# Coprescribed Benzodiazepines in Older Adults Receiving Antidepressants for Anxiety and Depressive Disorders:
## Association With Treatment Outcomes

Helene Altmann, BA[a,‡]; Sarah T. Stahl, PhD[a,‡,*]; Marie Anne Gebara, MD[a]; Eric J. Lenze, MD[b]; Benoit H. Mulsant, MD[c]; Daniel M. Blumberger, MD[c]; Charles F. Reynolds III, MD[a]; and Jordan F. Karp, MD[a]

**ABSTRACT**

***Objective:*** There is a paucity of data on the effects of coprescribed benzodiazepines on treatment response variability and adherence to antidepressant pharmacotherapy for depression and anxiety in late life. The objective of this transdiagnostic analysis was to examine the effect of benzodiazepines on treatment outcomes in older patients with generalized anxiety disorder (GAD) or major depressive disorder (MDD).

***Methods:*** Secondary analyses of data from 2 clinical trials of antidepressant pharmacotherapy for GAD (escitalopram vs placebo, 2006–2009) or MDD (open treatment with venlafaxine, 2009–2014) were conducted. Participants included 640 adults aged 60+ years with *DSM-IV*–defined GAD (n = 177) or MDD (n = 463). Benzodiazepine data were collected at baseline. Adherence and treatment response were assessed over 12 weeks. The analysis addressed whether coprescribed benzodiazepines are associated with treatment response, antidepressant medication adherence, dropout, final dose of antidepressant medication, and report of antidepressant-related adverse effects.

***Results:*** Participants with GAD and coprescribed benzodiazepines were treated with a lower mean dosage of escitalopram and were less likely to complete the trial; there was no difference in adherence or treatment response. Participants with MDD and coprescribed benzodiazepines were less likely to tolerate a therapeutic dose of venlafaxine and reported more medication-related adverse effects; there was no difference in adherence, dropout, or treatment response.

***Conclusions:*** Coprescription of benzodiazepines was associated with increased dropout in older patients with GAD and more medication-related adverse effects in older patients with MDD. However, with the systematic clinical attention offered in a clinical trial, they do not impede treatment response. Clinicians should be aware that a coprescribed benzodiazepine may be a marker of a more challenging treatment course.

***Trial Registration:*** Data analyzed were from studies with ClinicalTrials.gov identifiers NCT00892047 and NCT00105586.

*J Clin Psychiatry 2020;81(6):20m13283*

***To cite:*** Altmann H, Stahl ST, Gebara MA, et al. Coprescribed benzodiazepines in older adults receiving antidepressants for anxiety and depressive disorders: association with treatment outcomes. *J Clin Psychiatry*. 2020;81(6):20m13283.

***To share:*** https://doi.org/10.4088/JCP.20m13283



[a]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[b]Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri

[c]Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

‡Co-first authorship.

**Corresponding author:* Sarah T. Stahl, PhD, Department of Psychiatry, University of Pittsburgh, 3811 O'Hara St, Pittsburgh, PA 15213 (sarah.stahl@pitt.edu).

Late-life depression has a point prevalence of 1%–3% in the community and 6%–9% in primary care settings,[1,2] with lifetime prevalence estimates of 21% in women and 10% in men.[3] The lifetime and point prevalences of generalized anxiety disorder (GAD) in late life have similar estimates.[4,5] The high occurrence of both of these psychiatric conditions impacts many aspects of general medical care in older adults, including treatment adherence,[6] increased number of medical appointments or length of hospital admissions,[7] and increased all-cause mortality.[8] The negative clinical effects of major depressive disorder (MDD) and GAD make identifying factors that interfere with antidepressant pharmacotherapy important, since a quarter to a third of older adults receiving treatment for depression do not remit[9,10] and older patients with GAD often have a more brittle response to treatment.[11]

Prescription of benzodiazepines increases with age, and adults 60 years and older are the age group most likely to be prescribed benzodiazepines. Benzodiazepines are often prescribed to older adults for anxiety,[12,13] and older adults visiting an ambulatory clinic for anxiety are 5 times more likely to receive a benzodiazepine.[14] In 2008, it was estimated that 9% of American adults aged 65–80 used benzodiazepines; almost a third used benzodiazepines for more than 4 months (ie, they were considered "long-term users"), and a quarter were prescribed benzodiazepines with long half-lives.[2] Benzodiazepine use in older adults has been increasing over time, as has the combination of benzodiazepines with other central nervous system active drugs.[15,16] While benzodiazepines can be useful in carefully selected older adults, their potential benefits must be balanced with their well-established risks including falls,[17] fractures, cognitive impairment,[18] and delirium.[19,20]

In late life, antidepressant pharmacotherapy (eg, serotonin specific reuptake inhibitors) is a recommended first-line treatment for anxiety and depressive disorders.[21] Approximately 12.5% of adult American patients are coprescribed benzodiazepines prior to or while receiving antidepressant pharmacotherapy.[22] The coprescription of a benzodiazepine and an antidepressant may occur for several reasons: (1) a more severe condition that requires a rapid reduction

**Clinical Points**

- Benzodiazepine use in adults aged 60 years or older is common; however, there are few data on how benzodiazepine coprescription impacts antidepressant outcomes in depressed and anxious older adults.
- A coprescribed benzodiazepine may be a marker of a more challenging treatment course for older adults with generalized anxiety disorder and major depressive disorder.

in emotional distress or insomnia that can be relieved with a benzodiazepine[2]; (2) somatic preoccupation, fearfulness of, or sensitivity to antidepressant side effects[23,24]; or (3) a poor response to antidepressant pharmacotherapy because of pharmacokinetic and pharmacodynamic interactions.[25] In midlife adults, several trials have shown that benzodiazepine use does not worsen antidepressant treatment outcomes and may actually improve antidepressant treatment outcomes.[2,26,27] Similar results have been reported in 1 trial in older adults coprescribed lorazepam with nortriptyline pharmacotherapy.[28] However, there is a paucity of data on how benzodiazepine coprescription impacts antidepressant outcomes in depressed and anxious older adults.

