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Efficacy of hypnotherapy compared to cognitive-behavioural therapy for mild-to-moderate depression: study protocol of a randomised-controlled rater-blind trial (WIKI-D)

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ABSTRACT

Introduction Despite a substantial number of studies providing evidence for the efficacy of psychological treatment for mild-to-moderate depression, maximally only 50% of participants respond to treatment, even when using gold-standard treatments such as cognitive-behavioural therapy (CBT) and interpersonal therapy. New approaches such as the 'third wave' psychotherapies have provided promising results; however, studies concerning the comparison with evidence-based treatments are lacking. This study aims to compare the efficacy of clinical hypnotherapy (HT) with gold-standard psychotherapy (CBT) in the treatment of mild-to-moderate major depressive episodes.

Methods and analysis The present study comprises a monocentric, two-armed, randomised-controlled, rater-blind (non-inferiority) clinical trial. A total of 160 participants with mild-to-moderate major depression episode will be randomly assigned to either CBT or HT involving 20 sessions of psychotherapy over a period of 24 weeks. We predict that the average improvement in the Montgomery-Åsberg Depression Rating Scale score will not be inferior in HT compared with CBT (non-inferiority hypothesis). Further outcome parameters will include the number of participants responding to treatment following the completion of treatment and 1 year after. Additionally, quality of life, treatment expectations and hypnotic susceptibility before and after end of treatment will be assessed.

Ethics and dissemination The study protocol and the documents for the informed consent have been approved by the Ethics Committee of the University Hospital Tuebingen (061/2015B02). The results of this trial will be submitted for publication in peer-reviewed journals, and will be presented at national and international conferences.

Trial registration number NCT02375308; Pre-results.

Strengths and limitations of this study

- This is the first clinical trial following the Good Clinical Practice guidelines concerning hypnotherapy for depression.
- The external risk-adapted monitoring, external data management and biometry, as well as the assessment of safety due to (serious) adverse events will further enhance the quality of the trial.
- The therapists and patients will not be blind to the treatment condition in the current trial; however, the raters of the follow-up assessments will be blind.

INTRODUCTION

The national S3 guideline and the international guidelines for the treatment of unipolar depression[1–3] recommend psychotherapy alternatively with psychopharmacological treatment for mild-to-moderate major depressive episodes (MDEs). Monotherapy with cognitive-behavioural therapy (CBT), as well as interpersonal therapy (IPT), are the most evident treatments. For mild and moderate forms of major depressive disorder (MDD), psychotherapy is as effective as pharmacotherapy and even shows a higher long-term efficacy, especially for the prevention of relapses.[4] For chronic major depression with a duration of 2 years or longer, as well as for severe unipolar episodes, long-term psychotherapy is needed and yet the evidence concerning psychotherapy is ambiguous.[3] Regarding the years lived with disability (YLD) as assessed by WHO, mental disorders are the first cause for chronic conditions in the population of Europe. In Europe, unipolar depressive disorder is the first and leading reason for chronic condition, leading alone 11% of all YLD.[5] The response rates to CBT and IPT even for mild-to-moderate depressive episodes, however, only achieve approximately 50%.[6] Thus, improvements in the efficacy of treatment for unipolar disorders are greatly needed. This could be achieved by modification of the existing therapies

or by an increase in the variety of treatments. Until, interventions of the so-called 'third wave' of CBT such as schema therapy,[7 8] emotion-focused therapy[9] and cognitive behavioural analysis system of psychotherapy (CBASP)[10] have received increasing attention. Furthermore, some therapies influenced by East Asian culture such as mindfulness-based cognitive therapy and acceptance and commitment therapy are becoming more and more popular.[11 12] Other new interventions are regarded as a synthesis of psychodynamic and CBT-oriented techniques with special consideration of early life experiences (ie, CBASP respectively schema therapy). Evidence for the third wave of CBT is growing, while at the same time trials comparing third wave interventions with the gold-standard CBT or IPT are lacking.[13]

Beyond the therapies mentioned, hypnotherapy (HT) could provide a promising add-on effect to these treatment methods. Clinical HT according to Milton H. Erickson is understood as a resource-oriented approach which aims to enhance self-efficacy and to support the patient in regard to his/her individual problem-solving strategies.[14] In addition to formal trance induction, techniques such as the usage of the symptoms and resources of the client, indirect techniques as the use of metaphors or via the representative technique (eg, using an animal or landscape or another 'agent' that best represents the current problem), or those working with time perception, also play important roles in HT.[14] Thus far, few randomised-controlled trials on the efficacy of HT, especially for the treatment of depression, have been conducted.[15–17] Additionally, 'cognitive HT' as described in a previous study for patients with depression[15] was also investigated among patients with anxiety disorders.[18] Research on the efficacy of HT in addition to CBT confirms additive effects of HT.[19] However, further support concerning the efficacy of HT compared with CBT especially for the treatment of depression is missing.

