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The MiPsy Trial

Mindfulness-based behavioural therapy (MIBT) versus psychodynamic therapy for patients with major depressive disorder in psychotherapeutic day treatment. A randomised clinical pilot trial.

Abstract

Background

According to the WHO, major depressive disorder is the second largest healthcare problem worldwide in terms of disability caused by illness. It afflicts an estimated 17% of individuals during their lifetimes at tremendous costs. A number of depressive patients are treated with antidepressant medication. The efficacy of antidepressant medication has been studied in a number of systematic reviews, and in recent years some of these reviews have shown that the efficacy is questionable for many patients. So are there other effective treatments for this serious illness?

Cognitive- and psychodynamic therapies are probably both significantly more effective for depression than no treatment, but only limited comparisons have been made between the two interventions. A Cochrane review shows that cognitive therapy has a preventive effect against recurrent depression, and that this effect may surpass the preventive effect of antidepressant medication. Mindfulness training may be an effective technique in preventing relapse in patients who have had at least 3 previous depressive episodes. But efficacy in treating currently depressed patients has not been studied.

Objective

To perform a randomised clinical trial with blinded assessment of efficacy variables in order to study the effects of mindfulness based behavioral therapy (cognitive therapy and mindfulness) versus psychodynamic therapy in depressive patients.

Methods

A randomised clinical trial of 84 consecutive patients diagnosed with major depressive disorder, referred to the day clinic, Roskilde psychiatric services. The patients will be randomised to one of two interventions:

1. MIBT (mindfulness-based behavioural therapy)
2. PT (psychodynamic therapy)

Outcome measures

Primary: 17 item Hamilton rating scale for depression (score at the end of 18 weeks of day- treatment)

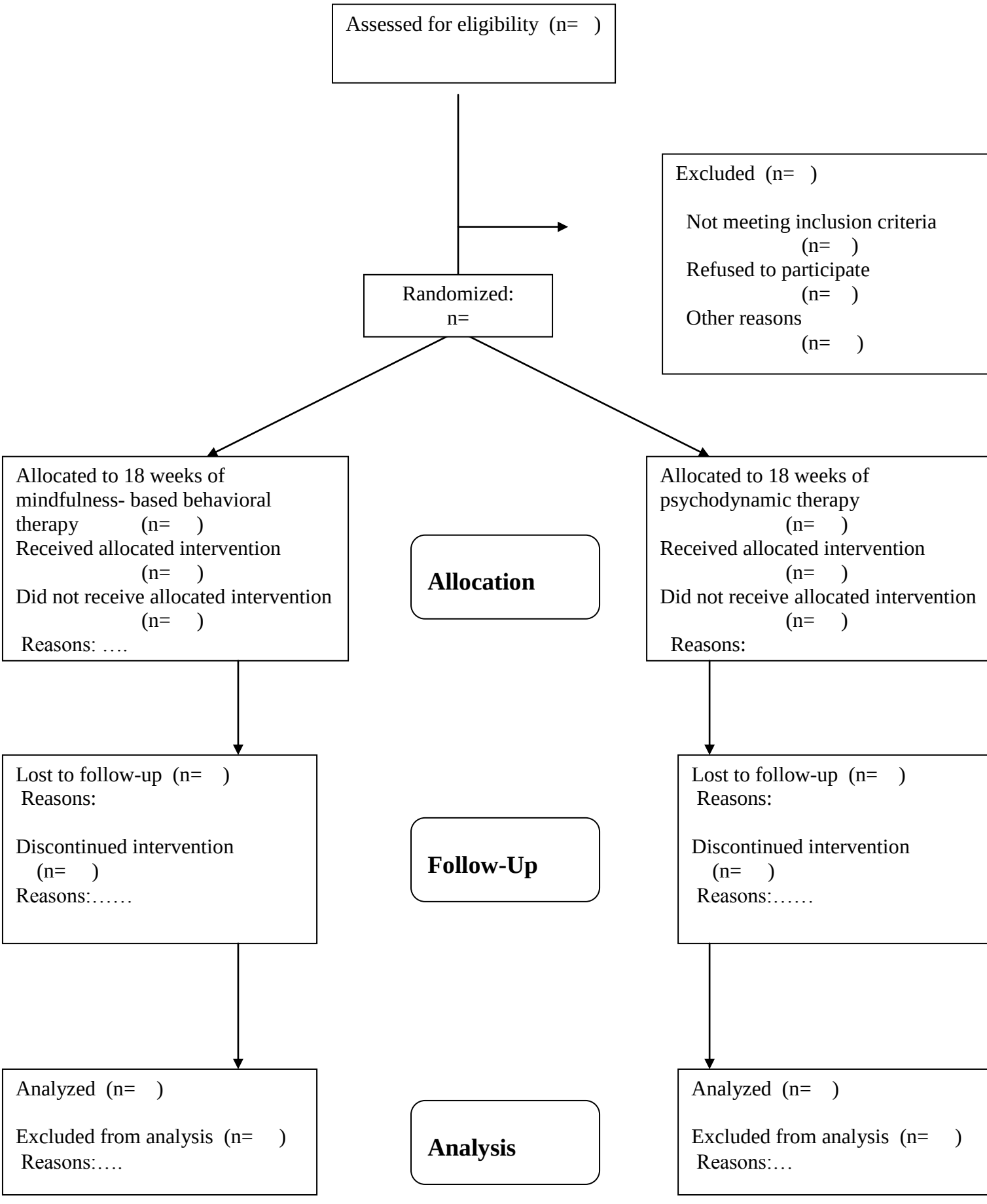
Secondary: SCL-90-R (GSI score at the end of 18 weeks of day- treatment) and the proportion of patients who achieve remission (Hamilton score < 8).

