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Regular Research Article

Sertraline and Mirtazapine Versus Placebo in Subgroups of Depression in Dementia: Findings From the HTA-SADD Randomized Controlled Trial

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Objective: *Studies have shown that antidepressants are no better than placebo in treating depression in dementia. The authors examined antidepressant efficacy in subgroups of depression in dementia with different depressive symptom profiles.* ***Methods:*** *This study focuses on exploratory secondary analyses on the randomized, parallel-group, double-blind, placebo-controlled Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) trial. The setting included old-age psychiatry services in nine centers in England. The participants included 326 patients meeting National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association probable/possible Alzheimer disease criteria, and Cornell Scale for Depression in Dementia (CSDD) scores of 8 or more. Intervention was placebo (n = 111), sertraline (n = 107), or mirtazapine (n = 108). Latent class analyses (LCA) on baseline CSDD items clustered participants into symptom-based subgroups. Mixed-model analysis evaluated CSDD improvement at 13 and 39 weeks by randomization in each subgroup.* ***Results:*** *LCA yielded 4 subgroups: severe (n = 34), psychological (n = 86), affective (n = 129), and somatic (n = 77). Mirtazapine, but not sertraline, outperformed placebo in the psychological subgroup at week 13 (adjusted estimate: −2.77 [standard error (SE) 1.16; 95% confidence interval: −5.09 to −0.46]), which remained, but lost statistical significance at week 39 (adjusted estimate:*

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−2.97 [SE 1.59; 95% confidence interval: −6.15 to 0.20]). Neither sertraline nor mirtazapine outperformed placebo in the other subgroups. ***Conclusion:*** *Because of the exploratory nature of the analyses and the small sample sizes for subgroup analysis there is the need for caution in interpreting these data. Replication of the potential effects of mirtazapine in the subgroup of those with depression in dementia with "psychological" symptoms would be valuable. These data should not change clinical practice, but future trials should consider stratifying types of depression in dementia in secondary analyses.* (Am J Geriatr Psychiatry 2019; 27:920−931)

INTRODUCTION

Depression is common in dementia with prevalence of depressive symptoms in people with dementia ranging between 10% and 62%.[1] Depression in dementia is associated with reduced quality of life,[2] exacerbation of cognitive and functional impairment,[3] and increased stress and depression in caregivers.[4] Effective treatment of depression in dementia is therefore a clinical priority. Older clinical guidelines advocate the use of antidepressants for depression in dementia such as the American Psychiatric Association workgroup on Alzheimer's Disease and other dementias,[5] and as many as 22%−47% of community-dwelling persons with dementia are prescribed antidepressants.[6,7] However, the current evidence from well-designed placebo-controlled trials, as summarized in the most recent 2018 Cochrane review,[8] suggests that some early and small trials found positive results, whereas larger, more recent studies have been largely negative and that, on balance, there is little evidence of the efficacy of antidepressants for depression in dementia. They found that of the eight studies reviewed, which included 614 participants in total, the only study that showed significant benefit of antidepressant over placebo on average depressive symptom severity was the small Depression in Alzheimer's Disease Study (DIADS)[9]. This study showed a significant benefit of sertraline over placebo on average depressive symptom severity at 12 weeks in 44 participants. However, the other seven studies, including the follow-up DIADS-2,[10,11] showed no beneficial effects of antidepressants over placebo, resulting in a pooled effect size of −0.13 (95% confidence interval [CI]: −0.33 to 0.07) for selective serotonin reuptake inhibitors (SSRIs) and −0.10 (95% CI: −0.26 to 0.06) for antidepressants in general. There is however evidence that antidepressants are associated with more adverse events than placebo.[8,12,13] It is also the case that relatively few antidepressants have been trialed in depression in dementia and that further investigation is needed, particularly of newer medications.[8] As a response to this emerging evidence, the most recent guidelines suggest that antidepressants should not be routinely offered as a first-line treatment to those with mild to moderate depression in dementia.[14]

The Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) trial was a large randomized controlled trial of the efficacy of sertraline (n = 107) and mirtazapine (n = 108) versus placebo (n = 111) in people with probable or possible Alzheimer's disease and depression.[15] In all three groups, an improvement in total Cornell Scale for Depression in Dementia (CSDD)[16] scores was seen from week 0 to week 13, which persisted to week 39. However, sertraline and mirtazapine did not outperform placebo. This lack of observed antidepressant efficacy may in part be owing to the heterogeneity of depression in dementia.[12] Therefore, there may be value in evaluating antidepressant efficacy in subgroups of depression in dementia.