Objectives

The present study aims to be the first randomised-controlled trial to evaluate the efficacy of HT compared with an evidence-based gold-standard treatment (ie, CBT) for mild-to-moderate MDE. According to the actual treatment guidelines, CBT is recommended with the highest evidence of successful outcomes.[1–3]

The following primary hypothesis will be tested:

1. Regarding reduction of the depressive symptoms, HT will not be inferior to CBT after the end of treatment (mean percentage symptom reduction in the clinician-administered rating Montgomery-Åsberg Depression Rating Scale (MADRS)).

Additionally, the following secondary target parameters will be examined exploratively:

2. A non-superiority of one of both interventions related to a further symptom reduction in the MADRS, but also in the Quick Inventory of Depressive Symptoms—Clinician Rating ($QIDS_{C16}$) and the Patient Health Questionnaire—Depression Scale (PHQ-9) over the follow-up period occurring up to 12 months after end of treatment.
3. The response rate of patients in both treatment conditions at the end of treatment and in the follow-up period will be analysed (assessed via the clinical results: MADRS, $QIDS_{C16}$, response defined as symptom reduction ≥50%).
4. The rate of remission (number of weeks) and of patients with relapses in the 12 months following therapy in both treatment conditions will be analysed (assessed via LIFE (Longitudinal Interval Follow-up Evaluation for Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5))).
5. Variables predicting the treatment response will be analysed. The following variables will be regarded as potential predictors for a response:
   - Sociodemographic variables: gender, age, family status, further hypnotic susceptibility, expectations concerning treatment, perceived self-efficacy, behavioural activation, working alliance between patient and therapist, early response in the first 6 weeks of treatment.
   - Disorder-related variables: number of previous episodes, severity of actual episode, global functional level at inclusion in the study, comorbidities.

METHODS AND ANALYSIS

Study design

The clinical trial will be based on a 4×2 mixed factors design with the factors Time (four time intervals: prior to (t1) and immediately after treatment (t2) as well as 6 (t3) and 12 months (t4) after treatment for the follow-up period) and Treatment condition (CBT vs HT). Half of the participants will be randomly assigned to either HT or CBT.

Sample

Patients with MDD with an actual mild-to-moderate episode according to the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5)[20] will be included in the study (assessed via Structured Clinical Interview for DSM-IV Axis I (SCID-I)[21] adapted for DSM-5).

Patients will be recruited starting in 2015 via the depression outpatient clinic of the University Hospital Tuebingen in the Department of Psychiatry and Psychotherapy and via a network of referring institutions (licensed psychiatrists, psychotherapists, university outpatient clinics, institutes for psychotherapy training, self-help groups, general practitioners, psychiatric hospitals) from the region Tuebingen, Reutlingen, Rottenburg and if applicable, Stuttgart, via flyers, newspaper advertisements, and university and university hospital mailing lists. Interested individuals will be informed about the study in written form and will undergo a personal interview at the study centre

by one of the trained and authorised study coordinators. Following written consent, interested individuals will be invited for participation in the study after assessment of the following inclusion and exclusion criteria:

Inclusion criteria

- Written informed consent.
- Patient fulfils criteria for a mild-to-moderate MDE according to DSM-5.
- 18–70 years of age.
- Sufficient knowledge of the German language in order to participate in the study.
- Sufficient availability to participate in weekly therapy sessions.
- In cases of existing antidepressive medication: stable medication since 3 months without planned changes during the duration of therapy.

