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Is sertraline treatment or depression remission in depressed Alzheimer's patients associated with improved caregiver wellbeing? The Depression in Alzheimer's Disease Study 2 (DIADS-2)

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Conflicts of Interest and Sources of support

These disclosures refer to the period between 7/1/02 and 10/31/08, and include any anticipated conflicts through 12/31/09, according to the DIADS-2 Conflict of Interest Policy (available upon request from the study PI).

- Crystal Flynn Longmire has no conflicts of interest.
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- Barbara Martin is involved in another trial for which Pfizer donated a different drug.
- Paul Rosenberg has received research funds from Pfizer and Merck in amounts greater than \$10,000.
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Abstract

Objectives—To assess if sertraline treatment (vs. placebo) or remission of depression at 12 weeks (vs. non-remission) in Alzheimer’s patients is associated with improved caregiver wellbeing.

Design—A randomized, double-blind, placebo-controlled clinical trial of the efficacy and safety of sertraline for the treatment of depression in individuals with Alzheimer’s disease.

Setting—Five clinical research sites across the United States.

Participants—Caregivers of patients enrolled in the Depression in Alzheimer’s Disease Study 2 (N=131).

Intervention—All caregivers received standardized psychosocial support throughout the study.

Measurements—Caregiver outcome measures included depression (Beck Depression Inventory), distress (Neuropsychiatric Inventory), burden (Zarit Burden Interview), and quality of life (Medical Outcomes Study Short Form Health Survey).

Results—Fifty-nine percent of caregivers were spouses, 63.4% were female, and 64.1% were white. Caregivers of patients in both treatment groups had significant reductions in distress scores over the 24 week study period, but there was not a greater benefit for caregivers of patients taking sertraline. However, caregivers of patients whose depression was in remission at week 12 had greater declines in distress scores over the 24 weeks than caregivers of patients whose depression did not remit by week 12.

Conclusions—Patient treatment with sertraline was not associated with significantly greater reductions in caregiver distress than placebo treatment. Distress but not level of depression or burden lessened for all caregivers regardless of remission status and even more so for those who cared for patients whose depression remitted. Results imply an interrelationship between caregiver distress and patient psychiatric outcomes.

Keywords

sertraline; depression; Alzheimer’s; caregivers; DIADS-2

Objective

It has been estimated that over 5 million Americans have Alzheimer's disease (AD; 1). As people are living longer, and the risk of AD increases exponentially with age, the number of AD cases is also expected to increase (2). By 2050, the number of people with AD is projected to reach 16 million in the U.S. and 106 million worldwide (3).

AD is characterized by gradual cognitive deterioration followed by functional decline, decreased quality of life, and loss of independence. Patients often need caregivers to assist them with day-to-day living activities. Accordingly, as the number of older adults with AD increases, so will the number of caregivers. The social, economic and health effects of caring for adults with dementia have been well documented (4; 5; 6; 7).

Neuropsychiatric symptoms (NPS) such as depression are common in persons with AD (34). Up to 90% develop at least one neuropsychiatric symptom over the course of the disease (8; 9). More specifically, 10 to 24% of AD patients develop major depression and an additional 40% to 50% have milder depressive symptoms (10; 11; 12). Depression of AD (dAD) has been associated with poorer patient quality of life (13; 34), more rapid cognitive decline (14; 34), poorer functioning (15; 16; 34), earlier entry into nursing homes (17; 34), and relatively higher mortality (34).

Depression in AD patients also has been associated with more caregiver stress (18), depression (37; 34; 39), burden (34; 39) and distress (19). Thus, while dementia caregiving can be challenging already, there are additional negative effects on the caregiver if the patient is also depressed (20). In previous studies, patient depression has been shown to be one of the "most consistent and powerful predictors of psychological morbidity" in caregivers, and 75–100% of caregivers of depressed AD patients were found to be depressed also (19; 38).

Psychological interventions for patients to improve symptoms related to dAD have been developed as well as interventions for caregivers (41; 42). In particular, Teri and colleagues have developed behavioral treatment and caregiver training programs to address the needs of AD patients with depression that also have been related to positive, lasting effects in caregiver outcomes (40; 43). Other researchers have found aerobic exercise to be related to a reduction in NPS in Alzheimer's patients as well as attenuation of caregiver burden (44).

