to improved response rates. Other studies have also reported equivalent response rates with fewer dropouts for combined benzodiazepine/antidepressant treatment compared with antidepressants or benzodiazepines alone.[17,20,21] We did not find that the LZ+ showed a greater reduction in anxiety, insomnia, or depressive symptoms between baseline and remission compared with the matched LZ– group. However, the open design of this study is likely to underestimate the positive effects of an antidepressant/benzodiazepine combination, since patients who received lorazepam were likely to have more severe illness in terms of endogenous features, anxiety, and insomnia symptoms relative to the total sample of depressed patients who were not treated with lorazepam (N = 84). Moreover, benzodiazepines were not started until 6 weeks into acute treatment, on average. Positive clinical effects may have been more substantial if the benzodiazepine had been started earlier in acute treatment. Nonetheless, the more conservative assessment of our findings would be that lorazepam did not impair the response to antidepressant treatment, although its positive effects were seen in treatment adherence rather than in greater symptom reductions.

Taken together, our results suggest a role for benzodiazepines as short-term adjuncts to antidepressant and psychotherapy for treatment of anxiety and insomnia symptoms in late-life depression. In their recent review of benzodiazepines in depression,[9] Birkenhager et al. reached a similar conclusion regarding combined pharmacotherapy. Issues that remain to be addressed include the optimal dose, timing, and duration of adjunctive benzodiazepines. Finally, concerns about benzodiazepine withdrawal symptoms after both short-term[41] and long-term use[42] mandate caution in prescribing practices.

Drug names: alprazolam (Xanax), chlordiazepoxide (Librium and others), diazepam (Valium and others), lorazepam (Ativan and others), nortriptyline (Pamelor and others).

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