We used data from 2 clinical trials of antidepressant pharmacotherapy for GAD or MDD in older adults to address the following questions: (1) Are coprescribed benzodiazepines associated with treatment response, antidepressant medication adherence, and dropout? (2) Is benzodiazepine use predictive of receiving a lower dose of antidepressant medications? and (3) Do patients coprescribed benzodiazepines report more antidepressant-related adverse effects?

## METHODS

### Overview

This secondary analysis uses data collected in 2 clinical trials of antidepressant pharmacotherapy funded by the National Institute of Mental Health: Escitalopram for Older Adults with Generalized Anxiety Disorder (RELIEF, 2006–2009; NCT00105586) and Incomplete Response in Late-Life Depression: Getting to Remission (IRL-GRey, 2009–2014; NCT00892047). The methods of these 2 trials have already been published.[29,30] In both trials, procedures were approved by the institutional review board at each study site. All participants provided signed informed consent.

In brief, RELIEF was a single-site randomized controlled trial testing the efficacy, safety, and tolerability of escitalopram in older adults with GAD. Participants were randomized to escitalopram 10 mg/d or matching placebo pill using a permuted-block, 1:1 randomization list. Participants took 1 pill daily for 4 weeks; for those who did not achieve response (defined below), dosage was increased to 2 pills daily (ie, 20 mg/d). Participants took study medication for 12 weeks, or until they dropped out. They were assessed weekly for the first 4 weeks and then every other week.

IRL-GRey was a multisite clinical trial for adults 60 and older with MDD. For this analysis, we used data from the open-label first phase of the trial, during which participants received open-label venlafaxine extended-release (XR) for 12–24 weeks. Venlafaxine XR was initiated at a dosage of 37.5 mg/d, which was increased by 37.5 mg/d (with a minimum interval of 3 days between increases, depending on side effects) up to 150 mg/d. After 6 weeks, venlafaxine XR dose was increased further up to 300 mg/d in participants who did not achieve remission (defined in the Measures section). The titration could be slowed or stopped based on lack of tolerability. Most participants were treated for 12 weeks, but a few were treated for up to 24 weeks if needed to clarify remission status.

In both trials, participants who were coprescribed a benzodiazepine were typically long-term users (eg, mean [SD] = 3.7 years [6.1] in RELIEF and 5.0 years [7.9] in IRL-GRey). Discontinuing benzodiazepines was carefully considered by study investigators, including factors such as risks of falls, exacerbation of sleep apnea, and/or increased confusion versus the temporary relief of suffering related to anxiety or insomnia. To retain participants in the studies and minimize risks to external validity, each trial minimized and standardized the dose of benzodiazepines to 2 mg or equivalence of lorazepam.

### Participants

Participants in RELIEF were 60 years and older; they met *DSM-IV* criteria for GAD and reported clinically significant anxiety symptoms, defined as a score of ≥ 17 on the Hamilton Anxiety Rating Scale.[31] Participants with comorbid non-bipolar depression or other anxiety disorders were included if GAD was the primary diagnosis: 24.9% met diagnostic criteria for comorbid MDD or another depressive syndrome. Participants with a history of alcohol or other substance abuse were included if their substance abuse was in full remission for at least 3 months. Exclusion criteria included lifetime psychosis or bipolar disorder, dementia, imminent suicide risk, medical instability, ongoing psychotherapy, and current antidepressant or anxiolytic use, except for benzodiazepines up to 2 mg/d equivalent of lorazepam. Of the 257 participants who provided signed consent, 35 were ineligible, 43 refused randomization, and 2 did not receive medication after randomization, leaving 177 who were randomized and received study medication: 85 to escitalopram and 92 to placebo.

Participants in IRL-GRey were 60 years and older; they met *DSM-IV* criteria for MDD and reported at least moderate symptoms of depression, defined as a score ≥ 15 on the Montgomery-Asberg Depression Rating Scale (MADRS).[32] Forty-two percent met diagnostic criteria for comorbid GAD or another anxiety disorder. Exclusion criteria included dementia (based on medical records and cognitive screening), bipolar disorder, schizophrenia, current psychotic symptoms, and alcohol or substance abuse or dependence within the past 6 months. A comorbid

anxiety disorder was not a reason for exclusion. Similar to RELIEF, in IRL-GRey, benzodiazepines could be continued or started for insomnia or anxiety up to 2 mg/d equivalent of lorazepam. Of the 608 adults who provided signed consent, 93 did not meet inclusion criteria, 45 withdrew consent, 1 experienced significant worsening of MDD, and 1 took contraindicated medication, leaving 468 older adults who started open-label treatment with venlafaxine.