Tertiary: BDI II (Beck Depression Inventory), WHO 5 (The World Health Organization-Five Well-Being Index 1999)

Time schedule

Launch of first randomisation: 8/2 2010. End of trial: 1/3 2012

Consort flowchart for Mipsy trial



Organisation

The project is a cooperation between the psychiatric research unit, Region Sjælland and the day clinic for treatment of non-psychotic disorders (Roskilde Psychiatry), the unit management from Roskilde Psychiatry, and the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 3344, Rigshospitalet, Copenhagen.

Time schedule

Launch of first randomisation: 8/2 2010. End of trial: 1/3 2012

Authors

Principal clinical investigator, unit consultant, Ph. D. student Janus Jakobsen.
Head of research, research lecturer, Erik Simonsen .
Consultant, lecturer Per Sørensen Ph.D.
Lead consultant, Ulf Søgaard.
Lead consultant at the day clinic, Kirsten Aaskov Larsen
Head of Department, associate professor, Dr Christian Gluud

Principal investigator :
Unit Consultant, Janus Jakobsen
Specialist in general medicine
Day clinic for specialised treatment of non-psychotic disorders
Region Sjælland, Roskilde Psychiatry, Roskilde District

Abbreviations

BDI = Beck Depression Inventory

CTU = Copenhagen Trial Unit

DAPP- BQ = Dimensional Assessment of Personality Pathology– Basic Questionnaire

SCID = The Structured Clinical Interview for DSM-IV Disorders

DBT = Dialectic behavioural therapy

FALB = The four basic mindfulness skills : Focusing, Acceptance, Labelling techniques, Body awareness)

FDA = Food and Drug Administration

GSI = Global Severity Index

Ham D17 =17 item Hamilton rating scale for depression

MAR = Missing at random

MBCT = Mindfulness-based cognitive therapy

MD = Medical doctor

MNAR = Missing not at random

MIA = Multiple imputation program

MIBT = Mindfulness- based behavioural therapy (cognitive therapy and mindfulness)

PT = Psychodynamic therapy

PLoS = Public Library of Science

TAU = Treatment as usual

SCL 90 = Symptom Checklist 90

SD = Standard deviation

SPSS = Statistical Package for the Social Sciences

WHO 5 = The World Health Organization-Five Well-Being Index

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Background

Depression

According to the WHO, major depressive disorder is the second largest healthcare problem worldwide in terms of disability caused by illness (1). It afflicts an estimated 17% of individuals during their lifetimes at tremendous cost to society (2;3). About 20% of depressions still persist after two years and roughly a third of all depressive disorders take a chronic course (4;5). Compared to other medical disorders, depressive illness causes the most significant deterioration in individual life quality (6). Approximately 15% of depressive patients will commit suicide over a 10-20 year period (7).