Exclusion criteria

- Lifetime diagnosis of a bipolar disorder or psychotic disorder.
- Diagnosis of chronic MDD (duration ≥2 years).
- Severe MDE according to SCID-I respectively MADRS ≥35 or $QIDS_{C16}$ ≥16.
- Remission of actual episode since 4 weeks or longer.
- Depression with psychotic characteristics according to SCID-I.
- Acute suicidality (intended action, concrete plans or intermittent pronounced suicidal ideation).
- Severe cognitive impairments (in cases of suspicion evaluation via Mini-Mental StateTest (MMST) <26, will be conducted).
- Other severe mental disorders to be treated: dominant panic disorder, severe personality disorder of borderline type with self-injury, active alcohol or drug dependence, actual post-traumatic stress disorder, anorexia nervosa via SCID-I.
- Somatic disorder impeding participation in regular psychotherapy sessions.
- Outpatient psychotherapy during the last 12 months.

Sample size and power analysis

The primary target size is defined as the percentage reduction of the depressive symptoms (MADRS) between baseline and the end of treatment. The following assumptions are made on the basis of the available data: an assumed improvement in the MADRS of 50% (SD of 32.9 points), on the basis of the results for the efficacy of CBT, see Luty *et al*[6] (p500) and half SD (16.4) as the non-inferiority range. A CI of 95% using a randomisation proportion of 1:1 and an alpha level of 5% will be used. Under these conditions, a one-sided t-test applied to a sample size of n=70 in each group will have 80% statistical power for refusal of the null hypothesis that HT is inferior to CBT.

Assuming a maximal drop-out rate of 12.5%, a total of 160 patients with current mild-to-moderate MDE should be employed to reach at least a number of 140 assessable patients.

The sample size definition was established using nQuery 7.0.

Intervention

The two single outpatient treatments include 20 sessions at 50 min each during a period of 20 weeks (maximum of 24 weeks).

The treatment is based on the respective manuals of both therapy methods. The manual for CBT, entitled 'activating cognitive depression therapy (ACDT)', delineates already well-established CBT approaches.[22] The manual for the HT is based on established materials[23] and is named 'hypnotherapeutic depression therapy (HDT)'.

Overall, four therapists with adequate qualification (education in behavioural therapy or HT and at least 3 years of professional experience) each in ACDT and HDT will be trained (1–2 days) related to the treatment manuals. Each therapist (four therapists per treatment condition) will treat 20 patients within the scope of the study. The therapy sessions will be recorded when agreement of the patient is attained. Therapists' adherence to the manual will be enhanced by regular supervisions on a monthly basis. Adherence to the manual will be tested by a therapist that is not involved in the study procedure. Thus, randomly chosen, digitally recorded sessions will be evaluated regarding treatment adherence based on a list of the relevant techniques of the given treatment manual. Additionally, for each session, therapists will be required to document which elements of the manual for ACDT or HDT were conducted.

Activating cognitive depression therapy

The ACDT consists of techniques already well established and well examined in depression research such as psychoeducation, behavioural activation, cognitive restructuring techniques, problem-solving skills and interpersonal skills. In this treatment condition, homework will be assigned, exercises will be performed and daily routine structure will be reviewed with the overall goal to reduce depressive symptoms and to build up skills which enable individuals to cope with their disorder independently. Additional elements will also be optionally applied, such as by addressing ruminative thoughts or sleeping problems, and practising progressive muscle relaxation.

Hypnotherapeutic depression therapy

The modules of the HDT promote hypnotic activation and reinforcement of one's own resources, the use of relevant positive and negative experiences from the biography and the development of positive solution imagery. Furthermore, formal trance induction, utilisation techniques, indirect techniques such as the use of metaphors or the representative technique, or work with time progression will be used. Additional elements will be applied as needed, such as by addressing ruminative

Table 1 Assessments

Variables	t1: Baseline assessment	Treatment period (24 weeks)	t2: end of treatment 6 months	Follow-up t3 (12 months)	Follow-up t4 (18 months)
Clinician-administered assessments					
SCID-I	X	–	–	–	–
SCID-II	X	–	–	–	–
MADRS	X	–	X	X	X
QIDS	X	–	X	X	X
LIFE	–	–	X	X	X
Self-report measures					
Sociodemographic data	X	–	–	–	–
ADP-IV	X	–	–	–	–
PHQ-9	X	X Weekly	X	X	X
WHOQOL-BREF	X	–	X	–	–
WHODAS	X	–	X	–	–
RSQ	X	–	X	–	–
BADS	X	–	X	–	–
GSES	X	–	X	–	–
Expectations regarding treatment/ contentment with treatment	X	–	X	–	–
HGSHS	X	–	X	–	–
WAI-P	–	X*		–	–
WAI-T	–	X*	–	–	–
Documentation during treatment					
Documentation concerning techniques applied by therapists	–	Weekly	–	–	–

