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Cognitive Behavioral Therapy for Late-Life Depression (CBTlate): Results of a Multicenter, Randomized, Observer-Blinded, Controlled Trial

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Keywords

Late-life depression · Geriatric depression · Cognitive behavioral therapy · Supportive psychotherapy · Randomized controlled trial

Abstract

Introduction: Different psychotherapeutic interventions for late-life depression (LLD) have been proposed, but their evaluation in large, multicenter trials is rare. ***Objective:*** The present study evaluated the efficacy of a specific cognitive behavioral therapy (CBT) for LLD (LLD-CBT) in comparison with a supportive unspecific intervention (SUI), both administered in a specialist psychiatric outpatient setting. ***Methods:*** In this randomized, controlled, parallel group trial, we recruited participants (≥60 years) with moderate to severe depression at 7 trial sites in Germany. Participants were randomly assigned to the LLD-CBT or SUI group. The primary outcome was depression severity at the end of treatment measured by change on the Geriatric Depression Scale (GDS). Secondary outcomes included change in observer-rated depression, anxiety, sleep ratings, and quality of life throughout the treatment phase and at 6-month follow-up. ***Results:*** Between October 1, 2018, and November 11, 2020,

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we randomly assigned 251 patients to either LLD-CBT (n = 126) or SUI (n = 125), of whom 229 provided primary-outcome data. There was no significant between-group difference in the change in GDS scores at the end of treatment (estimated marginal mean difference: −1.01 [95% CI: −2.88 to 0.86]; p = 0.287). Secondary analyses showed significant improvements in several outcomes after 8 weeks and at follow-up in both treatment arms. ***Conclusions:*** Our data suggest that LLD-specific CBT and a supportive unspecific treatment both provide clinical benefit in patients with moderate to severe LLD without evidence for superiority of LLD-CBT.

Introduction

Late-life depression (LLD) can be defined as a depressive episode occurring after the age of 60 years. Meta-analyses observed a prevalence rate of 17.1% of clinically relevant depressive symptoms in this age-group [1]. LLD accounts for 5.7% of years lived with disability among the population over 60 years [2]. It is associated with reduced quality of life (QoL), increased suicide rates, negative impact on several diseases, increased mortality, and increased risk for all-cause dementia [3–5].

LLD is often not recognized or misdiagnosed and insufficiently treated [6, 7]. Compared with depression in early and mid-adulthood, treatment options of LLD are often less effective. Meta-analyses have shown that the number needed to treat for remission by antidepressant medication is around 7 in patients younger than 65 years and increases to 14.4 in adults older than 65 years [8–11]. In addition, intolerability and contraindications of antidepressants increase with age, and higher rates of adverse effects limit their application. A more recent network meta-analysis concluded that there is evidence for the efficacy of pharmacological treatment in LLD, but given the limited data, the findings cannot be considered robust [12]. Compared with pharmacological treatment, psychotherapy is better tolerated and provides potential benefit in LLD [11]. Cognitive behavioral therapy (CBT) is an established and effective type of psychotherapy for depression in younger adults [13]. The application of CBT in LLD is less well studied. The majority of CBT trials in LLD are either of limited sample size, single-center studies, or recruited participants through primary care or as self-referrals, which limits the generalizability to clinical populations with moderate to severe LLD in the psychiatric care setting [14–17]. In the abovementioned recent network meta-analysis on treatments of LLD, which included only trials with patients with operationalized major depressive disorder (MDD) diagnosis, a randomized design and without a high risk of bias, only one single-center 3-arm CBT study with 204 patients in total recruited through primary care was included [12]. This trial showed a significant effect of CBT on symptoms of depression in comparison with two control conditions [18].

A confirmatory trial testing the efficacy of age-specific CBT in a psychiatry-based multicenter setting in patients with moderate to severe LLD is missing. Importantly, CBT protocols for LLD need to be adapted to the specific needs and topics of patients at higher age, which are in part distinct from younger adults, including loss of significant others, retirement, physical impairment, and closeness to end of life among others. In a single-center pilot study, one author (M.H.) investigated the short- and long-term outcomes of a manualized 15-session CBT, specifically designed for patients with LLD (LLD-CBT), in comparison to a manualized supportive unspecific intervention (SUI), delivered in an individual or group setting. Both interventions reduced depressive symptoms significantly over a follow-up period of 1 year, and LLD-specific CBT reduced depressive symptoms more than SUI, specifically in the individual setting [19]. In the present randomized trial, we aimed to confirm the superior efficacy of LLD-CBT in comparison to SUI for moderate to severe LLD in a large sample in a multicenter setting.

Materials and Methods

Study Design and Participants

We recruited 251 patients with LLD at 7 trial sites in Germany, which were either psychiatric university hospitals or psychotherapeutic university centers. Eligible participants were aged ≥60 years, outpatients, and met diagnostic criteria for moderate to severe MDD assessed by trained raters using the validated standard clinical Mini International Neuropsychiatric Interview for DSM-5 (M.I.N.I. Version 7.0.2). We included participants with a Geriatric Depression Scale (GDS) score >10, Quick Inventory of Depressive Symptomatology – Clinician Rating (QIDS-C) score >10, and Mini-Mental Status Test (MMST) score >25. We excluded individuals with bipolar depression, schizophrenia or other psychotic disorders, substance abuse or addiction, and dementia as well as with anxiety disorder or obsessive-compulsive disorder as standalone diagnoses. Acute suicidality or a high likelihood of prospectively regular use of benzodiazepines during the 8-week treatment period was an additional exclusion criterion. Patients with any planned psychotherapeutic treatment outside of the study or planned brain stimulation throughout the 8-week treatment period were excluded. Severe or instable medical conditions clearly impacting on depression or patients with a brain disease with

relevant functional impairment (e.g., aphasia, Parkinson's disease) were excluded. In case of existing pharmacological treatment, the antidepressive medication had to be stable for at least 6 weeks prior to baseline and had to remain stable during the 8-week treatment period. All participants provided written informed consent prior to all study procedures. The study was approved by the Institutional Review Board/Institutional Ethical Committee (IRB/IEC) of the University of Cologne and by all other local IRBs/IECs at the participating sites prior to initiation of the trial. The study protocol has been published previously [20]. The trial is registered at ClinicalTrials.gov (NCT03735576) and DRKS (DRKS00013769).