Different symptoms of depression in dementia may have a different underlying etiology. Some depressive symptoms, for example, may occur as a reaction to perceived cognitive deficits, whereas others may have a common underlying (neuro) pathology with cognitive deficits.[17] For instance, vascular disease and a disruption of frontal-subcortical pathways may underlie both motivational-related symptoms of depression (i.e., loss of interest in activities, psychomotor retardation) and executive deficits.[18] Also, the substantial overlap of symptoms of depression and dementia (e.g., psychomotor change, apathy, lack of interest, sleep difficulties, concentration problems)[19−21] make it possible that symptoms

of dementia are misclassified as symptoms of depression. Because different symptoms of depression in dementia may have a different underlying etiology, response to antidepressant treatment might differ according to the depressive symptom profile of the patient. It would therefore be of clinical relevance if it were possible to identify subgroups of patients who might be more likely to respond to antidepressants based on their symptom profile.

Aims of the Study

We therefore completed exploratory secondary analyses of the HTA-SADD trial data using latent class analyses (LCA) on the 19 baseline CSDD items to identify different patient groups and examined the response to randomized treatment in these subgroups. We hypothesized that patients with a symptom profile dominated by core depression items (such as sadness, pessimism) would respond better to antidepressants than patients with other symptom profiles more likely to be owing to underlying physical pathology (such as somatic symptoms and apathy).

METHODS

Study Design and Participants

The HTA-SADD was a randomized double-blind placebo-controlled trial to evaluate the clinical effectiveness of sertraline and mirtazapine in those with depression in dementia. Details of this study have been reported previously.[15] Participants were recruited from old-age psychiatry services in nine centers in England. Inclusion criteria were: 1) National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable or possible Alzheimer disease;[22] 2) co-existing depression of at least 4 weeks duration assessed as potentially needing antidepressants as ascertained by the referring psychiatrist (however, diagnostic criteria for major depressive disorder were not evaluated); and 3) a CSDD score of 8 or more ascertained by a trained research worker. Exclusion criteria were: 1) clinically too critical for randomization (e.g., suicide risk); 2) absolute contraindication to trial drugs; 3) already using antidepressants; 4) in another trial; and 5) no family or professional caregiver informant. The study was approved by the North West 7 (Greater Manchester, United Kingdom) ethics committee, and consent or assent was obtained from all participants. The study is registered under ISRCTN88882979 and EudraCT 2006-000105-38.

Randomization and Masking

Participants were independently allocated to receive placebo, sertraline, or mirtazapine in a ratio of 1:1:1. Randomization was stratified by center (n = 9) using a computer-generated randomization sequence with randomly varying block sizes of three or six. The trial was double-blind: patients, referring clinicians, research workers who did baseline and follow-up assessments, and statisticians were masked to group identity. The researcher performing the secondary analyses in this article was not masked for group identity.

Dosages of Mirtazapine and Sertraline

Patients in the sertraline and mirtazapine group started on 50 mg for sertraline and 15 mg for mirtazapine. Over the first 2 weeks, the dosage was increased to 100 mg for sertraline and 30 mg for mirtazapine. At 4 weeks, the CSDD was re-administered: if the CSDD score was 4 or higher the dosage was increased to the maximum of 150 mg for sertraline and 45 mg of mirtazapine. If the CSDD score was below 4 the CSDD was administered again at 8 weeks, and the dosage was increased to 150 mg for sertraline and 45 mg for mirtazapine if the score was 4 or higher. After 8 weeks, clinicians were free to adjust the dose.

Assessment of Depressive Symptoms

At baseline, at 13 weeks, and at 39 weeks after baseline, the CSDD[16] was administered by a trained research worker who interviewed both the patient and the caregiver. The CSDD includes 19 questions that can be rated 0 (absent), 1 (mild), or 2 (severe). Therefore, the total score ranges from 0−38, with higher scores denoting higher severity of depression.

Baseline Characteristics

The following caregiver-rated scores were completed at baseline, prior to randomization: participant

quality of life (Short Form 12-item Survey mental and physical subscales, European Quality of Life Scale-Visual Analog Scale, and DEMQOL-Proxy), participant activity limitation (Bristol Activities of Daily Living), participant neuropsychiatric symptoms (Neuropsychiatric Inventory [NPI]), caregiver mental health (12-item General Health Questionnaire), and caregiver burden (Zarit Burden Interview score). The following participant-rated scores were assessed at baseline: participant cognition (Mini Mental State Examination), and participant quality of life (European Quality of Life Scale-Visual Analog Scale and DEMQOL). To assess dementia vascularity, a modified Hachinski ischemic score was calculated at baseline.

Analyses

All participants that were included at baseline (n = 326) were assigned into different classes according to their endorsed symptom profile by performing LCA[23,24] on the 19 items of the baseline CSDD. Before entering into the LCA, responses to the CSDD items were dichotomized into absent or present. Models with one to six classes were fitted using maximum likelihood estimator with robust standard errors. The optimal number of classes was determined by comparing fit statistics, interpretability of the classes, and absence of overly small classes (n <30). Details of the LCA can be found in the supplementary material.