*Only applied in session 6.
ADP-IV, Assessment of DSM-IV Personality Disorders Questionnaire; BADS, Behavioural Activation for Depression Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition; GSES, General Self-Efficacy Scale; HGSHS, Harvard Group Scale of Hypnotic Susceptibility; LIFE, Longitudinal Interval Follow-Up Evaluation; MADRS, Montgomery-Åsberg Depression Scale; PHQ-9, Patient Health Questionnaire—Depression Scale; QIDS, Quick Inventory of Depressive Symptomatology; RSQ, Response Styles Questionnaire; SCID-I,II, Structured Clinical Interview for DSM-IV Axis I,II; WAI-P, Working Alliance Inventory—Patient Perspective; WAI-T, Working Alliance Inventory—Therapist Perspective; WHODAS, WHO Disability Assessment Schedule; WHOQOL-BREF, WHO Quality of Life Instruments—BREF.

thoughts and sleeping problems. The therapy can be adjusted according to the individual needs of the patient.

Assessment

For an overview of the evaluations for each assessment time point, see table 1.

Primary endpoint

Montgomery-Åsberg Depression Rating Scale

As the primary endpoint of the study, the manifestation of the depressive symptoms will be assessed via the clinician-rating MADRS[24] at t1, t2, t3 and t4.

Secondary endpoints

Quick Inventory of Depressive Symptoms—Clinician Rating

$QIDS_{C16}$[25] for the assessment of the depressive symptoms at t1, t2, t3 and t4.

Patient Health Questionnaire—Depression Scale

Manifestation of depressive symptoms will be assessed using the self-report PHQ-9[26] at t1, t2, t3 and t4 and weekly (maximum of 24 weeks) during the therapy period.

Longitudinal Interval Follow-Up Evaluation for DSM-IV

The time intervals, duration of remission and possible relapses after the treatment, as well as the follow-up intervals will be assessed via the LIFE interview[27] to t2, t3 and t4, each over a period of 6 months retrospectively. Additionally, the LIFE will assess whether and which alternative treatments have been used in the meantime (eg, inpatient treatment, medication).

WHO Quality of Life

WHO Quality of Life Instruments (WHOQOL-BREF)[28] will assess patients' quality of life concerning physical

health, psychological health, social relationships and environment with 26 items at t1 and t2.

WHO Disability Assessment Schedule

WHO Disability Assessment Schedule (WHODAS)[29] will measure the global functional level with 12 items at t1 and t2.

Response Styles Questionnaire

Response Styles Questionnaire (RSQ)[30 31] for the assessment of coping and rumination at t1 and t2.

Behavioural Activation for Depression Scale

Behavioural Activation for Depression Scale (BADS)[32] for the assessment of behavioural activation at t1 and t2.

General Self-Efficacy Scale

General Self-Efficacy Scale (GSE)[33] will measure self-efficacy using 10 items at t1 and t2.

Therapy expectations

Questions to specific *therapy expectations* at t1 and to *contentment* at t2 will be included.

Harvard Group Scale of Hypnotic Susceptibility

Presently the Harvard Group Scale of Hypnotic Susceptibility (HGSHS)[34] is the most common scale for the assessment of suggestibility. A German validation is available including a standardised audio recording, which can be presented to each participant. The HGSHS will be applied at t1 and t2.

Working Alliance Inventory—Short and Revised Form

Once in treatment during week 6, there will be assessment of the therapeutic alliance between the therapist and the patient from both perspectives, resulting in a therapist and a patient version. The assessment of the Working Alliance Inventory (WAI)[35] early in therapy was chosen because this is a better predictor for therapy outcome.[36 37]

Study procedure

Following written informed consent, an initial test for depressive symptoms with the PHQ-9, a screening for personality disorders and the assessment of sociodemographic statements will be carried out via questionnaires. The baseline assessment diagnostics will then be performed (clinical interviews and questionnaires). This includes extensive diagnostics for the final examination of the inclusion and exclusion criteria (especially the current MDE and the actual severity of depression) by trained diagnosticians (baseline, t1, for an overview, see figure 1 and table 1). The SCID-I,[21] adapted for DSM-5, will be applied for the examination of inclusion and exclusion criteria and for the assessment of possible comorbid disorders. The diagnostics of personality disorders with SCID-II[38] will be only applied for related indications via the Assessment of DSM-IV Personality Disorders for screening of personality disorders.[39] In the case of suspected cognitive impairment/dementia, the MMST will be applied[40] in which a MMST score of 25 or below will lead to exclusion.