Randomization and Masking

Subjects were randomly assigned to one of two treatment arms (1:1 randomization) by a designated on-site researcher or trial manager, respectively, using the central 24–7 web-based internet randomization service ALEA, maintained by the Institute of Medical Statistics and Computational Biology (IMSB) at the University of Cologne. Randomization to the treatment arms was performed as stratified block randomization. The allocation sequence was derived from permuted blocks of varying length, in which block size was unknown to the investigators. The randomization was stratified by the trial site to prevent unbalanced allocation of the interventions to sites. The study was a single-blind (observer-blinded) trial. As such, all clinical interviews and outcome assessments were conducted by raters, who were blinded to the treatment arm allocation. The raters were centrally trained, certified, and supervised in the assessment of all outcomes. The sites implemented procedures to maintain rater blinding to the treatment assignment by informing and reminding patients at each visit, not to mention their treatment condition or content to the rater, and by locating the rater and the study therapists as well as documentation at different physical locations. Therapists refrained from any conversation about any aspects of individual treatments with the raters.

Procedures

The sequence of clinical assessments was standardized across all sites using uniform, manualized procedures. The first visit of the study was a screening and baseline (T0) visit, at which informed consent was obtained; the M.I.N.I. interview was conducted to establish the diagnosis of MDD, and the inclusion and exclusion criteria as well as the primary outcome were assessed. In those subjects who passed the screening procedure, the secondary outcomes were obtained. After the baseline assessment, subjects were randomized to either of the two treatment arms. In week 5 after randomization and 50% of the treatment session, the primary and secondary outcomes were assessed (T1). End-of-treatment primary and secondary outcomes were obtained in week 10 (T2). The final follow-up assessment (T3) was performed 6 months after randomization.

The interventions included 8 weeks of manual-based, individual, 15-session, twice weekly, outpatient treatment in each arm of the trial (LLD-CBT, SUI). Both are described in detail in the online supplementary 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000529445) and have been published previously [21]. All therapists were fully licensed in CBT and had several years of clinical experience. All were trained in both interventions and delivered either one according to individual randomization in order to avoid systematic therapist bias. All were obliged to adhere to the respective manuals in each individual therapy session. Adherence was assured by bimonthly continuous central supervision of all therapists provided by M.H. and by supervision by trained local therapy experts. In addition, all therapy sessions were recorded on film. Central assessment of adherence with a structured adherence scale was performed on randomly selected recordings. The assessment of treatment adherence by trained raters is described in the online supplementary 2.

Outcomes

The primary outcome was defined a priori as the change in the GDS score from baseline to end of treatment and was calculated by subtracting the GDS score at baseline from the GDS score at end of treatment. We used the 30-item GDS version (range 0–30, higher scores indicating more severe symptoms), a widely established, self-report measure of depressive symptoms in older subjects, used in clinical trials [16].

Secondary outcome measures included the Quick-Inventory of Depressive Symptomatology Clinician-Rated Version (QIDS-C), a 16-item clinician rating to measure the severity of MDD symptoms according to DSM-IV [22]. In addition, we applied the German translation of a depression-specific patient-reported outcome questionnaire (Patient-Reported Outcome in Major Depressive Disorder [PRO-MDD]) [23]. We assessed anxiety symptoms with the 20-item Geriatric Anxiety Inventory (GAI) as a self-report measure [24]. To assess subjective QoL, the World Health Organization Quality of Life Assessment (WHOQOL-BREF) was used which consists of the following domains: physical and psychological aspects of QoL, social relationships, environmental aspects, and overall QoL. For assessing specific aspects of QoL at higher age, this instrument was complemented by the 24-item add-on module WHOQOL-OLD [25]. In addition, physical and mental health-related QoL were measured with the 36-item Short-Form Health Survey (SF-36) [26]. Sleep disturbances and disruption of circadian rhythms were assessed with the self-report questionnaires Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS), and Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ).

The study protocol (online suppl. 1) included additional assessments, which will be analyzed and presented in subsequent reports. These comprised an extended cognitive assessment at baseline and follow-up, an assessment of the continuous longitudinal course of depressive symptoms over time at follow-up, and a process evaluation of patient satisfaction at the end of treatment [20]. Childhood trauma and personality traits were assessed at baseline to investigate mediator and moderator hypotheses on treatment outcomes. These findings will also be reported later.

Adverse and serious adverse events (AEs/SAEs) were recorded for the entire treatment duration and the 6-month follow-up period and were reported to the project's Data Safety and Monitoring Board (DSMB). SAEs were reported also to each IRB/IEC. We defined an SAE as any medical event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was any other important medical condition that might require medical or surgical intervention to prevent one of the outcomes listed. We also included suicide attempts as an SAE. An AE was defined as any unfavorable and unintended sign, symptom, or disease, whether or not considered to be related to the

treatment. This included worsening of symptoms, occurrence of new symptoms, occurrence of passive suicidal thoughts, active suicidal intentions or plans, problems in the patient-therapist relationship, private problems, occupational problems, or other medical conditions (e.g., influenza, fractures, etc.). We recorded reports of suicidal ideations and their relationship to treatment at every visit. Participants were specifically asked about illnesses and hospital admissions at the visits. After the onset of the SARS-CoV-2 pandemic in spring 2020, all participants were asked about a COVID-19 infection.

Statistical Analysis

The sample size and power calculations have been described previously [20] and are reported in the online supplementary 1. The power calculation was based on the results of the pilot trial [19]. Briefly, the current trial was powered to detect a difference of 2.5 GDS points in the change between baseline and end of treatment between both arms ($d = 0.4$). We calculated that the two-sample t test required 99 subjects per group to detect such a difference with 80% power at a two-sided significance level of $p < 0.05$. Accounting for up to 20% attrition, 248 subjects in total (124 per group) were calculated to be required. The applied mixed model for repeated measures (MMRM) approach with adjustment for baseline variables is likely to increase the statistical power further compared with a two-sample t test. The analyses followed the pre-specified statistical analysis plan (SAP, online suppl. 1). All analyses were performed with SPSS Statistics (IBM Corp., Armonk, NY, USA). Descriptive statistics summarizing all variables and outcome measures at all timepoints are reported by the treatment group and across the total sample. The primary full analysis set is derived from the intention-to-treat (ITT) population (all subjects randomized with a valid baseline assessment and at least one valid follow-up outcome assessment). The primary outcome was evaluated by an MMRM with the fixed effects of the baseline GDS score, therapist, treatment group, visit and the interaction treatment group*visit (ARH1-structured covariance matrix over time) with corresponding marginal means and contrast tests. We calculated a between-group effect size by dividing the difference of the mean change in GDS (end of treatment minus baseline) of the groups by the pooled standard deviation (SD). In addition to the analyses in the statistical analysis plan, we calculated remission (≤10 points on the GDS at end of treatment) and response rates (all remitted patients and patients with a reduction of 50% of the baseline GDS score at the end of treatment) and compared them between groups with Pearson's χ^2 test.