Antidepressant medication

A number of depressive patients are treated with antidepressant medication, the efficacy of which has been studied in a number of meta-analyses and systematic reviews. In their 1996 meta-analysis, Joffe et al. found medical antidepressant treatment to be significantly more effective than placebo (8). Similarly, in 2004, Moncrieff et al. in their Cochrane review found that antidepressant medication was significantly more effective than 'active' placebo (9). 'Active' placebo is a placebo preparation that mimics the adverse effect profile of the preparation with which it is being compared, but without the 'active' placebo preparation having any actual beneficial effect on the disease. However, Moncrieff et al. also found that there is little difference between antidepressant medication versus active placebo and that the efficacy of antidepressant medication probably has been overestimated in studies where active placebo has not been used. A recently published review in the New England Journal of Medicine shows that randomised trials of new antidepressants remain largely unpublished if their results are neutral or negative (10). Ninety-four percent of the published studies in the most widely-used databases showed a positive effect of the newer antidepressants. In the Food and Drug Administration (FDA) databases of all randomised trials submitted to the FDA, only 51% of the trials demonstrated significant effects from the medication. When the unpublished trial results were added to the

published ones, the updated meta-analyses showed no significant effects or very small significant intervention effects (10). In the majority of the trials, either no intervention or inactive placebo was involved as comparator. Similarly, a meta-analysis of the total number of trials recently published by the Public Library of Science (PLoS), in which the unpublished trials were included, revealed that the new antidepressants had failed to demonstrate any significant beneficial effects on depression in patients with mild to moderate forms of the disease (11). The meta-analysis revealed that significant effects from the new antidepressants were only achieved in severely depressed patients, and that this effect was clinically small (11). However, this meta-analysis also included trials in which inactive placebo was used, which questions even this small effect. It is therefore clear that the efficacy of antidepressant medication is somewhat doubtful and immediately raises the question: are there other effective treatments for this very serious illness?

Psychotherapy

It is our clinical impression that a majority of depressed patients seek psychotherapeutic assistance. Many depressed patients want help to find the possible contributing causes for their depression, as well as the psychological tools to escape their suffering. A number of trials, particularly in recent years, have attempted to establish the clinical efficacy of psychotherapy – either as add-on therapy to the medical treatment, or as monotherapy (12;13).

Cognitive therapy and mindfulness

Cognitive therapy and interpersonal therapy are the psychotherapeutic methods mostly studied in clinical trials for depression (14). Cognitive therapy (or cognitive-behavioural therapy) appears to be an effective treatment for depression (15). A systematic search of the literature identified five trials indicating that cognitive behavioural therapy is significantly better than no intervention for depressed patients (13;16-19).

A Cochrane review also shows that cognitive behavioural therapy has a

preventive effect against recurrent depression, and that this effect clearly surpasses the preventive effects of antidepressant medication (20).
Teasdale et al. studied 145 patients with a history of recurrent depression. The patients were randomised to either group treatment with MBCT (mindfulness-based cognitive therapy) or TAU (treatment as usual) (21). 45 % of patients in the MBCT group and 40% in the TAU group received medical treatment. 44 % of patients in the MBCT group experienced relapse/recurrence, compared to 58% in the TAU group. This difference was not significant. Sub-analyses of a group comprising patients having suffered at least three depressive episodes, showed a significant difference in relapse/recurrence of, respectively, 40 % in the group that received MBCT, and 66% in the TAU group (21).

As mentioned in the above, no randomised trials have been performed on currently depressed patients, including mindfulness techniques in classic cognitive therapy. Though including mindfulness/acceptance strategies in cognitive therapy has often been referred to as “the third wave” within cognitive therapeutic methods (the first two waves being behaviour-oriented and later cognitively-oriented treatment strategies) (21). Dialectic behavioural therapy (DBT) is one example of an alternative form of therapy including mindfulness in classical behavioural therapy. In randomised trials, DBT has been shown to be an effective treatment in reducing self-harming behaviour in patients with borderline personality disorder (22).

For pragmatic reasons we have elected to call cognitive therapy including mindfulness techniques *mindfulness-based behavioural therapy (MIBT).*

Psychodynamic therapy

Psychodynamic therapy is the most commonly used form of psychotherapy in the Danish health-care system (14). A systematic search of the literature identified three trials indicating that psychodynamic therapy is significantly better than no intervention for depressed patients (23-25).

We found only one relevant review in the Cochrane Library examining the effect of cognitive therapy versus psychodynamic therapy for depression (search on: Depression AND cognitive OR psychodynamic in 'Title, abstact or keywords') (26). In this review the authors included trials comparing the clinical effects of cognitive and psychodynamic therapy in treating currently depressed patients. The authors of the review conclude that the two interventions have comparable effects on almost all examined outcome measures, but the review included only six trials (26). There is therefore a risk of type 2 error. If we assume that both therapies are effective, we may need more trials to show a difference in effect.