### Measures

***Benzodiazepine use.*** Benzodiazepine use was analyzed as a dichotomous variable (yes or no) and was based on coprescription at the time of randomization in RELIEF and at baseline of the open-label phase in IRL-GRey. We included participants who were taking benzodiazepines on either a regular or "as needed" basis. In RELIEF, 13 different benzodiazepines were prescribed; the most frequently prescribed drugs were lorazepam (43% of prescriptions) and alprazolam (21%). In IRL-GRey, 15 different benzodiazepines were prescribed; the most frequently prescribed drugs were lorazepam (53% of prescriptions), clonazepam (18%), and alprazolam (9%).

***Response, adherence, and dropout.*** Treatment response in RELIEF was defined as a Clinical Global Impressions-Improvement scale score of 1 (very much improved) or 2 (much improved). In this analysis, we use the IRL-GRey definition of remission to define treatment response: a MADRS score ≤ 10 at the 2 final consecutive visits of the open-label venlafaxine-XR treatment phase. In both trials, medication adherence was defined as taking ≥ 80% of study pills per week. We selected 80% because this is the published and commonly accepted lower level of adherence considered to be necessary to achieve clinical benefit (ie, < than 80% is correlated with unstable treatment response).[33–36] Dropout from the study in both trials was defined as failing to complete 12 weeks of treatment.

***Antidepressant dosage.*** In RELIEF, 10 mg/d of escitalopram was considered the minimal therapeutic dosage, and dosages were categorized as follows: stayed at 10 mg/d (achieved therapeutic dosage); 11–20 mg/d (needed greater than the minimal therapeutic dosage); and reduced from 20 to 10 or mg/d (had needed a higher dosage but could not tolerate it). In IRL-GRey, 150 mg/d of venlafaxine was considered the minimal therapeutic dosage, and dosages were categorized as follows: 0–149 mg/d (did not tolerate the minimal therapeutic dosage), stayed at 150 mg/d (achieved and remained on the minimal therapeutic dosage), 151–299 mg/d (needed and tolerated higher than the minimal therapeutic dosage), and 300 mg/d (reached and remained on the maximum dosage). We also examined the highest mean dosage of escitalopram and venlafaxine achieved at any time in each trial.

***Medication-related adverse effects.*** We used the UKU scale to examine reported medication-related adverse effects. The UKU scale characterizes 46 physical and somatic symptoms associated with the use of psychotropic medications, including psychic, neurologic, and autonomic adverse effects.[37] In both trials, an adverse effect was considered present if there was a 2-point increase on the corresponding UKU item between the initiation and the completion of the trial.

### Statistical Analysis

After using descriptive statistics to characterize each sample, we compared intervention outcomes (treatment response, medication adherence, and dropout) and reports of adverse effects between participants who were or were not coprescribed benzodiazepine using the *F* test for continuous outcomes and the $\chi^2$ statistic for dichotomous outcomes. Ordinal regression was performed using a general linear model to examine the effect of coprescribed benzodiazepine (yes or no) on dosages (ie, 3 ordered categories in the RELIEF trial and 4 ordered categories in the IRL-GRey trial). All analyses were conducted using IBM SPSS statistical software (version 25.0).

## RESULTS

### Demographic Characteristics of the 2 Samples

Descriptive statistics for each sample are presented in Table 1. In both trials, participants were typically white women with a mean (SD) age of 70.0 years (7.5). Both samples were comparable in terms of education (mean of about 14 years, SD = 3.0), moderate burden of physical illness (Cumulative Illness Rating Scale—Geriatrics[38] mean [SD] score: 9.0 [4.1] and 9.9 [4.5] in participants with GAD and MDD, respectively), and moderate anxiety symptom burden (Penn State Worry Questionnaire [PSWQ][39] mean [SD] score: 56.7 [12.5] and 59.4 [13.1] in participants with GAD and MDD, respectively). Depression symptom burden was higher in participants with MDD than in those with GAD (Hamilton Depression Rating Scale [HDRS][40] mean [SD] score: 20.0 [5.0] vs 12.1 [3.9]).

Twenty percent (n = 36 of 177) of participants with GAD and 35% (n = 164 of 468) of participants with MDD were coprescribed a benzodiazepine. In RELIEF, there were no significant differences between those who were or were not coprescribed a benzodiazepine.

In IRL-GRey, there were several differences: participants coprescribed a benzodiazepine were more likely to be white (93% [n = 152] vs 85% [n = 258] of those who were not prescribed a benzodiazepine; $\chi^2_1 = 6.63$ [N = 468], $P = .006$) and had significantly more severe depression (mean [SD] HDRS scores: 21.1 [5.5] vs 19.30 [4.6]; $F_{1,466} = 13.82$, $P < .001$) and anxiety (mean [SD] PSWQ scores: 61.7 [12.5] vs 59.4 [13.1]; $F_{1,460} = 7.44$, $P = .007$) than participants not prescribed a benzodiazepine.