After the LCA, we described baseline characteristics for each class separately using one-way analysis of variance for normally distributed continuous variables, the Kruskal-Wallis test for not normally distributed continuous variables, and the χ^2 test for categorical variables. After this, we evaluated whether the LCA groups differed in response to sertraline or mirtazapine over time by calculating a three-way interaction between LCA-class × randomization arm × time. For this purpose, we used linear mixed models using a marginal model with unstructured covariance between the different time-points, and CSDD score at baseline, week 13 and 39 as dependent variable. Independent variables (and fixed effects) in this model were LCA class, randomization arm, time, the three-way interaction LCA-class × randomization arm × time, and clinical center where participants were recruited. In case of a statistically significant three-way interaction, we calculated the two-way interaction between randomization arm × time in each of the classes separately using linear mixed models (again, a marginal model with unstructured covariance between the different time-points, and total CSDD score as dependent variable). Independent variables (and fixed effects) in these models were: time (categorical variable indicating 0, 13, or 39 weeks), randomization arm, the interaction between time × randomization arm, and clinical center where participants were recruited. In case of a significant effect of time × randomization arm, estimated differences from placebo were reported for sertraline and mirtazapine at 13 and 39 weeks, and Hedges g was calculated to estimate the effect size. LCA was performed in Mplus version 7 (Muthén & Muthén),[25] and the other statistics in IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY).

RESULTS

Participants

A total of 326 participants were randomly assigned to placebo (n = 111), sertraline (n = 107), and mirtazapine (n = 108). At 13 weeks, 258 completed the CSDD (placebo: n = 95; sertraline: n = 78; mirtazapine: n = 85), and at 39 weeks, 226 completed the CSDD (placebo: n = 82; sertraline: n = 68; mirtazapine: n = 76).

Results of the LCA

The optimal solution of the LCA yielded four classes: 1) a "severe" class; 2) a "psychological" class with relatively severe endorsement of psychological symptoms (pessimism and low self-esteem) and absence of sleep problems; 3) an "affective" class with relatively low endorsement of psychological items and absence of appetite problems; and 4) a "somatic" class with mainly somatic symptoms and less affective/mood symptoms (Supplementary Figure 1). Details of the LCA results and the selection of the optimal number of classes can be found in the Supplementary material.

Baseline Characteristics for Each of the Four Classes

Patients in class 1 (severe symptoms) had worse quality of life scores, worse total CSDD scores, and higher NPI scores on depression and anxiety compared with patients in all other classes. They also had higher

scores on NPI appetite/eating disorders compared with patients in classes 2 and 3 (psychological and affective symptoms, respectively), and worse Bristol Activities of Daily Living scores compared with patients in class 2 (psychological symptoms). Patients in class 4 (somatic symptoms) had worse total CSDD scores than patients in class 2 (psychological symptoms) (Table 1).

Impact of Randomization Arm on Course Over Time of Total CSDD Scores in Each Class

Results of the linear mixed model analysis showed a statistically significant three-way interaction between LCA-class × randomization arm × time ($F(28, 368.1) = 2.474$; $p < 0.001$). The two-way interaction randomization arm × time was statistically significant only in class 2 (psychological symptoms; Table 2). Specifically, mirtazapine outperformed placebo at 13 weeks for patients in this subgroup with psychological symptoms (class 2). Based on the linear mixed model, the adjusted difference in change score baseline to 13 weeks was −2.77 points; 95% CI: −5.09 to −0.46; t (df) = −2.39 (68.2); p = 0.019 (Table 2). This effect persisted to 39 weeks but lost statistical significance (adjusted difference based on the linear mixed model baseline to 39 weeks: −2.97; 95% CI: −6.15 to 0.20; t (df) = −1.87 (58.2); p = 0.066; Table 2). Mirtazapine did not outperform placebo at week 13 and 39 in the remaining three groups. The Hedges *g* (standard error) for mirtazapine versus placebo was 0.70 (0.31) at week 13 and 0.65 (0.34) at week 39. Sertraline did not outperform placebo at week 13 and week 39 in all four groups (Table 2). Figure 1 shows the time-course of absolute unadjusted mean (95% CI) CSDD scores at baseline, 13 weeks and 39 weeks for each class separately.

DISCUSSION

Main Findings

To the best of our knowledge, this is the first study to explore antidepressant efficacy in subgroups of depression in dementia with different depressive symptom profiles. In these exploratory secondary analyses, we identified that a "psychological" subgroup with affective symptoms, relatively severe endorsement of psychological symptoms (pessimism and low self-esteem), and an absence of sleep problems appeared to respond better to mirtazapine compared with placebo. Those in this "psychological" subgroup receiving mirtazapine improved on average almost three CSDD points (95% CI: −5.1 to −0.5 points) more than those receiving placebo from week 0 to week 13, which was sustained to week 39. At week 39, the difference with baseline was as high as at week 13, but lost statistical significance due to smaller group sizes. The beneficial effects of mirtazapine compared with placebo in this group correspond to effect sizes (standard error) of 0.70 (0.31) at week 13 and 0.65 (0.34) at week 39, which would be considered moderate or medium effect sizes. Antidepressant treatment was not effective in reducing depression in any of the other subgroups. It is important to note that this is an exploratory secondary analysis from a study in which the primary findings were negative. As such, these data are in no way definitive and would benefit from replication.