Personality disorders

Close to 10% of the population would, at any given time, meet the criteria for a personality disorder (27), and about 80% of the patients in the day clinic where this trial is conducted has a personality disorder (28). One meta-analysis finds that depressed patients with a comorbid personality disorder have a poorer response to antidepressant treatment (excluding electric convulsive treatment (ECT)) than patients with a diagnosis of depression alone (29). Another meta-analysis finds that comorbid personality disorder in depressive patients is not a predictor of treatment efficacy in standard antidepressant therapy (30). The findings are therefore conflicting.

Conclusions

Depression is a serious illness. The degree to which medication has an effect on depression is questionable.

Cognitive and psychodynamic therapies are probably both effective treatments for depression vs no treatment, but only limited comparisons have been made between the two interventions. In essence, we do not know which of the two are offering more benefit and less harm. Furthermore, we do not know which subtype of MDD may respond best to the two treatments.

Mindfulness training may be an effective technique in preventing relapse in patients who have had at least three previous depressive episodes, but efficacy in treating currently depressed patients has not been examined.

Psychotherapeutic cognitive intervention in the acute phase of depression may appear to have a preventive effect against subsequent depressive episodes compared with medical treatment as monotherapy. Finally, there is limited information on the efficacy of psychotherapy in treating depressed patients with a comorbid personality disorder.

These factors make psychotherapeutic intervention increasingly relevant, from both a medical and societal perspective.

Objective

To conduct a randomised clinical pilot trial in order to establish the beneficial and harmful effects of mindfulness-based behavioural therapy (MIBT) versus psychodynamic therapy (PT) in patients with major depressive disorders in psychotherapeutic day treatment.

Null hypotheses for the randomised trial

- There is no significant difference between the clinical effects of respectively MIBT and PT, in respect of efficacy variables at 18 (end of day- treatment) and 26 (end of follow-up treatment) weeks after randomisation.
- Personality traits and psychopathological characteristics have no significance for the treatment-related effect.

Methods

A randomised clinical pilot trial of 84 consecutive patients diagnosed with major depressive disorder, referred to the day clinic, Roskilde psychiatric services. The trial is expected to run over two years

The patients will be randomised 1:1 to one of two interventions:

1. MIBT (mindfulness-based behavioural therapy), approximately n=42
2. PT (psychodynamic therapy), approximately n=42

The patients' personality traits and psychopathic characteristics are studied during the trial. The efficacy variables are studied at 18 (end of day-treatment) and 26 (end of follow-up treatment) weeks after randomisation.

Inclusion

GPs, practicing specialist physicians, as well as medical and psychiatric units will be free to refer patients they consider suitable for inclusion in the project. Referrals may be denied, either by virtue of the referral papers or via a physician interview. The patients must meet the inclusion criteria and none of the exclusion criteria. Trial participants are patients previously referred to the day clinic or referred during the conduct of the trial. No special announcement of the project will made to referrers.

The referral will be discussed at the patient conference on the day unit, and where relevant, patients called in for a preliminary consultation (collection of master data, which can be used by the therapists during the course of treatment) and subsequent medical consultation. During the medical consultation patients will be informed of, and offered participation in, the trial, if the patient is found to be suitable based on inclusion criteria. If the patient agrees to participate in the trial, an appointment will be made for completion of relevant questionnaires. If the patient then meets the inclusion criteria, he or she will be included in the trial and randomised to MIBT versus PT. We have chosen not to include study participants over 65 years. This is due to the risk of dementia impacting on treatment efficacy, and – for research-related grounds – the tradition is to treat this older patient group in a separate trial.

Inclusion criteria:

1. Aged 18 to 65 years

2. Major depressive disorder (SCID I) (31).
3. BDI II > 13 (32).
4. Written informed consent.

Exclusion criteria:

1. Current psychosis, diagnosis of schizophrenia or schizotypal personality disorder (DSM IV-TR) (33).
2. Alcohol or substance abuse judged to require treatment in preference to depression (assessed during patient conference).
3. Commenced or changed psychopharmacological treatment less than six weeks before randomisation.
4. Pregnancy.
5. No written informed consent.

Interventions

Common to both groups

The participants are treated on the day unit, Roskilde psychiatric unit, as per the manualized treatment programme.