### Are Coprescribed Benzodiazepines Associated With Response, Adherence, and Dropout?

Fifty-one percent of participants (n=91 with GAD) and 41% of participants (n=191 with MDD) responded to escitalopram and venlafaxine, respectively, and over 80% were adherent to study medication (n = 147 with GAD and

**Table 1. Baseline Characteristics of Participants Receiving or Not Receiving a Coprescribed Benzodiazepine[a]**

| | Participants With GAD | | | | Participants With MDD | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (N = 177) | Benzodiazepine (n = 36) | No Benzodiazepine (n = 141) | *P* Value[b] | Total (N = 468) | Benzodiazepine (n = 164) | No Benzodiazepine (n = 304) | *P* Value[b] |
| Demographics | | | | | | | | |
| Age, mean (SD), y | 71.68 (7.82) | 72.25 (7.71) | 71.53 (7.87) | .624 | 69.03 (7.20) | 69.50 (6.92) | 68.78 (7.35) | .299 |
| Black/minority status, % (n) | 18.08 (32) | 11.11 (4) | 19.86 (28) | .454 | 11.97 (56) | 6.71 (11) | 14.80 (45) | .006 |
| Men, % (n) | 32.77 (58) | 30.56 (11) | 33.33 (47) | .751 | 35.04 (164) | 32.9 (54) | 36.2 (110) | .274 |
| Education, y | 13.86 (2.90) | 13.72 (2.67) | 13.90 (2.97) | .743 | 14.39 (2.84) | 14.3 (3.09) | 14.5 (2.69) | .373 |
| Clinical characteristics | | | | | | | | |
| Physical illness burden, CIRS-G | 8.97 (4.07) | 8.81 (3.48) | 9.01 (4.22) | .785 | 9.85 (4.47) | 9.83 (4.13) | 9.87 (4.65) | .926 |
| Depression symptoms, HDRS | 12.06 (3.88) | 12.53 (4.77) | 11.94 (3.64) | .417 | 19.97 (5.00) | 21.12 (5.46) | 19.35 (4.63) | .000 |
| Anxiety symptoms, PSWQ | 56.75 (12.50) | 58.91 (10.11) | 56.21 (13.01) | .254 | 59.42 (13.11) | 61.67 (12.50) | 58.21 (13.30) | .007 |

[a]When we combine the 2 samples, benzodiazepine use was associated with greater anxiety and depression symptom burden. Given that patients with MDD are driving this effect, we report the clinical correlates of benzodiazepine use in each trial separately.
[b]*P* values are based on 2 group comparisons: Pearson $\chi^2$ test for categorical outcomes (presented as % [n]) and 1-way analysis of variance tests for continuous outcomes (presented as mean [SD]).
Abbreviations: CIRS-G = Cumulative Illness Rating Scale for Geriatrics, GAD = generalized anxiety disorder, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, PSWQ = Penn State Worry Questionnaire.

**Table 2. Rates of Response, Adherence, and Medication-Related Reported Adverse Effects in Participants Receiving or Not Receiving a Coprescribed Benzodiazepine[a,b]**

| | Participants With GAD | | | | Participants With MDD | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (N = 177) | Benzodiazepine (n = 36) | No Benzodiazepine (n = 141) | *P* Value | Total (N = 468) | Benzodiazepine (n = 164) | No Benzodiazepine (n = 304) | *P* Value |
| Response and adherence | | | | | | | | |
| Response to treatment, % (n) | 51.4 (91) | 52.8 (19) | 51.1 (72) | .50 | 40.8 (191) | 37.8 (62) | 42.4 (129) | .40 |
| Medication adherence, % (n) | 83.1 (147) | 80.6 (29) | 83.7 (118) | .54 | 85.9 (402) | 84.8 (139) | 86.5 (263) | .56 |
| Dropout from the study, % (n) | 18.6 (33) | 30.6 (11) | 15.6 (22) | .04 | 20.5 (96) | 24.4 (40) | 18.2 (56) | .08 |
| Medication-related adverse effects | | | | | | | | |
| UKU scale, mean (SD) | 9.6 (4.84) | 9.8 (4.77) | 9.54 (4.87) | .79 | 17.5 (6.88) | 18.5 (6.78) | 17.0 (6.89) | .02 |
| Medication dosage, mg/d, mean (SD) | | | | | | | | |
| Escitalopram | 14.7 (5.9) | 12.5 (5.1) | 15.2 (5.5) | .03 | … | … | … | … |
| Venlafaxine XR | … | … | … | … | 224.4 (81.1) | 228.7 (83.7) | 222.2 (79.7) | .41 |

[a]Benzodiazepine use was not significantly associated with the failing memory item of the UKU in either trial (MDD trial: $F_{1,387} = 0.002$, $P = .96$; GAD trial: $F_{1,142} = 1.680$, $P = .21$).
[b]Treatment response, adherence, and adverse effects were assessed after 12 weeks of treatment. Study medication dosage was the highest average dose achieved at any time during 12 weeks of treatment.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

**Table 3. Participants With GAD (RELIEF Trial) or MDD (IRL-GRey Trial) Who Reached the Target Dosage of Study Medication, % (n)**

| | Participants With GAD | | |
|---|---|---|---|
| Escitalopram | Total (N = 143) | Benzodiazepine (n = 24) | No Benzodiazepine (n = 119) |
| Stayed at 10 mg/d | 11.9 (17) | 4.2 (2) | 12.6 (15) |
| 11–20 mg/d | 79.7 (114) | 83.3 (20) | 79.0 (94) |
| Reduced from 20 mg/d to 10 mg/d | 8.4 (12) | 4.2 (2) | 8.4 (10) |
| | Participants With MDD | | |
| Venlafaxine XR | Total (N = 486) | Benzodiazepine (n = 164) | No Benzodiazepine (n = 304) |
| 0–149 mg/d | 10.5 (51) | 14.0 (23) | 9.2 (28) |
| Stayed at 150 mg/d | 23.5 (114) | 16.5 (27) | 28.6 (87) |
| 151–299 mg/d | 18.2 (85) | 20.1 (33) | 17.1 (52) |
| 300 mg/d | 44.9 (218) | 49.4 (81) | 45.1 (137) |

Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

402 with MDD). In both trials, there were no significant differences for either treatment response or medication adherence between those who were or were not coprescribed a benzodiazepine (Table 2). In the RELIEF trial, participants taking benzodiazepines were significantly less likely to complete the trial than those who were not prescribed a benzodiazepine (31% [n = 11] vs 16% [n = 22] dropped out, $\chi^2_1 = 4.20$ [N = 177], $P = .04$). In both trials, the causes for dropout did not differ significantly between those who were or were not coprescribed a benzodiazepine. Of the 33 participants who dropped out of RELIEF, 18 (55%) were noncompliant, 7 (21%) experienced intolerable side effects, 6 (18%) preferred other treatment, 1 (3%) experienced an increase in depression symptoms, and 1 (3%) reported medical burden. Of the 96 participants who dropped out of IRL-GRey, 32 (33%) experienced intolerable side effects, 25 (26%) were noncompliant, 18 (19%) preferred other treatment, 15 (16%) reported medical burden, 5 (5%) experienced an increase in depression symptoms, and 1 (1%) died by suicide.

### Is Benzodiazepine Use Predictive of Final Dose of Antidepressant Medications?

Table 3 shows the dosage distribution for escitalopram (RELIEF trial) or venlafaxine (IRL-GRey trial). In the RELIEF trial, most participants with GAD (80%; n = 114) received 20 mg/d (ie, more than the minimal therapeutic dosage); 12% (n = 17) remained on 10 mg/d; and 8% (n = 12) required

**Table 4. Multinomial Logistic Regression Examining the Association Between a Coprescribed Benzodiazepine and Antidepressant Dosage in Participants With GAD (RELIEF Trial) and MDD (IRL-GRey Trial)[a]**

| | Coefficient | SE (*B*) | Wald | *df* | *P* Value[b] | Exp (*B*) | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower Bound | Upper Bound |
| Escitalopram[c] | | | | | | | | |
| Stayed at 10 mg/d | 0.467 | 0.792 | 0.348 | 1 | .56 | 1.596 | 0.338 | 7.536 |
| Reduced from 20 mg/d to 10 mg/d | 0.062 | 0.813 | 0.006 | 1 | .94 | 1.064 | 0.216 | 5.233 |
| Venlafaxine[d] | | | | | | | | |
| 0–149 mg/d | −0.329 | 0.314 | 1.094 | 1 | .30 | 0.720 | 0.389 | 1.333 |
| Stayed at 150 mg/d | 0.645 | 0.261 | 6.093 | 1 | **.014** | 1.905 | 1.142 | 3.178 |
| 151–299 mg/d | −0.071 | 0.263 | 0.072 | 1 | .79 | 0.932 | 0.556 | 1.560 |

[a]10 mg/d was the minimal target dosage in RELIEF; 150 mg/d was the minimal target dosage in IRL-GRey.
[b]Boldface indicates statistical significance.
[c]Reference category = 11–20 mg/d (needed greater than the minimal therapeutic dosage).
[d]Reference category = 300 mg/d (reached maximum dosage).
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

but could not tolerate 20 mg/d. Table 4 shows the ordinal regression analysis that examined differences in dosage categories based on coprescription of a benzodiazepine: there were no significant group differences. However, the mean highest dose of escitalopram was lower in those who were coprescribed a benzodiazepine than in those who were not (mean [SD]: 12.5 mg/d [5.1] vs 15.2 mg/d [5.5]; $F_{1,139} = 4.84$, $P = .03$) (see Table 2).

In IRL-GRey, 45% (n = 218) of participants received the venlafaxine maximum dosage of 300 mg/d; 24% (n = 114) remained on 150 mg/d; 18% (n = 85) received 151–299 mg/d; and 10% (n = 51) did not tolerate the minimal therapeutic dosage. Table 4 shows that participants coprescribed a benzodiazepine were less likely to tolerate the minimal therapeutic dosage of 150 mg/d of venlafaxine than those who were not prescribed a benzodiazepine (27 of 164 [17%] vs 87 of 304 [29%]). There were no significant differences between the mean highest average dosage in the 2 groups.

### Do Patients Coprescribed Benzodiazepines Report More Antidepressant-Related Adverse Effects?

Reports of adverse effects were associated with benzodiazepine use in the IRL-GRey trial but not in the RELIEF trial (Table 2): in IRL-GRey, participants who were coprescribed a benzodiazepine reported more antidepressant medication–related adverse effects than those who were not prescribed a benzodiazepine (UKU mean [SD] score: 18.5 [6.8] vs 17.0 [6.9], $F_{1,464} = 5.40$, $P = .02$).