Unlike non-pharmacologic interventions, fewer controlled trials that have been conducted for feasibility and effectiveness of pharmacological interventions in dAD have included caregiver outcomes (35). Since less is known about dAD pharmacologic treatments' effects on caregivers, inclusion of mood and burden outcomes for caregivers was an important aspect of the DIADS-2 design (24) and is the primary focus of this report. Furthermore, the literature has less discussion of how improvements in patient symptoms relate to improvements in caregiver outcomes (35; 38; 43; 44), and more is needed to answer such questions.

Previous reports of results from DIADS-2, a randomized controlled trial (RCT) of sertraline for dAD (21; 22; 23), indicated no effect of sertraline on patient-centered outcomes. Nonetheless, we extended these observations to caregiver outcomes via two a priori hypotheses. First, since the main focus of the DIADS-2 project was to examine the effects of sertraline, one of our original aims was that sertraline treatment would improve caregiver outcomes compared to placebo. Earlier descriptions of DIADS-2 conceptualize sertraline treatment as directly related to patient depression reduction. Here, a secondary aim was to evaluate whether patient depression reduction, i.e., remission, regardless of the mechanism

through which it might occur, would benefit caregivers. Specific caregiver outcomes evaluated were depression, distress, burden, and quality of life.

Methods

Design

DIADS-2 was a randomized, double-blind, placebo-controlled, multi-site clinical trial evaluating the efficacy and safety of sertraline for the treatment of dAD patients. There were two treatment groups: sertraline (target dose 100 mg/day) + psychosocial treatment, and placebo + psychosocial treatment. Potential participants were recruited from a variety of clinical settings and from multiple sites across the U.S. To be eligible to participate they had to have dementia due to Alzheimer's disease and meet the criteria for dAD. Study participants who did not improve (remission of depression) by week 12 had the option to continue randomized study treatment or to begin a treatment plan based on doctor, patient and caregiver collaboration. Remission in patients was defined as simultaneously meeting both modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (mADCS-CGIC) score ≥ 2 (corresponding to moderate or marked improvement in depressive symptoms from baseline) and Cornell Scale for Depression in Dementia (CSDD) score ≤ 6 . The study methods have been reported in greater detail previously (24).

Procedures

All participants were required to have a primary caregiver who also agreed to accompany them at study visits. Caregivers provided information about patients and their own psychological and physical health. Caregiver outcomes were assessed at baseline and weeks 8, 16, and 24. Participants, regardless of treatment assignment, and caregivers were provided a psychosocial intervention. At baseline, caregivers received educational materials such as dementia care handouts on various topics e.g., wandering. Each month there were scheduled opportunities for caregivers, and sometimes patients, to seek advice from or ask questions of a study clinician. Sessions included a patient-caregiver supportive care plan that was reviewed throughout the study. Caregivers also received 24-hour access via pager to the on-call nurse or physician in case of any emergencies that might occur after office hours.

Caregiver Outcome Measures

Depression—The Beck Depression Inventory (BDI; 25) is composed of 21 questions each assessing a specific symptom of depression. The sum of BDI item scores indicates depression severity. A score of >20 suggests clinical depression. The BDI has been extensively tested for validity and reliability.

Distress—The Neuropsychiatric Inventory (NPI; 26) was developed to assess NPS in dementia patients. It evaluates 12 NPS common in dementia. NPI also assesses the amount of caregiver distress associated with each of the neuropsychiatric disorders. Caregiver distress caused by each symptom is scored from 0 (no distress) to 5 (extremely distressing). A total NPI score and a total caregiver distress score (NPI-Distress) are calculated, in addition to scores for the individual symptom domains. Validity and reliability of the NPI are established. Only the distress scores were considered in this study.

Burden—The Zarit Burden Interview (ZBI) was used to assess severity of burden experienced by caregivers of adults with dementia (27). The 22-item version was used in this study. Twenty-one of the items are designed to measure several aspects of burden, while Item 22 is a global measure of burden. The items are scored from 0 (Never) to 4 (Nearly always) with higher scores indicating higher burden.