Comparison to Literature

In the DIADS of 44 people with depression in Alzheimer disease, response to sertraline was observed to be highest on the mood subscale of the CSDD compared with other instruments.[26] In the larger DIADS-2, there was no differential response to sertraline compared with placebo in subgroups of depression in dementia with 1) major depression; 2) minor depression; and 3) Alzheimer-associated affective disorder.[27]

Studies have evaluated antidepressant efficacy on specific depressive symptoms and symptom profiles in depressed populations without dementia. Patients with depression without dementia were not the subject of this study, and there will be major limitations in generalizability from populations without dementia to those with dementia. However, these studies do provide an illustration of the potential for exploration of differential response in subgroups of people with depression. A pooled analysis from 32 randomized controlled trials evaluating the efficacy of an SSRI against placebo found that SSRIs were more effective in improving mood than in reducing other symptoms of depression.[28] Secondary analyses from the Sequenced Treatment Alternatives to Relieve Depression and the Combining Medications to Enhance Depression Outcomes trials showed that core

TABLE 1. Association of Baseline Characteristics With Class

	Class 1: Severe (n = 34)	Class 2: Psychological (n = 86)	Class 3: Affective (n = 129)	Class 4: Somatic (n = 77)	Overall statistic (df); p value	Significant group difference[d]
Age (years), mean (SD)	78.0 (10.4)	79.1 (7.9)	79.5 (8.6)	80.1 98.1)	F (3, 322) = 0.5; p = 0.672	
Sex (male), n (%)	12 (35.3)	32 (37.2)	46 (35.7)	15 (19.5)	χ^2 (3) = 7.6; p = 0.056	
Ethnicity (white), n (%)	31 (91.2)	83 (96.5)	121 (93.8)	68 (88.3)	χ^2 (3) = 4.5; p = 0.213	
Marital status (married): n = 311, n (%)	13 (40.6)	50 (60.2)	61 (47.7)	35 (51.5)	χ^2 (3) = 4.8; p = 0.188	
Lives in care home, n (%)	5 (14.7)	10 (11.6)	24 (18.6)	11 (14.3)	χ^2 (3) = 2.0; p = 0.563	
Duration of depression: n = 319						
<1 month, n (%)	2 (5.9)	2 (2.3)	5 (4.1)	1 (1.3)	χ^2 (9) = 12.0; p =	
1−2 months, n (%)	0 (0.0)	4 (4.7)	8 (6.6)	8 (10.4)	0.214	
2−6 months, n (%)	7 (20.6)	12 (14.0)	30 (24.6)	19 (24.7)		
>6 months, n (%)	25 (73.5)	68 (79.10	79 (64.8)	49 (63.6)		
Dementia vascularity: modified HIS score; n = 240; mean (SD)	2.4 (1.2)	2.0 (1.3)	2.2 (1.3)	2.1 (1.4)	F (3, 236) = 0.7; p = 0.574	
Total CSDD score[a] at baseline: n = 322; mean (SD)	20.5 (5.3)	11.4 (3.0)	12.2 (3.1)	13.0 (3.2)	F (3, 318) = 64.1; p <0.001	1 versus 2: t (df) = 9.3 (40.0); p <0.001 1 versus 3: t (df) = 8.7 (37.6); p <0.001 1 versus 4: t (df) = 7.6 (42.7); p <0.001 2 versus 4: t (df) = −3.12 (158.0); p = 0.002
Randomization arm						
Placebo (n = 111), n (%)	14 (41.2)	28 (32.6)	45 (34.9)	24 (31.2)	χ^2 (6) = 2.1; p =	
Sertraline (n = 107), n (%)	8 (23.5)	29 (33.7)	42 (32.6)	28 (36.4)	0.913	
Mirtazapine (n = 108), n (%)	12 (35.3)	29 (33.7)	42 (32.6)	25 (32.5)		
Participant rated scores						
Cognition (MMSE[b]): n = 251, mean (SD)	18.5 (6.6)	18.4 (6.4)	17.5 (7.2)	18.5 (6.4)	F (3, 247) = 0.4; p = 0.719	
Participant generic quality of life: Euro-QOL[b]-VAS (0−100): n = 269, mean (SD)	51.3 (21.3)	64.9 (21.3)	66.1 (19.9)	67.4 (18.5)	F (3, 265) = 4.7; p = 0.003	1 versus 2: t (df) = −2.90 (102.0); p = 0.005 1 versus 3: t (df) = −3.47 (134.0); p = 0.001 1 versus 4: t (df) = −3.59 (83.0); p = 0.001
Participant disease-specific quality of life: DEMQOL[a] (28−112): n = 260, mean (SD)	69.9 (18.7)	82.9 (13.4)	85.1 (14.6)	89.1 (10.8)	F (3, 256) = 11.7; p <0.001	1 versus 2: t (df) = −3.24 (34.5); p = 0.003 1 versus 3: t (df) = −4.46 (127.0); p <0.001 1 versus 4: t (df) = −4.87 (32.7); p <0.001 2 versus 4: t (df) = −2.94 (129.0); p = 0.004