Secondary outcomes, including all other clinical measures as well as the GDS differences at 6-month follow-up, were analyzed along the same lines. In addition, we investigated the change in primary and secondary outcome measures from baseline to week 5, end of treatment, and follow-up for LLD-CBT and SUI groups separately. We calculated effect sizes (Cohen's d) for the LLD-CBT and SUI groups separately by dividing the difference from the GDS scores at end of treatment to baseline by the SD of the baseline GDS score. Subgroup analyses were done by baseline severity of depression (moderate: GDS score <20, severe: GDS score ≥20), trial site, and sex with interaction analysis of sex, site, and depression severity.

Analysis of the set of subjects treated and observed per protocol (PP) defined as all subjects without major protocol violations and at least 9 sessions in one of the interventions and all outcome assessments were analyzed along the same lines as the ITT population. Time-to-event (dropout) distributions of dropouts were summarized by the Kaplan-Meier method and compared by the (stratified) log-rank test. All results are reported uncorrected for multiple comparison. As such, in the primary end point analysis, the difference of the GDS change between both treatment arms in the ITT population is considered confirmatory.

All safety parameters (AE, SAE) were analyzed by subject, treatment group, category, seriousness, severity, and relatedness to treatment. The analyses were performed for the safety population and stratified by treatment group.

Results

Between October 1, 2018, and November 11, 2020, we screened 299 participants for the study and randomly assigned 251 patients to either the LLD-CBT ($n = 126$) or SUI ($n = 125$) group (shown in Fig. 1). Recruitment by site is shown in online supplementary Table S2 in Supplement 2. The ITT population comprised 229 participants (91.2%), including 115 of 126 (91.3%) of the LLD-CBT and 114 of 125 (91.2%) of the SUI group. 213 of 251 participants (84.9%) fulfilled the criteria of the PP population, including 105 of 126 (83.3%) in the LLD-CBT group compared with 108 of 125 (86.4%) in the SUI group. There was no significant difference in dropout rates between groups (online suppl. Table S8–9 in Suppl. 2).

Demographic data for the participants in the ITT population are shown in Table 1. Patient characteristics at baseline were balanced between groups (Table 1). The mean age across both groups was 70.2 years (SD 7.1). Most participants were women and not employed or retired. Fifty two percentage were without spouse. The participants were all outpatients, and all resided independently at home either alone, with their spouse, or other family members (siblings, children). None of the patients lived in a nursing care or assisted living. The mean age at onset of the first depressive episode was 42.6 (median 42 years; IQR 25–59). Seventy six percent of patients had their first depressive episode before 60 years of age. The mean number of lifetime depressive episodes without the current was 4.4 (SD 9.8; range 0–99). The median duration of the current depressive episode was 1.15 years. The mean number of antidepressants taken over lifetime was 1.8 (SD 2.2; range 0–10).

Participants received a mean of 13.3 LLD-CBT sessions (SD 2.8) or 13.6 SUI sessions (SD 2.4) in the ITT population. In the PP population, participants received a mean of 14.1 LLD-CBT sessions (SD 1.6) or 14.0 SUI sessions (SD 1.6). Ratings of the delivered therapy sessions showed very good adherence to therapy manuals in both treatment arms (online suppl. 2).