Quality of Life—The Medical Outcomes Study Short Form Health Survey (SF-12; 28) is a 12-item subset of the SF-36 that measures eight domains of health. It is a brief, reliable measure of overall health status. Seven questions relate to physical health (SF-12-Physical) and 5 relate to psychological well-being (SF-12-Mental). Responses to questions include yes/no and 3 to 5-point Likert scales. Higher scores indicate higher reported quality of life.

Analysis

Missing patient mood and caregiver outcome data were imputed using the method of multiple imputation. Prediction models of the missing data were estimated based on available baseline and follow-up data, and these models were used to impute the missing outcomes five times. The results of the five imputations were synthesized using simple combination rules to yield estimates of the comparisons (29; 30).

Analyses of treatment effects on caregiver outcomes were performed according to original treatment assignment (intention-to-treat; regardless of changes in treatment status at week 12). The medians of the caregiver outcome scores at baseline and at weeks 8, 16 and 24 were compared between the two patient treatment groups. Analyses of the association of patient remission status at week 12 with the trajectory of caregiver outcomes were performed in a similar manner. Patient remission status at week 12 was described earlier (see Design). The standard errors of medians were calculated by ordinary, non-parametric bootstrapping without bias correction using 2000 iterations.

Scores of caregiver outcomes over the 24 weeks were compared using mixed effects models, allowing a random intercept and slope for each caregiver. Although mixed models do not require complete data, they do provide a method of adjusting for the multiple observations for each participant. Transformations of the outcomes and predictors were used when needed (i.e., when the outcome was not normally distributed or the relationship between the predictor and outcome was not linear over time). Statistical analyses and graphics were performed using R version 2.9.1 (31). No adjustments for multiple testing were made to the p-values. The mixed models accounted for multiple observations for each participant.

Results

Description of Patients

The flow of participants through the study (Consort Diagram) has been published in prior DIADS-2 reports (22; 23). To summarize, 7 participants from the sertraline group and 7 participants from the placebo group were lost to follow-up by week 24. This left 67 patients assigned to sertraline and 64 to placebo. The median age of the participants was 79 years, and 54% were female. Sixty-seven percent were non-Hispanic White, 21% were Black, 11% were Hispanic/Latino, and 1 participant was Asian. The patients had a median MMSE score of 20.

Caregiver Demographics

For each patient there was also a caregiver such that the total number of caregivers was also 131. The distribution of the relationships of caregivers to patients was similar in the sertraline and placebo groups; most caregivers were the patient's spouse (58.2 and 60.9% respectively). See Table 1.

Effect of patient treatment assignment on caregiver outcomes

Table 2a shows median caregiver outcome scores for each patient treatment group at baseline and weeks 8, 16, and 24. The baseline caregiver depression, distress, burden and

quality of life scores were similar in the sertraline and placebo groups. Burden and quality of life scores changed very little over the course of the 24 weeks in both treatment groups.

Table 2b shows the results of the mixed effects models of change in caregiver outcomes over time by treatment group. Distress scores decreased significantly in both treatment groups over 24 weeks as evidenced by the negative placebo change in slope estimated as -0.19 [95% Confidence Interval (CI): $-0.26, 0.12$]; $t = 2.43$, $df = 915$, $p < 0.01$] combined with the negative difference between the two treatment groups. However, the difference in the rate of decline [estimated as -0.08 ; with CI ($-0.18, 0.02$)] did not differ significantly between treatments ($t = -1.59$, $df = 915$, $p = 0.11$). Caregiver depression scores in the placebo group decreased over the 24 weeks [change in scores coefficient = -0.02 (CI: $-0.03, -0.01$); $t = -3.14$, $df = 391$, $p < 0.01$]. The change in the placebo group was greater than the change in the sertraline group per the positive difference in slopes between the two groups [difference coefficient = 0.02 (CI: $0.00, 0.03$); $t = 2.39$, $df = 391$, $p = 0.02$]. There were no differences in caregiver burden or quality of life over time or by treatment (see Table 2b for estimates). In essence, sertraline treatment was not related to significantly greater benefits for caregivers.