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TABLE 1. (*continued*)

	Class 1: Severe (n = 34)	Class 2: Psychological (n = 86)	Class 3: Affective (n = 129)	Class 4: Somatic (n = 77)	Overall statistic (df); p value	Significant group difference[d]
Carer rated scores						
BADL[a] (n = 324), mean (SD)	21.4 (11.4)	15.2 (11.6)	18.1 (10.1)	18.4 (11.4)	F (3, 320) = 2.9; p = 0.035	1 versus 2: t (df) = 2.64 (118.0); p = 0.009
Participant SF-12[b] physical component: n = 300, mean (SD)	48.1 (14.1)	46.7 (13.5)	49.3 (10.7)	47.7 (10.8)	F (3, 296) = 0.8; p = 0.508	
Participant SF-12[b] mental component: n = 300, mean (SD)	44.0 (11.6)	45.3 (11.8)	45.2 (11.3)	46.7 (11.1)	F (3, 296) = 0.5; p = 0.691	
Participant generic quality of life: EuroQOL-VAS[b] (0−100): n = 320, mean (SD)	39.7 (22.0)	52.2 (19.2)	56.4 (19.7)	52.4 (22.9)	F (3, 316) = 5.8; p = 0.001	1 versus 2: t (df) = −3.06 (116.0); p = 0.003 1 versus 3: t (df) = −4.24 (157.0); p <0.001 1 versus 4: t (df) = −2.71 (107.0); p = 0.003
Participant disease-specific quality of life DEMQOL-Proxy[a] (31−124): n = 279, mean (SD)	77.6 (14.9)	85.7 (13.0)	89.0 (14.9)	89.9 (14.4)	F (3, 275) = 5.8; p = 0.001	1 versus 2: t (df) = −2.69 (99.0); p = 0.009 1 versus 3: t (df) = −3.58 (134.0); p<0.001 1 versus 4: t (df) = −3.76 (94.0); p <0.001
Carer mental health: GHQ-12 (0−36)[a]: n = 306, mean (SD)	13.5 (4.5)	12.5 (5.2)	12.5 (5.2)	12.9 (5.8)	F (3, 302) = 0.4; p = 0.757	
Carer burden: ZBI score (0−88)[a]: n = 271, mean (SD)	31.6 (14.9)	28.2 (15.5)	26.9 (16.2)	24.6 (15.2)	F (3, 267) = 1.3; p = 0.279	
Participant neuropsychiatric symptoms (NPI)[a], IQR						
Delusions (n = 108)	3; 6; 8	2; 3; 6	2; 3; 5	1; 4; 7	H (3) = 6.21; p = 0.102	
Hallucinations (n = 71)	2; 4; 5	3; 5; 5	3; 4; 5	2; 4; 5	H (3) = 3.75; p = 0.289	
Agitation (n = 215)	2; 4; 6	1; 3; 4	2; 3; 6	2; 3; 6	H (3) = 4.80; p = 0.187	
Depression (n = 313)	4; 7; 8	2; 4; 8	2; 3; 6	2; 3; 6	H (3) = 18.27; p <0.001	1 versus 2: U = 836.0; p <0.001; 1 versus 3: U = 1180.5; p <0.001; 1 versus 4: U = 645.5; p <0.001
Anxiety (n = 235)	3; 6; 8	2; 3; 6	2; 4; 6	2; 3; 6	H (3) = 7.90; p = 0.048	1 versus 2: U = 708.5; p = 0.018; 1 versus 3: U = 982.5; p = 0.024; 1 versus 4: p = 0.009
Elation (n = 30)	1; 2; NA[c]	1; 2; 2	2; 3; 3	1; 2; 4	H (3) = 3.29; p = 0.349	
Disinhibition (n = 104)	2; 2; 3	1; 2; 3	1; 3; 4	1; 2; 6	H (3) = 0.24; p = 0.971	
Irritability (n = 228)	2; 4; 6	2; 3; 6	2; 3; 6	1; 4; 8	H (3) = 2.35; p = 0.502	
Apathy (n = 254)	4; 8; 8	3; 4; 8	2; 4; 8	3; 4; 8	H (3) = 6.98; p = 0.073	
Aberrant motor behavior (n = 171)	3; 4; 8	2; 4; 6	3; 6; 8	3; 4; 8	H (3) = 3.78; p = 0.286	
Sleep and night-time behavior disorders (n = 155)	3; 4; 7	3; 4; 4	3; 4; 8	3; 4; 8	H (3) = 1.53; p = 0.676	