## DISCUSSION

The goal of this analysis was to identify whether coprescription of benzodiazepines impacted treatment outcomes in older patients with GAD or MDD treated with an antidepressant. In RELIEF, a randomized trial of escitalopram vs placebo for GAD, participants coprescribed a benzodiazepine received a lower mean dose of escitalopram and had an increased likelihood of dropping out. In IRL-GRey, participants with MDD treated with open-label venlafaxine who were coprescribed benzodiazepines reported significantly more depressive and anxiety symptoms at baseline, were less likely to tolerate the minimally therapeutic target dosage of venlafaxine (150 mg/d), and reported more antidepressant medication–related adverse effects. There was no relationship between benzodiazepine use and treatment response or antidepressant adherence in either of the 2 trials.

In RELIEF, participants with GAD who were coprescribed benzodiazepines were almost half as likely to complete this antidepressant trial. However, there was no difference in adherence to escitalopram in participants with GAD who were or were not coprescribed a benzodiazepine. This is in contrast to findings by Wu et al,[41] who reported that in younger adults (aged 18–64) with an anxiety disorder, those who were coprescribed a benzodiazepine were less likely to be adherent than those who were not.[41] Also, in our analysis, treatment response was the same in participants with GAD who were or were not coprescribed a benzodiazepine. Overall, our results suggest that our older participants with GAD who required a combination of an antidepressant and a benzodiazepine may differ from midlife adults with an anxiety disorder treated with such combination. Unlike what has been reported in younger patients, in our older participants with GAD, the coprescription of a benzodiazepine was associated with early attrition but not poorer adherence or treatment response.

A recent meta-analysis of 10 randomized controlled trials has shown that in midlife adults with MDD, the combination of an antidepressant plus a benzodiazepine was more efficacious than an antidepressant alone during the first 4 weeks initial phase of treatment, but this initial advantage was not maintained subsequently.[2,26,27] Combined treatment was also associated with both a lower proportion of participants dropping out and a higher proportion reporting at least 1 adverse effect.[27] In our analysis, we similarly observed that older participants with MDD receiving a coprescribed benzodiazepine were more likely to report antidepressant-related adverse effects. However, their dropout rate or response to treatment was the same as in those without a coprescribed benzodiazepine. This observation replicates a similar finding from an observational study in older depressed veterans, for whom a coprescribed benzodiazepine

was not associated with either antidepressant adherence or improvement in depressive symptoms.[42] However, in this study, as in our analysis, coprescription of a benzodiazepine identified a group of more complex patients.

In our analysis, participants with MDD who were coprescribed a benzodiazepine presented with a higher level of both depression and anxiety symptoms, were less likely to tolerate the minimal target dosage of venlafaxine (150 mg/d), and were more likely to report medication-related adverse effects. Thus, as in the veterans study,[42] in a group of patients who may be predisposed to worse outcomes and may be harder to treat, the absence of difference in treatment outcomes should be interpreted as a positive finding.

The coprescription of an antidepressant and a benzodiazepine for older participants with MDD may be an indicator of both disease severity and potential treatment challenges. For more than 2 decades, it has been recognized that older patients with comorbid depression and anxiety are harder to treat and have poorer treatment outcomes.[23,43–48] In these patients, high levels of anxiety or depressive symptoms and a higher likelihood of reporting medication-related adverse effects may reflect somatic preoccupation. In our analysis, while the dropout rates in participants with MDD were not different between the benzodiazepine users and nonusers, almost 25% of those with a coprescribed benzodiazepine dropped out of the study. Providing more intensive clinical support to these at-risk patients—eg, more frequent clinic or telephone visits, provision of information about self-care, and active management of benign but irritating early adverse effects—may decrease nonadherence with, and premature discontinuation of, antidepressants and result in superior outcomes.

In the absence of randomization to a benzodiazepine or a placebo, we cannot conclude whether our data showing the association between coprescribed benzodiazepines and some negative outcomes (eg, inability to tolerate minimal target dosages, higher reporting of medication-related adverse effects, and higher dropout rates) reflect a causal relationship (ie, benzodiazepines cause adverse effects) or confounding by indication (ie, benzodiazepines are prescribed to those who are more likely to somatize and/or have more complex and severe illness). However, as discussed above, if benzodiazepine use is indeed a marker for more complex and therapeutically challenging patients, similar response rates in these harder-to-treat patients may reflect a positive effect of benzodiazepines. Other limitations must be considered when interpreting these results. First, the high number of statistical tests increases the risk for a type 1 error. Second, we assessed medication adherence solely based on self-report. Third, we are unable to account for the specific reasons benzodiazepines were coprescribed (eg, anxiety or insomnia), and we were not able to examine change in benzodiazepine use as it relates to treatment outcomes. Finally, it is unlikely that groups differ by benzodiazepine status alone; those who were coprescribed a benzodiazepine likely have other unmeasured characteristics that may make them more or less amenable to antidepressant treatment.