Patient remission status and caregiver outcomes

Median caregiver outcome scores for baseline and weeks 8, 16 and 24 by patient remission status are in Table 3a. Caregiver depression, burden and mental quality of life scores remained rather steady during the study period across remission statuses, but there was some change in the remitter group for physical quality of life. The median distress score for caregivers of remitters decreased 10 points from baseline to week 24 and caregivers of patients who did not remit decreased by 6.5 points.

The results of the mixed model analysis of the change over time in caregiver outcome scores by remission status are in Table 3b. Differences existed at baseline between caregivers of those who would be remitters at week 12 versus those who would not. At baseline, caregivers of patients who were in remission at week 12 had significantly lower distress ratings than the caregivers of patients that were not remitters at week 12 per the difference in scores coefficient = -0.48 (CI: $-0.94, -0.01$); $t = -2.02$, $df = 128$, $p = 0.04$). Caregivers of remitters also had significantly higher scores on the physical component of the quality of life scale at baseline [coefficient = 4.16 (CI: $0.20, 8.12$); $t = 2.05$, $df = 128$, $p = 0.04$]. The rates of change for four out of five of the caregiver outcomes did not significantly differ by patient remission status (see Table 3b for estimates). Only for caregiver distress did both caregivers of remitters and nonremitters significantly decline over the 24 weeks per the negative placebo change coefficient = -0.18 (CI: $-0.24, -0.12$); $t = -6.27$, $df = 915$, $p < 0.01$) and the negative difference in rates of change between the two groups (remitters – non-remitters). This result also reveals that distress ratings decreased faster in the caregivers of patients who were in remission at week 12 [difference coefficient = -0.20 (CI: $-0.32, -0.07$); $t = -3.18$, $df = 915$, $p < 0.01$].

Conclusions

In this 24-week RCT of sertraline for dAD, caregiver distress declined over time for caregivers of both treatment groups, and at similar rates. But, notably, while placebo caregivers had significant improvement in levels of caregiver depression during the 24-week study period, sertraline caregivers' depression levels remained relatively unchanged over the same amount of time. Since caregiver depression severity (per the BDI) was very modest for both caregiver groups, the differential improvement from 6 on the BDI to a lower score is of unclear clinical meaning and significance. There also could be a "floor effect" involved.

The finding of improvement in caregiver distress, but not depression, contrasts with the studies that find that behavioral interventions are effective in reducing depression in both AD patients and their caregivers (40; 43; 44). It also differs from the original DIADS where caregiver burden and depression decreased regardless of treatment assignment (32). This might be related to methodological differences as DIADS had a much smaller sample size and this study had multiple sites. However, the lack of sertraline effects on caregiver outcomes do correspond with the recent DIADS-2 reports that indicated no effect of sertraline on patient-centered outcomes (21; 22; 23) as well as other studies that demonstrated sertraline has been ineffective in treating depression in dementia (36), and that show inconsistent effects of antidepressants on caregiver burden (35). In the context of a commonly held belief that pharmacological treatments for depression are superior to non-pharmacological interventions, these findings could have major policy implications.

Caregivers of patients whose depression remitted were less distressed than caregivers of patients who did not remit both before treatment (baseline) and at the time depression remission was noted (week 12). Yet, even after accounting for better caregiver wellbeing at baseline, caregiver distress still improved more if the depression of the patients they cared for remitted, and thereby providing evidence that the correlation between remission and lessened caregiver distress is a robust one. These findings also seem to imply that patient and caregiver outcomes are closely linked and bolster the arguments made by others that improvements in patient depression can improve caregiver well being (40; 43). There were no differences in baseline levels of caregiver distress, depression, burden and quality of life among the randomly assigned treatment groups, but there were baseline differences among remission status groups. Findings intimate the import of further exploration of the potential effects of initial caregiver wellbeing levels on dAD patient outcomes.