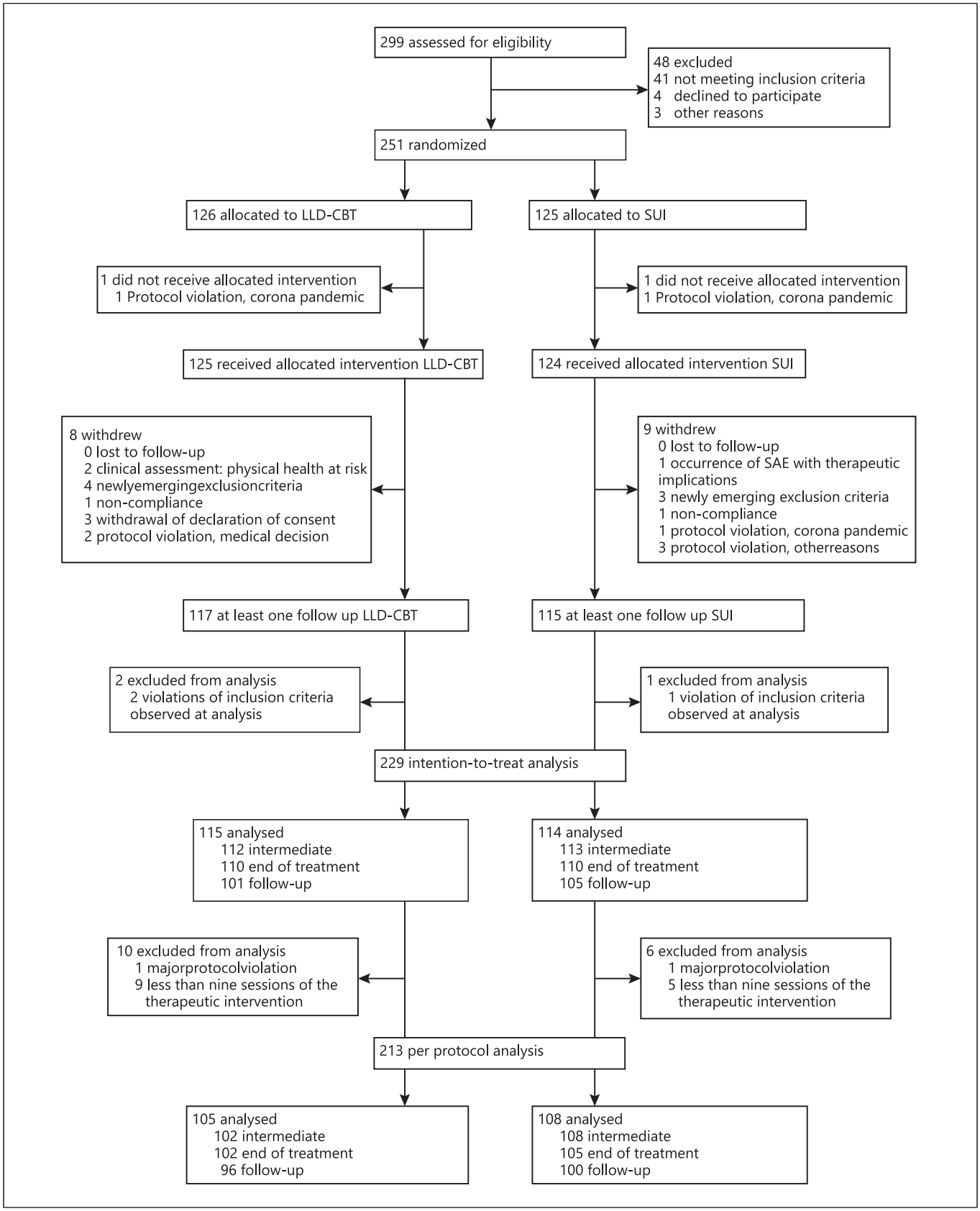

Fig. 1. Trial flowchart. LLD-CBT, cognitive behavioral therapy for late-life depression; SUI, supportive unspecific intervention.

Primary-Outcome Analysis

At baseline, the mean GDS score was 21.0 (SD 4.3) in the LLD-CBT arm and 20.4 (SD 4.2) in the SUI arm. A mean score of 13.5 (SD 7.6) was observed in the LLD-CBT arm and 14.2 (SD 6.9) in the SUI arm at the end of treatment (shown in Fig. 2; Table 2). There was no significant between-group difference in the change in GDS scores from baseline to the end of treatment (estimated marginal mean difference: −1.01 [95% CI: −2.88 to 0.86]; $p = 0.287$). The nonsignificant effect size difference of the two treatment groups was $d = 0.18$ (95% CI: −0.09 to 0.44), favoring the LLD-CBT group.

Additional Analyses of the GDS

Secondary analyses showed a significant reduction in GDS scores at the end of treatment compared to baseline in both groups (estimated marginal mean: −6.80 [95% CI: −8.17 to −5.44] in the LLD-CBT arm and −5.79 [95% CI: −7.18 to −4.40] in the SUI arm). The MMRM revealed a significant main effect for visit with a significant improvement of depressive symptoms over time ($F = 22.238$; $p < 0.001$) in both groups. The effect size estimates for the GDS reduction in single-group, pretest-posttest design was $d = -1.75$ (95% CI: −2.07 to −1.43) for the LLD-CBT arm and $d = -1.47$ (95% CI: −1.79 to −1.16) for the SUI arm. There was a significant between-group difference in the change in GDS scores at week 5 of treatment (estimated marginal mean difference: −1.59 [95% CI: −3.03 to −0.15]; $p = 0.030$) in favor of the LLD-CBT group. Both groups showed a persistent significant reduction in GDS scores 6 months after randomization compared to baseline (estimated marginal mean: −6.11 [95% CI: −7.50 to −4.71] in LLD-CBT and −5.15 [95% CI: −6.55 to −3.75] in SUI). There was no significant between-group difference in the change in GDS scores at follow-up (estimated marginal mean difference: −0.95, [95% CI: −2.85 to 0.94; $p = 0.323$).

There was no significant difference in response rates between the LLD-CBT and SUI groups at the end of treatment (44 of 109 [40.4%] vs. 40 of 110 [36.4%]; $\chi^2 = 0.371$; $p = 0.542$) or at follow-up (36 of 101 [35.6%] vs. 30 of 105 [28.6%]; $\chi^2 = 1.183$; $p = 0.277$). There was also no significant group difference in remission rates at the end of treatment (39 of 109 [35.8%] in LLD-CBT vs. 35 of 110 [31.8%] in SUI; $\chi^2 = 0.384$; $p = 0.535$) or at follow-up (35 of 101 [34.7%] in LLD-CBT vs. 26 of 105 [24.8%] in SUI; $\chi^2 = 2.417$; $p = 0.120$).

Pre-specified analyses for the severity of depressive symptoms showed a significant main effect of baseline severity of depression ($F = 25.653$; $p < 0.001$) with higher baseline GDS scores being associated with greater reduction in both arms. Both participants with severe and with moderate depression had a significant reduction of the GDS score at the end of treatment. The estimated marginal mean for participants with severe depression was −8.54 (95% CI: −10.34 to −6.73) in the LLD-CBT and −7.62 (95% CI: −9.58 to −5.66) in the SUI group at the end of treatment. The estimated marginal mean for participants with moderate depression was −3.65 (95% CI: −5.78 to −1.53) in the LLD-CBT and −3.23 (95% CI: −5.13 to −1.32) in the SUI group at the end of treatment. The sex-specific analysis revealed a reduction in GDS scores from baseline to end of treatment for female and male participants in both treatment arms with no significant sex-specific difference between the treatment groups at any timepoint. For the LLD-CBT group, the estimated marginal mean difference in the change in GDS scores at the end of treatment between female and male participants was 2.15 (95% CI: −0.83 to 5.13; $p = 0.156$) and for the SUI group, −0.06 (95% CI: −2.75 to 2.62; $p = 0.963$). Effects of the trial site were not significant. All analyses were repeated for the PP population, which confirmed the findings of the ITT population.

Secondary Outcomes

The QIDS-C score, which describes the clinician-rated depression, did not significantly differ between groups at any timepoint ($p = 0.114$, $p = 0.716$, and $p = 0.297$, respectively; Table 2). The nonsignificant effect size comparison of the two treatment groups was $d = 0.029$ (95% CI: −0.235 to 0.294). There was a significant reduction of the QIDS-C scores compared to baseline in both groups at all timepoints (Table 2; online suppl. Table S1 in Suppl. 2). The treatment effect size estimates in single-group, pretest-posttest design were $d = -2.94$ (95% CI: −3.41 to −2.49) for the LLD-CBT arm and $d = -2.72$ (95% CI: −3.15 to −2.29) for the SUI arm at the end of treatment. The PP analysis revealed no other finding, with the exception of a significantly greater reduction of QIDS-C scores in LLD-CBT compared to SUI at week 5 (estimated marginal mean difference: −1.06, [95% CI: −2.11 to −0.02; $p = 0.045$]).