If the first treatment session will be scheduled more than 3 weeks after the date of the baseline assessment, the depressive symptoms will be re-assessed via MADRS and QIDS.

A computerised random algorithm using nQuery 7.0 will be used to generate the random allocation of the participants to one of the two study groups: group 1: HDT and group 2: CBT. A randomisation procedure will be established by electronic interaction between the study centre and the data centre. The diagnosticians responsible for conducting the outcome assessments at the follow-ups will be blind to the patient's treatment. Both interventions will have the same number and duration of sessions. In all conditions, 20 50-minute outpatient sessions will be performed during a maximum period of 24 weeks. Furthermore, single sessions can maximally be combined to four double sessions. The interventions differ especially concerning the application of different CBT techniques (eg, behaviour activation, cognitive restructuring, establishing social competence) or HT techniques (eg, time progression, working with trance and metaphors, representative technique, reframing). After the end of therapy (t2), and 6 (t3) and 12 months (t4) later, patients will be evaluated in follow-up assessments concerning their symptoms by blind diagnosticians. To ensure the completion of the follow-up assessments, participants will receive reminder emails and up to three phone calls or a postal letter. After the follow-up at t4, participation in the study will be concluded for patients; see figure 1.

Patients who withdraw their participation from the study will be classified as discontinued. The patient will decide whether or not already assessed data may be included in the evaluation.

Treatment participation will be considered as completed per protocol (PP), if the patient will have attended at least 80% of sessions (≥16 of the 20 planned sessions). For the implementation of the 20 sessions, a maximum of 24 weeks (6 months) will be provided. This period can be exceeded up to 4 weeks in cases of impending loss of patients (those achieving less than 80% participation). Possible intermissions due to hospitalisation or for other reasons will be recorded as protocol violations. If a patient starts another inpatient, day-care or outpatient psychotherapeutic treatment, or if an inpatient crisis intervention takes longer than 14 days, the study therapy will be discontinued. The patient will then be considered as a therapy dropout, but will undergo follow-up evaluation on a regular basis. For all randomised patients, all planned follow-up intervals should be carried out (intention to treat (ITT)), regardless of whether or not the treatment was concluded according to the protocol. Study therapists are not permitted to maintain contact with the study patients during the follow-up period of 12 months after the end of therapy.