## CONCLUSIONS

Our secondary analysis of data from 2 clinical trials of antidepressant pharmacotherapy in older patients with GAD or MDD shows that participants who received a coprescribed benzodiazepine had a more challenging treatment course than those who did not receive one. However, they experienced a similar treatment response. This analysis could not clarify the direction of the causal relationships underlying these findings. In light of the risks of benzodiazepines in older adults, their potential benefits (eg, acute relief of anxiety or insomnia and prevention of early dropouts) continue to require a judicious individual assessment and decision in each older patient.[49,50]

***Submitted:*** February 6, 2020; accepted May 14, 2020.

***Published online:*** September 29, 2020.

***Potential conflicts of interest:*** **Dr Lenze** reports research funding (current/past) from Janssen, Alkermes, Takeda, Lundbeck, Barnes Jewish Foundation, Patient-Centered Outcomes Research Institute, and Taylor Family Institute for Innovative Psychiatric Research and has been a consultant for Janssen and Jazz Pharmaceuticals. **Dr Mulsant** currently receives research funding from Brain Canada, Centre for Addiction and Mental Health (CAMH) Foundation, Canadian Institutes of Health Research, Patient-Centered Outcomes Research Institute, and US National Institutes of Health (NIH). During the last 5 years, he also received research support from Bristol-Myers Squibb (medications for a NIH-funded clinical trial), Eli Lilly (medications for a NIH-funded clinical trial), and Pfizer (medications for a NIH-funded clinical trial), and he directly owns stocks of General Electric (less than $5,000). **Dr Blumberger** has received research support from the Canadian Institutes of Health Research, NIH, Brain Canada, and the Temerty Family through the CAMH Foundation and the Campbell Research Institute; received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd and is the site principal investigator for a sponsor-initiated study for Brainsway Ltd; receives in-kind equipment support from Magventure for investigator-initiated studies; and received medication supplies for an investigator-initiated trial from Indivior. **Dr Reynolds** has received research support from the NIH, Patient Centered Outcomes Research Institute, Center for Medicare and Medicaid Services, American Foundation for Suicide Prevention, Brain and Behavior Research Foundation, and the Commonwealth of Pennsylvania; Bristol-Myers Squibb and Pfizer have provided pharmaceutical supplies for his NIH-sponsored research; and he is a paid consultant for Merck. **Dr Karp** has received medication supplies for investigator-initiated trials from Pfizer and Indivior and receives honoraria from *American Journal of Geriatric Psychiatry* and *Journal of Clinical Psychiatry*. The other authors have nothing to disclose.

***Funding/support:*** Supported in part by grants P30 MH068579, P30 MH71944, P30 MH90333, R01 MH070547, R01 MH083660, R01 MH083648, R01 MH083643, and R01 MH118270 from the National Institutes of Health.

***Role of the sponsor:*** The sponsor had no role in the design, analysis, interpretation, or publication of this study.

***Disclaimer:*** Dr Karp, JCP Focus on Geriatric Psychiatry Section Editor, was not involved in the editorial review or decision to publish this article.

## REFERENCES

1. Unützer J, Katon W, Sullivan M, et al. Treating depressed older adults in primary care: narrowing the gap between efficacy and effectiveness. *Milbank Q*. 1999;77(2):225–256, 174.
2. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136–142.
3. Steffens DC, Skoog I, Norton MC, et al. Prevalence of depression and its treatment in an elderly population: the Cache County study. *Arch Gen Psychiatry*. 2000;57(6):601–607.
4. Kirmizioglu Y, Doğan O, Kuğu N, et al. Prevalence of anxiety disorders among elderly people. *Int J Geriatr Psychiatry*. 2009;24(9):1026–1033.
5. Balsamo M, Cataldi F, Carlucci L, et al.