Participation in the study itself could have been the primary explanation for the positive effects. Perhaps the psychosocial intervention or the combination of the drug treatment with the psychosocial intervention had an effect (45). Results may also be related to interactions with study staff or auto-regression, but the study was not designed to distinguish among these.

Though the data were collected from multiple sites across the U.S., the sample was clinic-based and results may not be generalized to all caregivers of Alzheimer's patients with depression. In addition, the study was originally powered for patient, not caregiver, outcomes. The analysis of associations between patient remission and later caregiver outcomes is observational and could be confounded by unknown factors related to remission status.

This study adds to the literature by being one of the first to consider the close relationships between pharmacologic treatment for depression, caregiver wellbeing, and remission of depression in dAD patients. Furthermore, this study confirms the importance of including caregiver measures in dementia clinical trials. Their inclusion can improve understanding about patient outcomes most affected by caregivers and vice-versa. Finally, this report responds to calls in the literature to increase caregiver research in geriatric psychiatry (33), and to include caregiver burden as part of clinical trials (35). Future drug trials should include psychosocial or behavioral interventions in the study design with methods to extract effects of the intervention on patient and caregiver outcomes.

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Table 1

Caregiver demographics by patient treatment group

	All n=131	Sertraline n=67	Placebo n=64
Relationship to patient (% of group)			
Spouse or significant other	59.6	58.2	60.9
Sibling	3.1	4.5	1.6
Son/son-in-law/daughter/daughter-in-law	26.7	22.4	31.3
Grandchild	2.3	1.5	3.1
Parent/parent-in-law	0.8	1.5	0
Paid caregiver	3.1	4.5	1.6
Other	4.6	7.5	1.6
Age, mean years (sd)	64.6 (15.0)	64.2 (15.8)	65.0 (14.2)
Gender (% of group)			
Female	63.4	56.7	70.3
Male	36.6	43.3	29.7
Ethnicity (% of group)			
White, non-Hispanic	64.1	68.7	59.4
African American	23.7	22.4	25.0
Hispanic / Latino	10.7	7.46	14.1
Asian	1.5	1.5	1.6
Marital status (% of group)			
Married	78.6	82.1	75.0
Widowed	3.1	1.5	4.7
Divorced / separated	8.4	6.0	10.9
Never married	9.9	10.5	9.4
Education, mean years (sd)	13.9 (4.4)	14.7 (4.4)	13.1 (4.4)

Table 2

a. Caregiver outcome measures by patient treatment group for each week of assessment (Medians, 95% CI [*]).												
Time	Caregiver Outcome						Quality of Life ^{††}					
	Depression (BDI) ^{**}		Distress (NPI-Distress) ^{***}		Burden (ZBI) [†]		Physical (SF-12-Physical)		Mental (SF-12-Mental)		Quality of Life ^{††}	
	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo
Baseline	6 (5, 7)	6.5 (4, 9)	19 (16.5, 22.5)	19 (15, 23)	24 (20, 28)	23 (17, 29)	46 (42, 50.5)	53 (51, 55.5)	53 (49, 56)	54 (50, 58)	54 (51.5, 56)	54 (47.5, 55)
Week 8	5 (2.5, 7.5)	5 (3, 7)	9 (5, 13)	13 (9, 17)	23 (17, 29)	21 (15, 27)	49 (45, 52)	49 (44, 54)	49 (45, 52)	54 (50, 58)	54 (51.5, 56)	54 (47.5, 55)
Week 16	6 (4, 8)	4 (2, 6)	8 (5, 11)	11 (8, 14)	25 (22, 28)	20 (16, 24)	46 (42, 51)	51 (47, 55)	51 (47, 55)	54 (50, 57)	54 (47.5, 55)	53 (49, 56.5)
Week 24	6 (4, 8)	4 (2, 6)	11 (8, 14)	9 (5, 13)	24 (19, 29)	23.5 (18, 29)	47 (43, 51)	52.5 (49, 56)	54 (51, 56.5)	54 (49, 56.5)	53 (49, 56.5)	53 (49, 56.5)