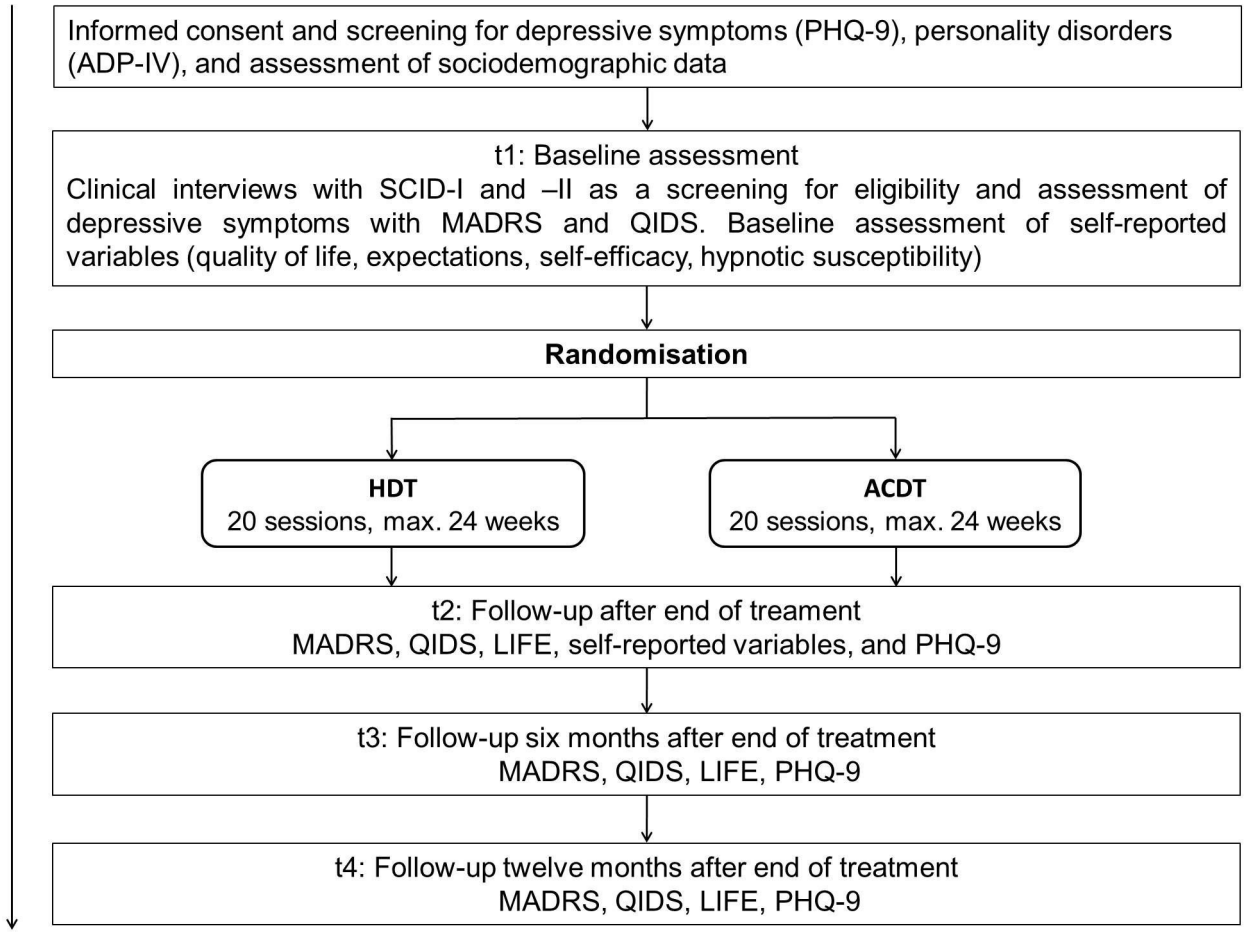

Figure 1 Study flow chart. ACDT, activating cognitive depression therapy; ADP-IV, Assessment of DSM-IV Personality Disorders Questionnaire; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition; HDT, hypnotherapeutic depression therapy; LIFE, Longitudinal Interval Follow-Up Evaluation; MADRS, Montgomery-Åsberg Depression Scale; PHQ-9, Patient Health Questionnaire—Depression Scale; QIDS, Quick Inventory of Depressive Symptomatology; SCID-I,II, Structured Clinical Interview for DSM-IV Axis I,II.

Statistical analysis

Analysis of primary endpoint

The primary endpoint of the study will be the comparison of HDT and ACDT regarding the mean percentage modification of symptoms (MADRS) between baseline at t1 and after the end of therapy (t2). The mean modification (%) will be estimated for both treatment groups using a 95% CI.

Definition of study population for the analysis

A modified ITT analysis will be applied.

The PP population will be a partial quantity of the ITT. Patients with one of the following protocol violations will be excluded:

- Randomised assignment despite violation of the inclusion and exclusion criteria.
- Error in the assignment to a randomised therapy group.
- Usage of another psychotherapy according to the patient's report.
- Negative compliance (participation in less than 16 sessions).
- Lacking follow-up participation (absence at the last follow-up session after 12 months).
- Missing data concerning depressive symptoms (MADRS) after the end of therapy (t2).

Statistical evaluation will be carried out after conclusion of the data assessment at t4 (data base conclusion) for the last randomly assigned patient.

The following hypotheses will be tested at a one-site significance level of 5%:

H_0: μACDT−μHDT≥16.4%

H_1: μHDT−μACDT<16.4%

μ stands for the mean percentage change of MADRS between the baseline score (t1) and the score at the end of therapy (t2) for each therapy group.

1. The primary hypothesis will be calculated by estimating the difference of the mean percentage change scores of both therapy groups using a one-sided 95% CI. HDT will be regarded as non-inferior compared with ACDT if the range of the CI is smaller than the allowed non-inferiority level of 16.4%. The range of 16.4% for non-inferiority will be employed for the available data.

The primary analysis will be performed according to PP population, which statistically represents the conservative approach for the analysis of non-inferiority. An additional analysis based on the ITT population will serve as the sensitivity analysis in order to estimate the robustness of the primary analysis.