Assessment of anxiety in older adults: a review of self-report measures. *Clin Interv Aging*. 2018;13:573–593.
6. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med*. 2000;160(21):3278–3285.
7. Luber MP, Hollenberg JP, Williams-Russo P, et al. Diagnosis, treatment, comorbidity, and resource utilization of depressed patients in a general medical practice. *Int J Psychiatry Med*. 2000;30(1):1–13.
8. Schulz R, Drayer RA, Rollman BL. Depression as a risk factor for non-suicide mortality in the elderly. *Biol Psychiatry*. 2002;52(3):205–225.
9. Beekman AT, Geerlings SW, Deeg DJ, et al. The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychiatry*. 2002;59(7):605–611.
10. Beekman AT, de Beurs E, van Balkom AJ, et al. Anxiety and depression in later life: co-occurrence and communality of risk factors. *Am J Psychiatry*. 2000;157(1):89–95.
11. Flint AJ, Rifat SL. Anxious depression in elderly patients: response to antidepressant treatment. *Am J Geriatr Psychiatry*. 1997;5(2):107–115.
12. Llorente MD, David D, Golden AG, et al. Defining patterns of benzodiazepine use in older adults. *J Geriatr Psychiatry Neurol*. 2000;13(3):150–160.
13. Kim AP. Continued use of benzodiazepines in older adults. *Hosp Pharm*. 2015;50(7):557–558.
14. Marra EM, Mazer-Amirshahi M, Brooks G, et al. Benzodiazepine prescribing in older adults in US ambulatory clinics and emergency departments (2001–10). *J Am Geriatr Soc*. 2015;63(10):2074–2081.
15. Day C. *Benzodiazepines in Combination With Opioid Pain Relievers or Alcohol: Greater Risk of More Serious ED Visit Outcomes. The CBHSQ Report*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013:1–9.
16. Agarwal SD, Landon BE. Patterns in outpatient benzodiazepine prescribing in the United States. *JAMA Netw Open*. 2019;2(1):e187399.
17. Machado-Duque ME, Castaño-Montoya JP, Medina-Morales DA, et al. Association between the use of benzodiazepines and opioids with the risk of falls and hip fractures in older adults. *Int Psychogeriatr*. 2018;30(7):941–946.
18. Crowe SF, Stranks EK. The residual medium and long-term cognitive effects of benzodiazepine use: an updated meta-analysis. *Arch Clin Neuropsychol*. 2018;33(7):901–911.
19. Airagnes G, Pelissolo A, Lavallée M, et al. Benzodiazepine misuse in the elderly: risk factors, consequences, and management. *Curr Psychiatry Rep*. 2016;18(10):89.
20. Bohlken J, Kostev K. Prevalence and risk factors for delirium diagnosis in patients followed in general practices in Germany. *Int Psychogeriatr*. 2018;30(4):511–518.
21. Kok RM, Reynolds CF 3rd. Management of depression in older adults: a review. *JAMA*. 2017;317(20):2114–2122.
22. Bushnell GA, Stürmer T, Gaynes BN, et al. Simultaneous antidepressant and benzodiazepine new use and subsequent long-term benzodiazepine use in adults with depression, United States, 2001–2014. *JAMA Psychiatry*. 2017;74(7):747–755.
23. Lenze EJ, Mulsant BH, Shear MK, et al. Comorbid anxiety disorders in depressed elderly patients. *Am J Psychiatry*. 2000;157(5):722–728.
24. Lenze EJ. Comorbidity of depression and anxiety in the elderly. *Curr Psychiatry Rep*. 2003;5(1):62–67.
25. Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. *Lancet*. 2007;370(9582):185–191.
26. Ogawa Y, Takeshima N, Hayasaka Y, et al. Antidepressants plus benzodiazepines for adults with major depression. *Cochrane Database Syst Rev*. 2019;6:CD001026.
27. Pfeiffer PN, Ganoczy D, Zivin K, et al. Benzodiazepines and adequacy of initial antidepressant treatment for depression. *J Clin Psychopharmacol*. 2011;31(3):360–364.
28. Buysse DJ, Reynolds CF 3rd, Houck PR, et al. Does lorazepam impair the antidepressant response to nortriptyline and psychotherapy? *J Clin Psychiatry*. 1997;58(10):426–432.
29. Lenze EJ, Rollman BL, Shear MK, et al. Escitalopram for older adults with generalized anxiety disorder: a randomized controlled trial. *JAMA*. 2009;301(3):295–303.
30. Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;386(10011):2404–2412.
31. Matza LS, Morlock R, Sexton C, et al. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res*. 2010;19(4):223–232.
32. Fantino B, Moore N. The self-reported Montgomery-Asberg Depression Rating Scale is a useful evaluative tool in major depressive disorder. *BMC Psychiatry*. 2009;9(1):26.
33. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc*. 2011;86(4):304–314.
34. Brook OH, van Hout HP, Stalman WA, et al. Nontricyclic antidepressants: predictors of nonadherence. *J Clin Psychopharmacol*. 2006;26(6):643–647.
35. Krivoy A, Balicer RD, Feldman B, et al. Adherence to antidepressant therapy and mortality rates in ischaemic heart disease: cohort study. *Br J Psychiatry*. 2015;206(4):297–301.
36. Sirey JA, Bruce ML, Kales HC. Improving antidepressant adherence and depression outcomes in primary care: the Treatment Initiation and Participation (TIP) program. *Am J Geriatr Psychiatry*. 2010;18(6):554–562.
37. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand suppl*. 1987;334:1–100.
38. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992;41(3):237–248.
39. Meyer TJ, Miller ML, Metzger RL, et al. Development and validation of the Penn State Worry Questionnaire. *Behav Res Ther*. 1990;28(6):487–495.
40. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
41. Wu CH, Farley JF, Gaynes BN. Evaluating the association of initial benzodiazepine use and antidepressant adherence among adults with anxiety disorders. *J Exp Clin Med*. 2012;4(6):338–344.
42. Leggett A, Kavanagh J, Zivin K, et al. The association between benzodiazepine use and depression outcomes in older Veterans. *J Geriatr Psychiatry Neurol*. 2015;28(4):281–287.
43. Andreescu C, Lenze EJ, Dew MA, et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *Br J Psychiatry*. 2007;190(4):344–349.
44. Andreescu C, Lenze EJ, Mulsant BH, et al. High worry severity is associated with poorer acute and maintenance efficacy of antidepressants in late-life depression. *Depress Anxiety*. 2009;26(3):266–272.
45. Dombrovski AY, Blakesley-Ball RE, Mulsant BH, et al. Speed of improvement in sleep disturbance and anxiety compared with core mood symptoms during acute treatment of depression in old age. *Am J Geriatr Psychiatry*. 2006;14(6):550–554.
46. Lenze EJ, Mulsant BH, Shear MK, et al. Comorbidity of depression and anxiety disorders in later life. *Depress Anxiety*. 2001;14(2):86–93.
47. Mulsant BH, Reynolds CF 3rd, Shear MK, et al. Comorbid anxiety disorders in late-life depression. *Anxiety*. 1996;2(5):242–247.
48. Saade YM, Nicol G, Lenze EJ, et al. Comorbid anxiety in late-life depression: relationship with remission and suicidal ideation on venlafaxine treatment. *Depress Anxiety*. 2019;36(12):1125–1134.
49. Lenze EJ, Mulsant BH, Shear MK, et al. Anxiety symptoms in elderly patients with depression: what is the best approach to treatment? *Drugs Aging*. 2002;19(10):753–760.
50. Davies SJC, Mulsant BH. Using sedatives-hypnotics or opioids in older adults: a narrow path. *Int Psychogeriatr*. 2018;30(7):925–927.

*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.