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TABLE 1. (*continued*)

	Class 1: Severe (n = 34)	Class 2: Psychological (n = 86)	Class 3: Affective (n = 129)	Class 4: Somatic (n = 77)	Overall statistic (df); p value	Significant group difference[d]
Appetite and eating disorders (n = 151)	6; 6; 8	2; 4; 6	2; 4; 8	4; 6; 8	H (3) = 9.20; p = 0.027	1 versus 2: U = 269.5; p = 0.008; 1 versus 3: 262.0; p = 0.020

Notes: For categorical variables the χ^2 test was used, for continuous variables one-way analysis of variance was used except for the individual symptoms of the NPI for which a Kruskal-Wallis test was used. BADL: Bristol Activities of Daily Living; EuroQOL-VAS: European Quality of Life Scale-Visual Analog Scale; GHQ-12: 12-item General Health Questionnaire; HIS: Hachinski ischemic score; IQR: interquartile range; MMSE: Mini Mental State Examination; NA: not applicable; SD: standard deviation; SF-12: Short Form 12-item Survey; ZBI: Zarit Burden Interview.

[a] Lowest score is best outcome.

[b] Highest score is best outcome.

[c] Not applicable; n = 2 in this class with data.

[d] Significant group difference represents t value (df), p value based on independent samples t test for normally distributed continuous variables, and the U statistic and p value based on the Mann-Whitney U test for not normally distributed continuous variables.

emotional symptoms (low mood, loss of interest, feelings of worthlessness) responded better to antidepressants than sleep symptoms, and sleep symptoms responded better to antidepressants than atypical symptoms (suicidality, psychomotor agitation/retardation, and hypersomnia).[29] The efficacy of antidepressant treatment on these different symptom clusters differed according to drug. For instance, core emotional symptoms responded better to high-dose duloxetine and paroxetine than escitalopram, which performed equal to placebo in reducing core emotional symptoms.[29] In the Genome-Based Therapeutic Drugs for Depression study, mood and cognitive symptoms improved more with escitalopram than with nortriptyline, whereas neurovegetative symptoms improved more with nortriptyline than escitalopram.[30] In a randomized controlled trial of 231 patients with depression, paroxetine treatment and cognitive therapy were associated with a greater reduction in cognitive/suicide symptoms relative to placebo, and cognitive therapy was associated with a greater reduction in atypical-vegetative symptoms than placebo or paroxetine.[31]

Although these specific findings cannot be generalized directly to depression in dementia, taken with the data presented here, it is possible that antidepressant treatments may be more beneficial for patients with relatively high endorsement of core mood and psychological symptoms than for patients with more of other (e.g., vegetative or atypical) symptoms of depression.

Interpretation and Clinical Implications

The results of the present analyses should be interpreted with caution, because they are based on exploratory secondary analyses in small groups. Small group size, or lack of power, not only results in false-negative findings, but also may result in false-positive findings.[32] Before making any conclusions, it is therefore essential that these results are replicated. Furthermore, it is counterintuitive that mirtazapine (a sedating drug that is often prescribed in patients with sleep problems) was effective in a subgroup without sleep problems, whereas sertraline is not effective in reducing depression in any of the four subgroups. This counterintuitive finding requires further investigation.

TABLE 2. Impact of Randomization Arm on Course Over Time of Total CSDD Scores in Each Class Separately[a]

Class 1: Severe Symptoms

	Placebo		Sertraline		Mirtazapine	
	n	CSDD score	n	CSDD score	n	CSDD score
Baseline, mean (SD)	13	22.8 (7.2)	8	19.3 (2.1)	12	19.0 (3.6)
Week 13, mean (SD)	11	11.4 (6.1)	6	9.5 (7.4)	10	10.5 (5.4)
Week 39, mean (SD)	11	11.7 (7.4)	6	13.0 (7.2)	9	14.3 (10.0)
Treatment × time interaction[a]			F (4, 24.2) = 0.540; p = 0.708			