All secondary outcomes will be evaluated using exploratory data analysis and compared in regard to the PP and the ITT population.

2. The endpoint of the study will be the comparison of HDT and ACDT regarding the mean percentage modification of symptoms as assessed with the MADRS, but also with the $QIDS_{C16}$ and the PHQ-9 between baseline t1 and after the end of therapy (t2), as well as to the follow-up intervals at 6 (t3) and 12 months (t4) after the end of treatment. The mean modification (%) will be estimated for both treatment groups (including 95% CIs).
3. Response will be defined as a symptom reduction at a rate of ≥50% in the MADRS/$QIDS_{C16}$. Incidence of response from baseline (t1) and the end of treatment (t2) as well as follow-up intervals (t3, t4) will be compared between both treatment conditions using Cochran-Mantel-Haenszel tests. The relative risk (HDT vs ACDT) including a 95% CI will be estimated.
4. The median rates of weeks in remission in the period of 12 months after the end of therapy for both treatment conditions will be analysed using a 95% CI and comparison with a Mann-Whitney U test. Concerning the rate of patients with relapses, both treatment conditions will be compared using a Cochran-Mantel-Haenszel test. The relative risk (HDT vs ACDT) will be estimated using a 95% CI.
5. A logistic regression analysis with the dummy variable response (1/0) as the outcome and the potential predictors at t1 (WHODAS, WHOQOL, RSQ, BADS, HGSHS, GSE, WAI, age, gender, number of previous episodes, early response in the first 6 weeks, severity of actual episode, global functional level at inclusion in the study and comorbidities) will be calculated based on significant correlations between the potential predictor and the outcome.

External data management and biometry

Data will be entered in a database (www.koordobas.de). All available data will be entered twice in the database and be checked for errors, consistency and completeness before being submitted to the statistical analyses.

Statistical analysis will be performed with SAS V.9.2 and SPSS V.22.

The data monitoring committee is independent from the sponsor and competing interests, from participant recruitment and conduction of the trial. The committee is involved in the establishment of the sample size and power calculation, the management of the database and the statistical analysis of the primary endpoint.

Methods for the assessment of safety

In order to guarantee the participants' safety, adverse events (AEs) and serious adverse events (SAEs) will be assessed in the study according to Good Clinical Practice (GCP) regulations.

In addition to commonly used SAEs, such as death and hospitalisation, expressed suicidal intentions and a 2 week or longer deterioration of the symptoms, will be encoded in the study as SAEs.

The occurrence of new symptoms of another mental disorder, or changes in the social or professional environment, will be defined as AEs.

In cases of crises or suicidality, the principal investigator (PI) will be informed and, if necessary, the appropriate steps will be discussed together with the patient and therapist (eg, hospitalisation). In case of multiple cases of suicidality in one of the intervention groups or completed suicides, the study will be considered to be stopped based on the reported SAEs.

Monitoring

To establish quality assurance, an external risk-adapted monitoring of the study will be conducted by the Centre for Clinical Trials in Tuebingen. The monitoring will include control of the informed consent documents and of the documentation associated with the inclusion and exclusion criteria and the primary endpoints (MADRS t1 and t2). Additionally, compliance to the implementation of the study protocol will be monitored and the documentation related to the AEs and SAEs will be controlled. In total, three visits are planned: at the beginning, in the middle and after completion of the trial. This will be independent from investigators and the sponsor.

Quality assurance

All procedures related to the implementation, evaluation and documentation of this study which are described in the present study protocol will be used to ensure that all persons involved in the study act in compliance with the GCP and the current Declaration of Helsinki. The study protocol has already been approved by the local ethics committee of the University Hospital Tuebingen (061/2015BO1).

Ethics approval

The implementation, evaluation and documentation of the study will be carried out in accordance with the GCP and the Declaration of Helsinki.

The study protocol and the documents for the informed consent were approved by the Ethics Committee of the University Hospital Tuebingen (061/2015B02).

Availability of data and material

The datasets analysed, the informed consent form and other material used for the current study will be available via request to the corresponding author.

The database will be closed after all data are entered and the last patient has completed or left the trial. The

PI, as well as the study centre, will have access to the final dataset only after the database has been closed.

All participants will be obliged to accept that the data assessment, data retention and data evaluation of the data assessed within the scope of the study will be retained in an encoded form using pseudonyms. Additionally, the participants obliged to agree to the storage of the data for 10 years in the archive of the University Hospital.