Detailed comparisons of all other secondary endpoints are listed in Table 2 and online supplementary Table S1 in Supplement 2. The analyses for the instruments PRO-MDD, GAI, WHOQOL-BREF, WHOQOL-OLD, SF-36, ISI, ESS, and RBDSQ did not show significant differences between the groups at the end of treatment. Overall, there was a significant reduction in the scores of the PRO-MDD, GAI, and the ISI from baseline to all other timepoints in both treatment groups. Additionally, there

Table 1. Baseline demographic and clinical characteristics of the ITT population.

	LLD-CBT (n = 115)	SUI (n = 114)	Overall (n = 229)
Age, years			
Mean (SD)	69.6 (7.3)	70.7 (6.9)	70.2 (7.1)
Median (IQR; range)	68 (64–74; 60–92)	70 (65–77; 60–87)	69 (64–75; 60–92)
Gender, *n* (%)			
Female	83 (72)	68 (60)	151 (66)
Male	32 (28)	46 (40)	78 (34)
Relationship status, *n* (%)			
Single, separated, or widowed	59 (51)	60 (53)	119 (52)
Married or with partner	56 (49)	54 (47)	110 (48)
Living alone, *n* (%)	51 (44)	49 (43)	100 (44)
Years of education			
Mean (SD)	14.7 (2.7)	14.8 (3.7)	14.8 (3.2)
Median (IQR; range)	15 (12–17; 8–20)	15 (12–17; 8–36)	15 (12–17; 8–36)
Employment, *n* (%)			
Currently employed	25 (22)	26 (23)	51 (22)
Unemployed or retired	90 (78)	88 (77)	178 (78)
Age at the first depressive episode			
Mean (SD)	43.4 (21.4)	41.8 (19.7)	42.6 (20.6)
Median (IQR; range)	45 (23–61; 4–85)	40 (25–58; 5–82)	42 (25–59; 4–85)
First depressive episode <60 years of age, *n* (%)			
Yes	83 (72.8)	85 (79.4)	168 (76)
No	31 (27.2)	22 (20.6)	53 (24)
Number of depressive episodes*			
Mean (SD)	3.9 (8.3)	5.0 (11.2)	4.4 (9.8)
Median (IQR; range)	2 (1–3; 0–50)	2 (1–5; 0–99)	2 (1–4; 0–99)
Duration of the current depressive episode (weeks, patient-reported)			
Mean (SD)	181.7 (421.0)	135.6 (226.1)	158.8(338.3)
Median (IQR; range)	64 (30–150; 3–3922)	52 (24.5–132.5; 2–1560)	60 (26–150; 2–3922)
Inpatient psychiatric treatment (lifetime), *n* (%)	44 (38)	46 (40)	90 (39)
Outpatient psychiatric treatment (lifetime), *n* (%)	80 (70)	80 (70)	160 (70)
Outpatient psychotherapy (lifetime), *n* (%)	79 (69)	75 (66)	154 (67)
Antidepressant medication in the past, *n* (%)			
Yes	78 (69.6)	70 (66)	148 (67.9)
No	34 (30.4)	36 (34)	70 (32.1)
Number of antidepressants in the past			
Mean (SD)	1.7 (2.2)	1.8 (2.2)	1.8 (2.2)
Median (IQR, range)	1 (0–2; 0–10)	1 (0–3; 0–10)	1 (0–2; 0–10)
Suicide attempts (lifetime), *n* (%)	6 (5)	16 (14)	22 (10)
Current outpatient psychiatric treatment, *n* (%)	51 (44)	52 (46)	103 (45)
Current use of psychopharmacological drugs (regular; patient-reported), *n* (%)	51 (44)	51 (45)	102 (45)
GDS, 30-item version score (possible range: 0–30)	21.0 (4.3)	20.4 (4.2)	20.7 (4.3)

Data are *n* (%), unless otherwise specified. IQR, interquartile range; LLD-CBT, cognitive behavioral therapy for late-life depression; SD, standard deviation; SUI, supportive unspecific intervention. *Exclusive of the current episode.

was a significant reduction in the score of the RBDSQ from baseline to end of treatment in the LLD-CBT group and from baseline to follow-up in both treatment groups. Further, there was an increase in the scores of the subjective QoL measurements (WHOQOL-BREF, WHOQOL-OLD, and SF-36) from baseline to all other timepoints in both treatment groups, with the exception of the physical health scale of the SF-36 (Table 2). All analyses were repeated for the PP population and confirmed these findings (online suppl. Table S1 in Suppl. 2). In the PP population, we additionally found a significantly greater reduction of GAI scores in LLD-CBT