Both interventions (during the course of day-treatment) run over 18 weeks. The groups are 'slow-open' (new patients enter the group continually) and contain a maximum of seven patients.

Participants are offered a communal breakfast twice a week, and group psychoeducation for one hour a week. Discussion of treatment plans will be offered after four weeks and 12 weeks. A medical consultation will be offered in respect of medication within 14 days, and thereafter as required. The medical consultations are performed by the lead clinical consultant, who are not otherwise involved in the trial. During the course of treatment, all trial participants with children are offered participation in parent groups (4 x 1 hour) and a talk about or with their child.

In the absence of therapists (illness, holidays, courses, etc.) the individual therapy will, as starting point, be postponed, but the groups will, to the extent that this is possible, continue. When project participants notify cancellation/do not attend, they will not normally be compensated for the missed sessions.

MIBT (mindfulness-based behavioural therapy)

The MIBT treatment consists of weekly individual MIBT therapy (45-50 min.), together with weekly mindfulness-skills training group (1.5 hours).

The treatment is based on the cognitive model of depression, but will, based on concrete problems, draw from alternative cognitive techniques in order to treat personality-related problems and will use elements from mindfulness.

Individual treatment:

- Introduction of the cognitive model and mindfulness.
- Identification of thoughts, feelings, behaviour and physical sensations.
- Work on assumptions.
- Stress reduction.
- Cognitive restructuring, behavioural experiments and acceptance of difficult feelings.
- Self esteem training.
- Mindfulness training.
- Preventing relapse.

Group therapy

Skills training with teaching of the four basic mindfulness skills ‘FALB’ (training in **F**ocusing, Acceptance, **L**abelling techniques, **B**ody awareness) together with self-esteem training and mindful communication. The skills training group will run in a continuous cycle of six sessions. Consequently, project participants go through the skills training group’s program three times during the course of the treatment.

Follow-up treatment

After 18 weeks of the intensive treatment-program described in the above, every participant is offered a course of follow-up treatment with weekly sessions of group-therapy (1.5 hours). This treatment is not manualized.

MIBT therapists

1. The principal clinical investigator (MD) is a specialist in general medicine. He has over 10 years of experience in cognitive behavioural therapy/mindfulness and is an approved specialist in cognitive behavioural therapy (Danish society of psychiatry)
2. An occupational therapist with five years of experience in cognitive behavioural therapy.

Please see the manual 'Mindfullnes-based behavioral therapy - a treatment manual' for a detailed description of the MIBT treatment (34).

The literature contains no discussion of side effects or other risks in respect of the intervention.

PT (psychodynamic therapy)

The PT treatment consists of weekly individual PT therapy (45-50 min.), together with weekly PT group therapy (1.5 hours).

The main elements of PT are the free-flowing, non-therapist guided dialogue, based on classic psychoanalytical free association. Basically, the role of the therapist is to set ground rules and organise the time, place and duration, to maintain a proper tone, and ultimately to ensure that a therapeutic process takes place using relevant interventions.

In PT the interventions are directed at the following areas:

I- Clarification.

Clarification in this context means explaining. The therapist is curious, inquisitive, inquiring and interested.

II- Confrontation.

This involves the therapist confronting the patient in an empathetic and validating way.
The patient is confronted with incongruencies in her words, actions, thoughts, body language and feelings.

III- Interpretation.

This means that the therapist provides explanations and interpretations that link the patient's actions and thoughts with his or her feelings; both conscious and unconscious.

IV- Mentalizing.

The focus of the work is on improving the patient's ability to mentalize; he or she is trained to mentalize. The therapist will demonstrate a mentalizing attitude and must always be affectively balanced in relation to the patient and must clearly mirror the patient.

The therapist has a hierarchy of interventions at his/her disposal for this purpose, and where the elements lowermost on the hierarchy (support, empathy, explanation) are used with high affect. More demanding interventions (interpretive mentalizing, mentalizing the transference, focus on counter-transference) are used in step with developments.

Follow-up treatment

After 18 weeks of the intensive treatment-program described in the above, every participant is offered a course of follow-up treatment with weekly sessions of group-therapy (1.5 hours). This treatment is not manualized.

Psychodynamic therapists

1. One psychiatrist with 20 years of experience with psychodynamic therapy
2. One nurse with five years of experience with psychodynamic therapy.

Please see 'Treatment manual for psychodynamic therapy' for further details.