b. Regression coefficients (95% CI) for differences by patient treatment assignment (sertraline vs. placebo) on caregiver outcomes at baseline and week 24 [*]												
Model variable	Caregiver Outcome						Quality of Life ^{††}					
	Depression (BDI) ^{**}		Distress (NPI-Distress) ^{***}		Burden (ZBI) [†]		Physical (SF-12-Physical)		Mental (SF-12-Mental)		Quality of Life ^{††}	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Baseline scores for caregivers of placebo group (Intercept)	1.53 (1.02, 2.03)	<0.01	4.49 (3.83, 5.15)	<0.01	22.84 (15.87, 29.81)	<0.01	47.08 (41.34, 52.81)	<0.01	51.60 (46.48, 56.72)	<0.01	51.60 (46.48, 56.72)	<0.01
Difference in baseline scores between caregiver groups (sertraline - placebo)	-0.06 (-0.37, 0.25)	0.71	0.09 (-0.33, 0.50)	0.68	1.11 (-3.38, 5.61)	0.63	-1.50 (-5.07, 2.06)	0.41	-0.30 (-4.04, 3.43)	0.87	-0.30 (-4.04, 3.43)	0.87
Linear slope over 24 weeks (change in scores) for placebo group	-0.02 (-0.03, -0.01)	<0.01	-0.19 (-0.26, -0.12)	<0.01	-0.06 (-0.17, 0.05)	0.29	-0.02 (-0.13, 0.10)	0.77	-0.01 (-0.13, 0.11)	0.88	-0.01 (-0.13, 0.11)	0.88
Difference in slopes between groups (sertraline - placebo)	0.02 (0.00, 0.03)	0.02	-0.08 (-0.18, 0.02)	0.11	0.03 (-0.13, 0.19)	0.71	-0.04 (-0.20, 0.13)	0.64	0.03 (-0.14, 0.21)	0.70	0.03 (-0.14, 0.21)	0.70

- * CI: Confidence Interval; Standard errors for medians calculated by bootstrapping. The results from all five imputations were combined.
- ** Caregiver depression as rated by the Beck Depression Inventory; higher scores indicate more depressive symptoms.
- *** Caregiver distress as rated by the Neuropsychiatric Inventory; higher scores indicate greater reported caregiver distress.
- † Caregiver burden as rated by the Zarit burden interview; higher scores indicate greater reported burden of caregiving.
- †† Caregiver quality of life as rated by the SF-12; higher scores indicate higher reported quality of life. Physical is the SF-12 Physical component score (PCS) and Mental is the SF-12 Mental component score (MCS).
- * CI: Confidence Interval; Estimation by mixed model regression with random intercept and slope for participant; p-values are from fixed effects t-tests. Models controlled for years of education of the patient.
- ** Caregiver depression as rated by the Beck Depression Inventory; higher scores indicate more reported depressive symptoms. A log transformation of the outcome was used for analysis.
- *** Caregiver distress as rated by the Neuropsychiatric Inventory; higher scores indicate greater reported caregiver distress. Square root transformations of the outcome and the time predictor were used for analysis.
- † Caregiver burden as rated by the Zarit burden interview; higher scores indicate more reported burden of caregiving.
- †† Caregiver quality of life as rated by the SF-12; higher scores indicate higher reported quality of life.

Table 3

a. Caregiver outcome measures by patient week 12 remission status for each week of assessment (Scores are medians with 95% CI)*.

Time	Caregiver Outcome									
	Depression (BDI) **		Distress (NPI-Distress) ***		Burden (ZBI) †		Quality of Life ††			
	Remission	No remission	Remission	No remission	Remission	No remission	Physical (SF-12-Physical)	Mental (SF-12-Mental)		
Baseline	5 (2.5, 7)	6 (5, 8)	15 (11.5, 18)	19 (17, 21)	21 (14, 27.5)	24 (21, 7.5)	54 (50, 58.5)	49 (44, 54)	55 (52, 59)	52 (49, 55)
Week 8	3.5 (1, 6)	7 (4, 9.5)	5 (2, 8)	13 (11, 15)	20 (12, 28)	25 (19.5, 31)	52 (45.5, 59)	48 (45, 51.5)	57.5 (54, 61)	53 (50.5, 56)
Week 16	5 (2, 7)	6 (4, 8)	5 (3, 7)	11 (8.5, 13)	20 (12.5, 27)	24 (20, 28)	51.5 (47, 56)	46 (42.5, 50)	56 (52, 60)	51 (48.5, 54)
Week 24	4 (0.5, 8)	6 (4.5, 7.5)	5 (2, 8)	12.5 (10, 15)	20 (13, 26.5)	25 (20, 29.5)	50 (44, 55.5)	49 (45, 53.5)	55 (52, 58.5)	53 (50, 56)