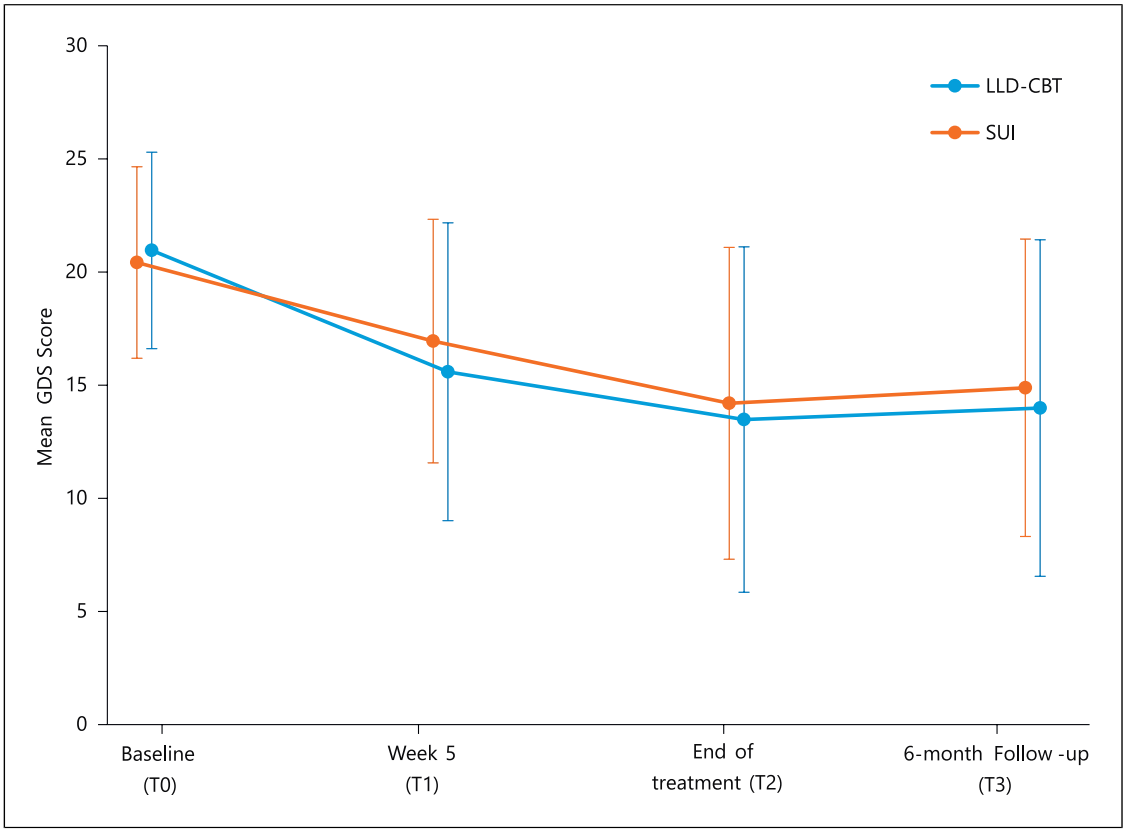

Fig. 2. Primary outcome (Geriatric Depression Scale, GDS) over the course of the study. The two treatment arms did not differ at the end of treatment. Error bars show the SD. LLD-CBT, cognitive behavioral therapy for late-life depression; SUI, supportive unspecific intervention.

compared to SUI at week 5 (estimated marginal mean difference: −1.06 [95% CI: −2.11 to −0.02; p = 0.046]). Further, at week 5, there was a significant difference in the psychological aspects of the QoL assessed with the WHOQOL-BREF between LLD-CBT and SUI, with a significantly greater increase in the LLD-CBT group (p = 0.03). The assessment of specific aspects of QoL at higher age with the WHOQOL-OLD revealed a significantly greater improvement in LLD-CBT compared to SUI in the subscales autonomy and social participation at week 5 (p = 0.025; p = 0.034) and intimacy and sensory abilities at follow-up (p = 0.003; p = 0.033). In the SF-36 mental health QoL measurement, there was a significant difference between LLD-CBT and SUI at the 6-month follow-up (estimated marginal mean difference: 4.77 [95% CI: 1.22–8.33]; p = 0.009) with LLD-CBT, showing a significantly higher mental health subscale score compared to SUI.

Safety

During the entire 6-month follow-up period, 24 SAEs were reported in the safety analysis set of 244 participants. Seven SAEs were reported in the LLD-CBT group (n = 122) and 17 in the SUI group (n = 122). Inpatient hospitalization was the most common SAE (LLD-CBT: 5; SUI: 15). In total, 205 AEs were reported (LLD-CBT: 113; SUI: 92). Medical AEs were the most common type (LLD-CBT: n = 49; SUI: n = 42). All SAEs and AEs are shown in online supplementary Table S3–7 in Supplement 2. No AE or SAE was considered to be related to LLD-CBT; 2 AEs were reported to be related to the SUI (worsening of symptoms and occurrence of problems in the patient-therapist relationship). No SAEs were considered to be related to SUI. There was no significant difference in the frequency of AE or SAE between the groups. No suicides or suicide attempts occurred during the study. No known SARS-CoV 2 infections occurred during the study.

Table 2. Comparison of outcome measures between the LLD-CBT and SUI groups (ITT population)

	LLD-CBT		SUI		Estimated marginal mean difference (95% CI)	*p* value	Cohen *d*
	No.	score, mean (SD)	No.	score, mean (SD)			
Primary outcome							
GDS score (possible range: 0–30)							
Baseline	115	21.0 (4.3)	114	20.4 (4.2)			
Intermediate (week 5)	112	15.6 (6.6)	113	16.9 (5.4)	−1.59 (−3.03 to −0.15)	0.030*	
End of treatment (week 10)	**109**	**13.5 (7.6)**	**110**	**14.2 (6.9)**	**−1.01 (−2.88 to 0.86)**	**0.287**	**0.18**
Follow-up (month 6)	101	14.0 (7.4)	105	14.9 (6.6)	−0.95 (−2.85 to 0.94)	0.323	
Secondary outcomes							
QIDS-C score (possible range: 0–27)							
Baseline	115	14.3 (2.3)	114	14.4 (2.5)			
Intermediate (week 5)	112	8.8 (4.4)	113	9.5 (4.2)	−0.82 (−1.83 to 0.196)	0.114	
End of treatment (week 10)	110	7.5 (4.9)	110	7.6 (4.7)	−0.23 (−1.45 to 0.996)	0.716	0.029
Follow-up (month 6)	101	7.5 (5.4)	104	8.3 (4.6)	−0.73 (−2.11 to 0.65)	0.297	
GAI score (possible range: 0–20)							
Baseline	113	11.2 (4.3)	111	11.9 (4.2)			
Intermediate (week 5)	109	9.0 (5.2)	111	10.3 (4.6)	−0.81 (−1.84 to 0.23)	0.128	
End of treatment (week 10)	106	8.2 (5.4)	106	9.0 (5.2)	−0.12 (−1.26 to 1.03)	0.839	
Follow-up (month 6)	97	7.4 (5.2)	99	8.6 (5.2)	−0.72 (−1.99 to 0.54)	0.261	
PRO-MDD score (possible range: 0–350)							
Baseline	113	142.1 (52.5)	112	139.3 (51.0)			
Intermediate (week 5)	108	115.4 (62.1)	111	121.8 (53.0)	−6.76(−18.86 to 5.34)	0.272	
End of treatment (week 10)	106	103.4 (64.0)	106	105.3 (55.6)	−1.95 (−16.41 to 12.52)	0.791	
Follow-up (month 6)	97	103.1 (63.5)	99	111.6 (55.9)	−9.28 (−25.08 to 6.51)	0.248	
WHOQOL-BREF total score (possible range: 0–100)							
Baseline	112	43.0 (18.2)	111	39.6 (16.8)			
Intermediate (week 5)	107	56.4 (20.2)	111	57.4 (16.5)	−3.57 (−7.96 to 0.82)	0.110	
End of treatment (week 10)	104	57.7 (20.5)	105	57.7 (19.6)	−1.91 (−6.1 to 3.096)	0.453	
Follow-up (month 6)	96	59.0 (20.3)	97	59.8 (17.1)	−2.61 (−7.53 to 2.31)	0.297	
WHOQOL-OLD total score (possible range: 0–100)							
Baseline	112	55.3 (11.5)	112	53.7 (11.7)			
Intermediate (week 5)	104	57.7 (13.5)	111	55.2 (12.2)	0.95 (−1.02 to 2.93)	0.343	
End of treatment (week 10)	106	60.5 (13.6)	106	57.5 (11.9)	1.65 (−0.797 to 4.09)	0.185	
Follow-up (month 6)	94	60.5 (13.6)	98	58.7 (12.1)	1.574 (−1.06 to 4.21)	0.240	
SF-36 physical health score (possible range: 0–100)							
Baseline	111	44.4 (11.1)	110	43.1 (10.7)			
Intermediate (week 5)	106	44.3 (10.2)	109	44.0 (10.6)	−0.98 (−2.82 to 0.86)	0.297	
End of treatment (week 10)	105	44.3 (11.5)	103	43.6 (11.2)	−0.44 (−2.53 to 1.64)	0.675	
Follow-up (month 6)	93	43.5 (10.1)	97	45.5 (10.5)	−2.31 (−4.16 to −0.46)	0.015*	
SF-36 mental health score (possible range: 0–100)							
Baseline	111	32.0 (10.7)	110	31.9 (8.8)			
Intermediate (week 5)	106	38.4 (13.3)	109	35.8 (9.6)	2.05 (−0.64 to 4.73)	0.134	
End of treatment (week 10)	105	41.0 (13.1)	103	39.1 (12.0)	1.84 (−1.32 to 4.99)	0.252	
Follow-up (month 6)	93	42.2 (13.1)	97	38.2 (11.6)	4.09 (0.65–7.54)	0.020*	
ISI score (possible range: 0–28)							
Baseline	112	13.5 (6.1)	110	14.1 (6.0)			
Intermediate (week 5)	108	11.9 (7.2)	111	12.4 (5.9)	0.222 (−0.948 to 1.392)	0.709	
End of treatment (week 10)	106	10.9 (6.7)	106	10.8 (6.3)	0.949 (−0.285 to 2.183)	0.131	
Follow-up (month 6)	97	10.3 (6.8)	98	10.8 (6.4)	0.177 (−1.232 to 1.585)	0.805	
ESS score (possible range: 0–24)							
Baseline	112	8.8 (4.5)	111	7.9 (4.7)			
Intermediate (week 5)	107	8.7 (4.8)	110	8.1 (4.7)	0.032 (−0.835 to 0.900)	0.941	
End of treatment (week 10)	106	8.0 (4.7)	106	7.0 (4.4)	0.328 (−0.536 to 1.192)	0.455	
Follow-up (month 6)	96	8.2 (4.8)	98	6.9 (3.9)	0.506 (−0.419 to 1.431)	0.282	