The literature contains no discussion of side effects or other risks in respect of the two interventions.

Adherence to treatment- manual

All individual sessions will be recorded on an audio recorder.

All group sessions will be recorded on video.

During the trial period an independent member of staff will rate 4 x 10 of the recordings (10 sessions from respectively: individual MIBT, individual PT, group PT and group MIBT sessions) to check compliance with the manual/the description of the intervention. This is done using a checklist (Please see 'Checklist for MiPsy trial').

The results of these reliability tests will be presented.

Assessment

Prior to randomisation: Hamilton rating scale for depression (17 item) (35), SCL 90- R (36), BDI II (32), WHO 5 (37), SCID I (the depression aspect) and II interviews (31;38), DAPP-BQ (39), use of medication, age and sex on the participants, marital status, and education level.

After 9 weeks: BDI II, WHO 5

After 18 weeks (end of day treatment): Hamilton rating scale for depression (17 item), BDI II, WHO 5, SCL 90- R, use of medication, recording of suicide attempts/suicide during course of treatment

After 26 weeks of follow- up treatment: Hamilton rating scale for depression (17 item), SCL 90- R, DAPP-SF, BDI II, WHO 5. Recording of suicide attempts/suicide during course of treatment. Employment status (working full time, in some kind of employment/ training, not working),

Flowchart

Referral: GPs, practicing specialist physicians, as well as medical and psychiatric units will be free to refer patients they consider suitable for inclusion in the project.

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Patient conference : The referral is discussed at the patient conference on the day- care unit, and where relevant, patients called in for a preliminary consultation

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Preliminary consultation: Collection of master data

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Medical consultation: BDI II, general information about the trial, patients are given written information about the trial.

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Patient conference: Discussion whether the patient the patient may be suitable based on inclusion and exclusion criteria. If so an appointment will be made for completion of relevant questionnaires

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Medical Assessment : BDI II, SCID I (the depression aspect), verbally information about the trial, use of medication, age and sex on the participants, marital status, and education level. Patients are finally allocated to be included in the trial, if they are found suitable
based on the inclusion and exclusion criteria.

Inclusion criteria: Aged 18 to 65 years, major depressive disorder (SCID I), BDI II >13, written informed consent.

Exclusion criteria: Current psychosis, diagnosis of schizophrenia or schizotypal personality disorder (DSM IV- TR), alcohol or substance abuse judged to require treatment in preference to depression (assessed during patient conference). Commenced or changed psychopharmacological treatment less than 6 weeks before randomisation. Pregnancy or aged over 65 years or under 18 years. No written informed consent

↓

Hamilton D17, SCID II, SCL-90-R, WHO 5, DAPP- BQ

↓

Randomisation (stratification variable Hamilton D17)

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Overview of assessment

Before randomisation: Hamilton rating scale for depression (17 item), SCL 90- R, BDI II, WHO 5, SCID I (the depression aspect) and II interviews, DAPP- BQ, use of medication, age and sex on the participants, marital status, and education level.

9 weeks: BDI II, WHO 5

18 weeks: Hamilton rating scale for depression (17 item), BDI II, WHO 5, SCL 90- R, use of medication, recording of suicide attempts/suicide during course of treatment

After 26 weeks of follow-up treatment: Hamilton rating scale for depression (17 item), SCL 90- R, DAPP-SF, BDI II, WHO 5. Recording of suicide attempts/suicide during course of treatment. Employment status (working full time, in some kind of employment/ training, not working),

Description of the assessment instruments

The severity of a depression can be assessed using the 17 item *Hamilton rating scale for depression*. This scale is recognised worldwide as the most valid. It is a continuous, observer-based assessment method and involves 17 questions. Using this scale, the degree of depression is assessed (13 to 17 points = mild depression, 18 to 28 points, = moderate depression, over 28 points = severe depression). All Hamilton ratings are preformed by an experienced psychologist, blinded to the intervention.

SCL 90-R is generally considered to be one of the most documented; most used instruments for evaluating the most frequently occurring psychological and psychopathological symptoms. Each item takes the form of a symptom you might suffer, and the patient's task is to state to what degree he/she has suffered this symptom in the previous week. SCL-90 is a questionnaire-based study. Global Severity Index (GSI) derived from the questionnaire is designed to measure overall psychological distress.