Class 2: Psychological Symptoms

	Placebo		Sertraline		Mirtazapine	
	n	CSDD score	n	CSDD score	n	CSDD score
Baseline, mean (SD)	28	11.5 (3.2)	29	11.6 (3.0)	28	11.3 (2.8)
Week 13, mean (SD)	22	8.2 (4.2)	25	8.5 (4.9)	22	5.3 (3.1)
Week 39, mean (SD)	17	7.3 (3.4)	19	9.2 (5.4)	19	4.8 (4.0)
Treatment × time interaction[a]			F (4, 61.2) = 2.827; p = 0.032			
Mean difference from placebo based on the linear mixed model (SE, 95% CI; t (df); p value)[a]						
13 weeks			47	0.31 (1.13; −1.93 to 2.56; t (df) = 0.28 (68.0); p = 0.783)	44	−2.77 (1.16; −5.09 to −0.46; t (df) = −2.39 (68.2); p = 0.019)
39 weeks			36	1.41 (1.57; −1.73 to 4.56; t (df) = 0.90 (59.2); p = 0.372)	36	−2.97 (1.59; −6.15 to 0.20; t (df) = −1.87 (58.2); p = 0.066)

Class 3: Affective Symptoms

	Placebo		Sertraline		Mirtazapine	
	n	CSDD score	n	CSDD score	n	CSDD score
Baseline, mean (SD)	45	12.4 (3.4)	42	12.0 (2.8)	42	12.1 (2.9)
Week 13, mean (SD)	40	7.0 (3.1)	28	8.7 (4.6)	33	8.5 (5.3)
Week 39, mean (SD)	33	7.2 (5.0)	25	8.2 (5.1)	29	8.5 (5.8)
Treatment × time interaction[a]			F (4, 98.0) = 1.023; p = 0.400			

Class 4: Somatic Symptoms

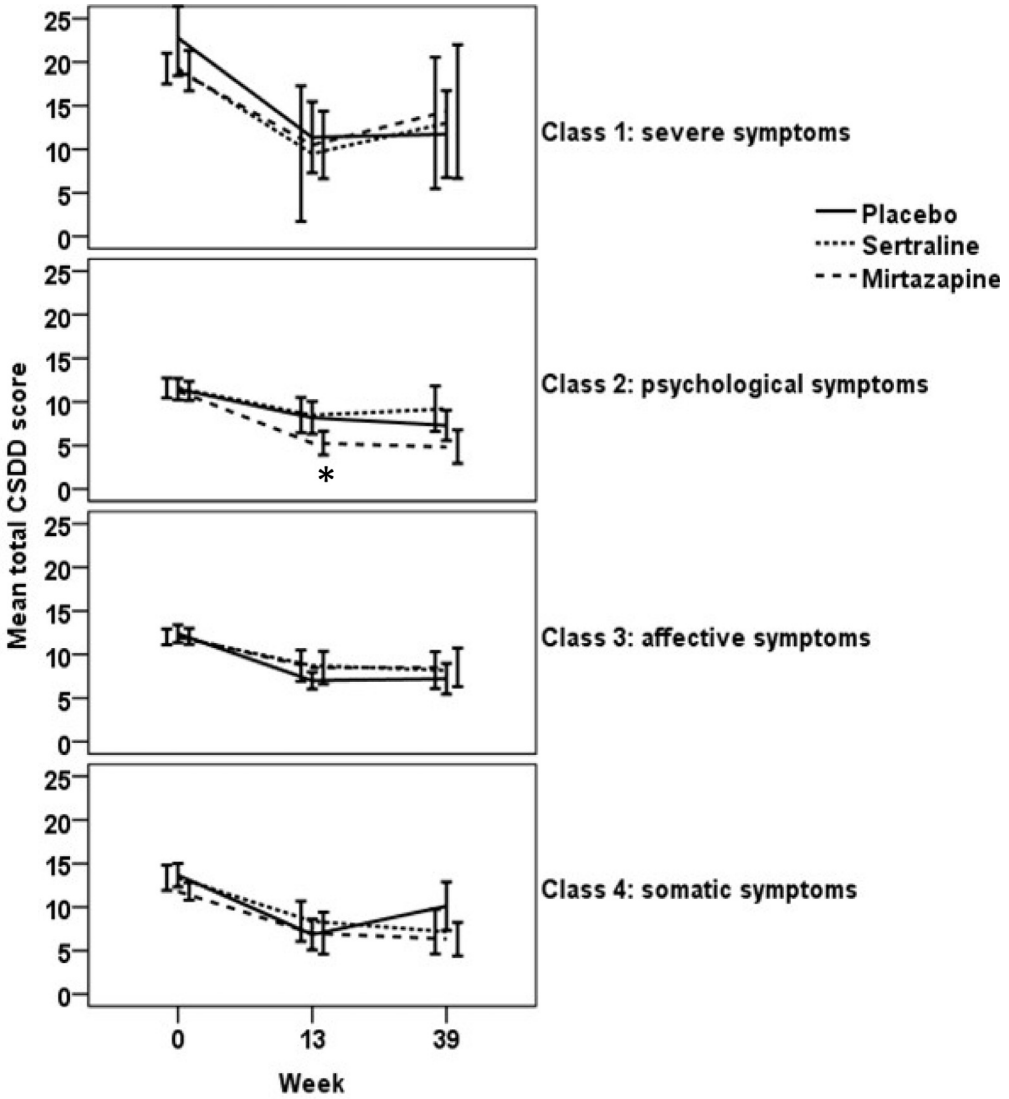
	Placebo		Sertraline		Mirtazapine	
	n	CSDD score	n	CSDD score	n	CSDD score
Baseline, mean (SD)	24	13.7 (3.2)	27	13.4 (3.7)	24	11.8 (2.3)
Week 13, mean (SD)	20	6.9 (3.8)	19	8.4 (4.8)	21	7.0 (5.2)
Week 39, mean (SD)	20	10.1 (5.9)	16	7.2 (4.8)	18	6.3 (3.9)
Treatment × time interaction[a]			F (4, 57.8) = 1.689; p = 0.165			