b. Regression coefficients (95% CI) for the associations between week 12 patient remission status (remitter vs. non-remitter) and caregiver outcomes at baseline and week 24*

Model variable	Caregiver Outcome								
	Depression (BDI) **		Distress (NPI-Distress) ***		Burden (ZBI) †		Quality of Life ††		
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value	Physical (SF-12-Physical) Coefficient	Mental (SF-12-Mental) Coefficient	p-value
Baseline scores for caregivers of non-remitters	1.50 (1.01, 1.99)	<0.01	4.58 (3.97, 5.19)	<0.01	23.41 (16.58, 30.23)	<0.01	46.14 (40.54, 51.74)	50.88 (45.87, 55.89)	<0.01
Difference in baseline scores between caregiver groups (remitters - non-remitters)	-0.27 (-0.64, 0.09)	0.14	-0.48 (-0.94, -0.01)	0.04	-3.74 (-8.98, 1.50)	0.16	4.16 (0.20, 8.12)	2.79 (-1.40, 6.98)	0.04 0.19
Linear slope over 24 weeks (change in scores) for caregivers of non-remitters	-0.01 (-0.01, 0.00)	0.13	-0.18 (-0.24, -0.12)	<0.01	-0.04 (-0.13, 0.05)	0.43	-0.01 (-0.11, 0.09)	0.03 (-0.08, 0.14)	0.63
Difference in slopes between groups	0.00 (-0.02, 0.01)	0.72	-0.20 (-0.32, -0.07)	<0.01	-0.03 (-0.23, 0.16)	0.72	-0.10 (-0.30, 0.10)	-0.08 (-0.27, 0.12)	0.45

b. Regression coefficients (95% CI) for the associations between week 12 patient remission status (remitter vs. non-remitter) and caregiver outcomes at baseline and week 24*

Model variable (remitters - non-remitters)	Depression (BDI) **			Distress (NPI-Distress) ***			Caregiver Outcome		
	Coefficient	p-value		Coefficient	p-value		Burden (ZBI) †	Physical (SF-12-Physical)	Quality of Life ††
							Coefficient	Coefficient	Coefficient
							p-value	p-value	p-value
									Mental (SF-12-Mental)

* CI: Confidence Interval; Standard errors for medians calculated by bootstrapping. The results from all five imputations were combined.

** Caregiver depression as rated by the Beck Depression Inventory; higher scores indicate more reported depressive symptoms.

*** Caregiver distress as rated by the Neuropsychiatric Inventory; higher scores indicate greater reported caregiver distress.

† Caregiver burden as rated by the Zarit burden interview; higher scores indicate more reported burden of caregiving.

†† Caregiver quality of life as rated by the SF-12; higher scores indicate higher reported quality of life. Physical is the SF-12 Physical component score (PCS) and Mental is the SF-12 Mental component score (MCS).

* CI: Confidence Interval; Estimation by mixed model regression with random intercept and slope for participant; p-values are from fixed effects t-tests. Models controlled for years of education of the patient.

** Caregiver depression as rated by the Beck Depression Inventory; higher scores indicate more reported depressive symptoms. A log transformation of the outcome was used for analysis.

*** Caregiver distress as rated by the Neuropsychiatric Inventory; higher scores indicate greater reported caregiver distress. Square root transformations of the outcome and the time predictor were used for analysis.

† Caregiver burden as rated by the Zarit burden questionnaire; higher scores indicate more reported burden of caregiving.

†† Caregiver quality of life as rated by the SF-12; higher scores indicate higher reported quality of life.