Table 2 (continued)

	LLD-CBT		SUI		Estimated marginal mean difference (95% CI)	*p* value	Cohen *d*
	No.	score, mean (SD)	No.	score, mean (SD)			
RBDSQ score (possible range: 0–13)							
Baseline	113	4.0 (2.1)	113	4.5 (2.7)			
Intermediate (week 5)	108	4.0 (2.5)	110	4.5 (2.7)	−0.218 (−0.701 to 0.264)	0.374	
End of treatment (week 10)	106	3.6 (2.5)	106	4.1 (2.8)	−0.155 (−0.655 to 0.344)	0.541	
Follow-up (month 6)	95	3.6 (2.5)	97	3.9 (2.7)	0.145 (−0.357 to 0.647)	0.568	

Bold letters: primary endpoint analysis. CBT, cognitive behavioral therapy; ESS, Epworth Sleepiness Scale; GAI, Geriatric Anxiety Inventory; GDS, Geriatric Depression Scale; ISI, Insomnia Severity Index; PRO-MDD, Patient-Reported Outcome in Major Depressive Disorder; QIDS-C, Quick Inventory of Depressive Symptomatology – Clinician Rating; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire; SF-36, 36-item Short-Form Health Survey; SUI, supportive unspecific intervention; WHOQOL-BREF, World Health Organization Quality of Life Assessment; WHOQOL-OLD, WHO Quality Of Life OLD. *Statistically significant secondary endpoint effects, uncorrected for multiple comparisons.

Discussion

In this multicenter, randomized controlled trial on the efficacy of an LLD-adapted CBT in a psychiatric outpatient setting in patients over the age of 60 years with moderate to severe depression, we did not find evidence that LLD-CBT leads to greater reduction of depressive symptoms compared with a supportive unspecific intervention over 8 weeks of treatment. The observed difference of $d = 0.18$ in the ITT population ($d = 0.21$ in the PP population) did not reach significance. As such, we could not confirm the hypothesis that LLD-specific CBT is superior to a supportive unspecific intervention of the same quantity. This may imply that the observed large effects on symptoms of depression in both treatment arms are mainly attributable to nonspecific effects of psychotherapy. This finding is in accordance with studies indicating the efficacy of nonspecific psychological interventions in depression compared to a waiting-list control group [27, 28]. These effects are attributed to generic factors of psychotherapy which include, but are not limited to, the positive therapeutic alliance between the patients and therapist, patients' levels of expectancy regarding the process and outcome of treatment, empathy, verbalizing emotions, as well as general support of the patient [29, 30]. The SUI intervention in this study was a manual-based therapeutic intervention including these elements. Therapists acted patient-centered; were empathic listeners; and followed patients, verbalized their expressed feelings, showed positive regard, and created a warm, understanding therapy atmosphere. Since all therapy sessions in both interventions were recorded on video and the ratings of the delivered therapy sessions showed very good adherence to therapy manuals in both treatment arms, the SUI effects are attributed to common factors of psychotherapy. Our data are in disagreement with a meta-analysis across different psychotherapeutic interventions in LLD, which reported a much larger standardized mean difference of 0.39 for the comparison of specific versus supportive control interventions [15]. The inherent limitation of the data underlying this and other meta-analyses of psychotherapeutic interventions in LLD, however, is the limited quality of the included studies with regard to sample size, control interventions, blinding, single-centeredness, and other factors.

In our secondary analyses, we showed that both interventions significantly reduced depressive symptoms. We detected a mean difference of 7.5 points in the GDS scores after 8 weeks of treatment in LLD-CBT and 6.2 GDS points in SUI compared to baseline, corresponding to a pre-post effect size of $d = 1.75$ in LLD-CBT and $d = 1.47$ in SUI. We consider these effects large and clinically meaningful. The meta-analytical estimate of a waiting-list control group in LLD has been reported as a standardized mean difference of 0.11, which is substantially smaller than the effect we observed in the two intervention arms in our study, indicating strong effects in comparison with no treatment [15]. Of note, the pre-post effect sizes on depressive symptoms in each group where even larger on the clinician-rated secondary outcome QIDS-C (LLD-CBT: $d = 2.94$; SUI: $d = 2.72$). The effects in both groups were sustained over the follow-up period of 6 months.