[a] Estimates of the mean (SD) were based on the final adjusted linear mixed model. Independent variables (and fixed effects) in these models were: time (0, 13, or 39 weeks), randomization arm, the interaction between time × randomization arm, and clinical center where participants were recruited. In case of a statistically significant time × randomization interaction, the lower part of the table shows the mean difference with placebo (with SE; 95% CI, t value, df, and p value). SD: standard deviation; SE: standard error.

Another methodological issue is that patients in all three arms, including the placebo-group, improved considerably. This improvement may be due to artifacts such as regression to the mean, the Hawthorne effect, or the natural course of depression in dementia. This last possibility is less likely because 221 of 326 participants had been depressed for more than 6 months before randomization. Perhaps the greatest contributor to the improvements in depression is the non-drug treatment as usual by the old-age psychiatry services. This treatment as usual is personalized, including a broad range of supportive and problem-solving interventions, and is commonly delivered by a community psychiatric nurse in the patient's own household. Antidepressants may not be effective over and above the effects of this personalized non-drug intervention.

In the context of conflicting conclusions in clinical guidelines,[5,14] clinicians should continue to be cautious in prescribing antidepressants in people with dementia. Surprisingly, in the "severe" depression subgroup, no beneficial effects of sertraline and mirtazapine were found at 13 weeks, with worse (but statistically non-significant) effects at 39 weeks. This is important as general guidelines for treatment of

FIGURE 1. Unadjusted mean CSDD scores by treatment group for each class separately. Class 1: severe; class 2: psychological; class 3: affective; class 4: somatic. Lowest score is best. Error bars show 95% CI. *Difference with placebo: p <0.05.



clinical depression,[33,34] as well as the updated clinical guideline National Institute for Health and Care Excellence 2018 for depression in dementia,[14] have different guidelines according to initial depression severity, and thus, physicians generally rely on the severity of the depression rather than symptom profile when starting drug treatment. However, a recent individual patient data meta-analysis also concluded that antidepressant efficacy does not differ according to initial depression severity.[35]

Strengths and Limitations

This study uses the data from the largest completed double-blind randomized placebo-controlled trial of depression in dementia. Because of the large sample size, we were able to explore antidepressant efficacy in subgroups of depression in dementia. However, these results must also be interpreted with caution. The first and most important limitation of the analyses reported here is that this is a

set of secondary analyses and the sample size for these subgroup analyses is smaller than for the primary outcomes. The relatively small sizes of the subgroups and the number of analyses may have resulted in both lack of power, and positive findings due to chance. Therefore, the results reported should be interpreted cautiously and before making any conclusions, replication of these findings is needed. Second, although data driven, the interpretation of the LCA and the choice of the optimal number of classes has an element of subjectivity. The four-class model was chosen based on the Bootstrap Likelihood Ratio Test and the interpretability of the classes of the four-class model and the small sample sizes of the five- and six-class models. However, the BIC preferred the two-class model. Third, the study included only sertraline and mirtazapine, whereas studies in depressed non-demented populations have found evidence that efficacy on specific symptoms might vary for different antidepressants. Fourth, data on non-drug interventions outside the study protocol were not gathered. There is a possibility that the observed differences might have been influenced by non-drug treatments for depression outside the study protocol; however, the randomization should have assorted these equally across the three intervention groups.

CONCLUSIONS

Because of the exploratory nature of the analyses and the small sample sizes for subgroup analysis, there is the need for caution in interpreting these data. Replication of the potential effects of mirtazapine in the subgroup of those with depression in dementia with "psychological" symptoms would be valuable. These data should not change current clinical practice. Nevertheless, these analyses demonstrate the potential value of stratifying groups of depression in dementia and examining differential effectiveness in subgroups of depression in dementia when studying the efficacy of depression treatment. Future studies should consider complementing clinically derived symptom profiles with empirically derived phenotypes when evaluating the efficacy of other antidepressant or psychological treatments across subgroups.

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SUPPLEMENTARY MATERIALS

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