Dissemination

The results of this trial will be submitted for publication in peer-reviewed journals, and will be presented at national and international conferences. The trial is registered within ClinicalTrials.gov with trial registration number: NCT02375308. For details concerning the registration according to WHO Trial Registration Data Set, see table 2.

Roles and responsibilities

The coordinating centre is represented by the affiliation of the first and the last authors. These authors are responsible for the supervision and realisation of the study, in addition to maintaining communication with the sponsor, the external data monitoring committee and the external monitoring committee, as well as with dissemination of the results. Data will be obtained and collected at the study centre. The data management team is independent of the data acquisition. For the data monitoring committee, see the External data management and biometry section.

DISCUSSION

The present randomised-controlled study will compare the efficacy of HT with the standard treatment, CBT, in

Table 2 Registration details (according to WHO Data Set)

1	Primary registry and trial identifying number: Trial registration number: NCT02375308 (ClinicalTrials.gov)
2	Date of registration in primary registry: 24 February 2015
3	Secondary identifying numbers: not applicable
4	Source of monetary or material support: Milton Erickson Gesellschaft, Waisenhausstraße 55, 80637 Munich, Germany
5	Primary sponsor: Professor Anil Batra; Department of Psychiatry and Psychotherapy, University Hospital of Tuebingen, Calwer Str. 14, D-72076 Tuebingen, Germany; anil.batra@med.uni-tuebingen.de
6	Secondary sponsor(s): not applicable
7	Contact for public queries: see 5.
8	Contact for scientific queries: see 5.
9	Public title: Psychotherapy for depression (WIKI-D)
10	Scientific title: Efficacy of HT compared with cognitive-behavioural therapy for mild-to-moderate depression: study protocol of a randomised-controlled rater-blind trial (WIKI-D)
11	Countries of recruitment: Germany
12	Health condition(s) or problem(s) studied: Mild-to-moderate major depressive episode (MDE)
13	Intervention(s): 1. Cognitive behavioural therapy—activating cognitive depression therapy 2. Hypnotherapeutic depression therapy
14	Key inclusion and exclusion criteria: Inclusion criteria: ► Mild-to-moderate depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition ► 18–70 years of age Exclusion criteria: ► Lifetime diagnosis of a bipolar disorder or psychotic disorder ► Diagnosis of chronic major depressive disorder (duration ≥2 years) or severe MDE ► Other severe mental disorders to be treated
15	Study type: Randomised-controlled rater-blind trial
16	Date of first enrolment: 15 April 2015
17	Target sample size: n=160
18	Recruitment status: still recruiting
19	Primary outcome(s): Depressive symptoms assessed via the Montgomery-Åsberg Depression Rating Scale between baseline and the end of treatment
20	Key secondary outcomes: Response rate, rate of remission, predictors for response (sociodemographic and disorder-related variables)

individuals with mild-to-moderate depressive episodes. It is one of the first studies which will systematically examine HT as monotherapy for the treatment of depression in an evidence-based study design. The techniques of HT have already been integrated in other therapy approaches for quite some time; however, thus far scientific evidence for the efficacy has been lacking. For this reason, this study aims to contribute further evidence regarding the therapeutic efficacy of HT. Furthermore, within the scope of third wave psychotherapy, certain efforts have been made during recent years to extend and improve existing therapy concepts. Techniques such as acceptance-based approaches and working with patient's resources have already been described during the early developments related to the HT.

A special strength of the present study is the highly methodological quality of the study protocol. Beyond the systematic assessment and documentation of the AEs and SAEs, an external database and independent monitoring of the data quality will be applied for this study which is in accord to the GCP regulations of pharmacotherapy research.

Additionally, further variables such as expectations about the therapy and various clinical and sociodemographic factors will be assessed within the scope of the present study, which allow for further analyses such as subgroup analyses and an analysis of the responders. Furthermore, the LIFE interview enables for each patient evaluation of the manifestation of depressive symptoms (eg, depression-free weeks), the time of remission and relapses during the entire study period. The assessment of weekly depressive symptoms scores with the PHQ-9 during the treatment period will allow for closer examination of the early change patterns and their correlation with the treatment outcome.

Overall, the present study will make a contribution to the significance of HT in the treatment of depression. Additionally, this study can also provide results about the extent to which highly methodological standards can be implemented in studies of psychotherapy.

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