In our secondary outcomes, we also did not observe group differences. However, both interventions

significantly reduced sleep disturbances (ISI, RBDSQ) and anxiety symptoms (GAI). They also increased subjective QoL (WHOQOL-BREF, WHOQOL-OLD) and mental health related QoL (SF-36).

In addition, LLD-CBT was superior to SUI in reducing the GDS and GAI scores as well as in increasing psychological aspects of subjective QoL after 5 weeks and in increasing mental health related QoL (SF-36) after 6 months. Of note, the results from the secondary analyses are exploratory and should therefore be interpreted with caution. They are not confirmatory and only hypothesis-generating.

A recent two-center randomized controlled trial in LLD with a similar sample size as our study showed non-inferiority of a novel community social worker delivered intervention ("engage") in comparison with problem-solving therapy over 9 weeks [31]. The effect on the reduction of symptoms of depression was similar to our effect size. Importantly, that study also did not observe a between group effect.

We aimed at rigorously assessing the specific efficacy of CBT in LLD. As such, the main strength is the multicenter study design with a sufficiently large number of patients, randomization, adherence-to-manual monitoring, rater-blinding, and posttreatment follow-up.

We focused on patients with moderate to severe depression and recruited these patients from a clinical psychiatric setting. As such, we believe that our sample is distinct from that of many other studies as many of previous CBT trials in LLD recruited participants through primary care or as self-referrals. In addition, we recruited a large sample size which makes our study more robust against type II error. Finally, the active control condition was of identical intensity and delivered by the same therapist as the LLD-CBT intervention.

A limitation of the study is the lack of a less intense control condition or waiting list to test the effect directly against the untreated natural course of the disorder, including pharmacological treatment in all arms. This design decision was taken to ensure a significantly large number of patients in both treatment arms to address the primary research question of the study, namely, the specific efficacy of CBT in LLD. However, symptom changes of waiting-list LLD control groups have been reported in the literature, and the effects we observed in both treatment arms of our study are substantially larger [15, 32–35]. A further limitation is that treatment integrity was not assessed throughout all rated videos by multiple raters using a measure previously shown to be reliable and valid as well as in this sample. In addition to the main analysis, the influence of moderating and mediating variables on the outcome measures and the treatment response, particularly age subgroups, age of depression onset (early-onset vs. late-onset depression), childhood trauma, personality traits, neuropsychological deficits, previous pharmacotherapy, and comorbidities will be investigated and reported separately.

In summary, our data do not confirm superiority of LLD-CBT over an unspecific supportive intervention in the treatment of moderate to severe LLD, when provided in identical quantity by trained psychotherapists. However, we did observe high adherence and robust effects on depressive symptoms of both interventions, which sustained at follow-up. Our results have significant clinical and public health implications. Depression is a prevalent mental disorder at higher age, and LLD patients are often insufficiently treated. Since a supportive intervention is more straightforward to learn and teach than CBT, more mental health providers with less expensive training might offer supportive therapy to a larger number of patients who might otherwise continue to suffer without effective care. This strongly argues for a wider implementation of individual psychotherapy in patients at higher age with moderate to severe depression and for further research on the effective components of psychological interventions in LLD.

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Statement of Ethics

The study protocol was reviewed and approved by the Institutional Review Board/Institutional Ethical Committee (IRB/IEC) of the University of Cologne (Project No. 18-129) and by all other local IRB/IEC at the participating sites prior to initiation of the trial. All participants provided written informed consent.

Conflict of Interest Statement

Frank Jessen is a member of the executive board of the German Psychiatric Association (DGPPN), the European Alzheimer's

Disease Consortium (EADC), and the German Memory Clinic Network (DNG). He received fees for advice and presentations from AbbVie, AC Immune, Biogen, Boehringer, Danone/Nutricia, Eisai, GE Healthcare, Green Valley, Grifols, Hummingbird, Janssen, Lilly, MSD, OM Pharma, Oxford PharmaGenesis, Roche, and Vifor. Katharina Domschke is a member of the executive board of the German Psychiatric Association (DGPPN) and the German Society of Biological Psychiatry. She serves as Chair of the Anxiety Disorders Research Network (ADRN) of the European College of Neuropsychopharmacology (ECNP) and is a member of the Steering Committee Neurosciences, Janssen Inc. Lutz Frölich received fees for consultancy and lectures from Avanir, Axon Neuroscience, Biogen, Charité Berlin, Eisai, Forschungszentrum Jülich, Grifols, Hummingbird, Medscape, Medical Tribune, MerckSharpe & Dohme, Neurimmune, Neuroscios, Noselab, NovoNordisk, Pharmatropix, Roche, Schwabe, TauRX, and Vivoryon. Oliver Peters received fees for consultancy and lectures from Biogen, Eisai, Grifols, Medscape, Noselab, NovoNordisk, and Roche. All the other authors have no conflicts of interest to declare. The authors declare that they have no competing interests with regard to the content of the manuscript.

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Author Contributions

F.S.D. coordinated the study at all stages and drafted the manuscript. F.J. and M.H. formulated the research question, the conception and design of the study, obtained the funding, and guided the study at all stages. M.He. defined the statistical methods. W.M. and M.He. performed the statistical analyses. M.H. developed the interventions and oversaw the training and supervision of therapists and raters. F.J., M.H., E.S., S.R.-H., L.F., O.P., and M.W. were the principal investigators at the trial sites. B.B., K.D., and M.Lu. coordinated and supervised the trial at the study sites Bonn, Freiburg, and Leipzig. S.B., M.E., M.Lo., L.P., J.P., S.S., and A.-J.S. conducted the research and investigation process, specifically performing data collection at the study sites Cologne, Freiburg, Leipzig, Berlin, and Mannheim. All the authors were involved in the conduction of the trial and the interpretation of the data. All critically reviewed and revised the manuscript and approved the final version. The corresponding author had access to all study data and had final responsibility for the decision to submit for publication.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethics restrictions but available from the corresponding author upon reasonable request with individual permission from local institutions ethics board. Researchers who provide a methodologically sound proposal should direct these to forugh.salimi-dafsari@uk-koeln.de, and data requestors will need to sign a data access agreement with the study sponsor (University of Cologne, Germany).

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