BDI II (Beck Depression Inventory) is one of the assessment methods most used to measure severity of depression. BDI is a questionnaire-based study. 10–18 indicates mild-moderate depression, 19–29 indicates moderate-severe depression and 30–63 indicates severe depression. Higher total scores indicate more severe depressive symptoms.

WHO 5 (The World Health Organization-Five Well-Being Index 1999) is a questionnaire-based study that attempts to assess the trial participant's satisfaction and life quality. The study consists of 5 items and results in a score of between 0 and 100.

DAPP-BQ (Dimensional Assessment of Personality Pathology– Basic Questionnaire) (Livesley 1990). Personality disorder traits can assessed using the DAPP-BQ. It is a questionnaire-based study involving 290 items and 18 scales.

The **S**tructured **C**linical **I**nterview for DSM-IV **D**isorders (*SCID*) is a diagnostic exam used to determine DSM-IV Axis I disorders [major mental disorders, SCID 1] and Axis II disorders [personality disorders, SCID 2]. There are at least 700 published studies in which the SCID was the diagnostic instrument used.

Reliability tests for assessment

The staff performing the Hamilton ratings will record five interviews on DVD and an independent, experienced member of staff from the Ph.D. group will rate these interviews.

The two members of staff who perform the SCID II interview will rate five SCID interviews prior to start of the trial period.

The results of these reliability tests will be presented.

Outcome measures

Primary outcome measure

- 17 item Hamilton rating scale for depression (score after 18 weeks of treatment)

Secondary outcome measures

- SCL-90-R (GSI- score after 18 weeks of treatment)
- The proportion of patients who achieve remission (score after 18 weeks of treatment). We have, pragmatically, chosen to define remission as a Hamilton score of less than 8 (40).

Tertiary outcome measures

- BDI (score after 18 weeks of treatment)
- WHO 5 (score after 18 weeks of treatment)

Other outcome measures

- DAPP-BQ
- Adverse events

We will classify adverse events as serious or non-serious. Serious adverse events will be defined as any untoward medical occurrence that was life threatening, resulted in death, or persistent or significant disability, or any medical event, which might have jeopardised the patient, or required intervention to prevent it (ICH- GCP 1997); all other adverse events (that is, any medical occurrence not necessarily having a causal relationship with the treatment, but did, however, cause a dose reduction or discontinuation of the treatment) will be considered as non-serious.

Data-management

All data are stored in the principal investigator's office and/ or at Copenhagen Trial Unit (CTU), and all data are anonymised on conclusion of the project, i.e., after publication of all results. Privacy of trial participants is protected in accordance with the Act on Processing of Personal Data and the Health Act. The project has been notified to the Data Protection Agency.

All Hamilton scores (blinded data) and SCL 90 scores are sent directly to CTU by the independent rater for data-management.

Randomisation

The randomisation will be preformed by CTU. The computer generation of the randomisation sequence is unknown to the investigator. A research secretary will randomise by calling the CTU providing a personal pincode, patient number, and the entry Hamilton score (stratification variable). The patient will be randomised to either MIBT or psycodynamic treatment.

Blinding

The outcome assessor of the primary outcome (Hamilton score) is blinded to which treatment each patient has been a part of, and is instructed to avoid other questions besides the Hamilton rating. All patients are instructed not to

mention witch treatment they have been a part of. The randomised treatments are not blinded to participants or therapists.

All information given to the participants before filling in every questionnaire is the same for every participant and is standardised.

Missing data

If outcomes are not present due to missing follow-up, retraction of informed consent, or dropout - the pattern of the missing data will be investigated by the authors. If the authors conclude that MAR (MAR=missing at random) is the plausible interpretation, a multiple imputation with the multiple imputation analyse program (MIA) will be preformed. If MAR is not the plausible interpretation, MNAR (missing not at random) will be analysed in sensitivity analyses.

Comparability of characteristics on randomising

To assess the comparability of the two intervention groups before treatment, the two groups will be compared with regard to Hamilton score (stratification variable), age, sex, SCL 90 score and diagnoses (SCID 2). The results will be presented.

Sample size

Power calculation shows that with an effect size of 5 point difference in the Hamilton score, an alpha of 0.05, a power of 0.90, and a SD=7 a total of 84 participants are necessary (12). The calculation is performed using the programme “Power and sample size calculations”, version 2.1.31.

Analyses

The two forms of intervention are compared regarding the primary, secondary, tertiary, and other outcome measures.

The prognostic significance of personality-related and psychopathological features is assessed by studying the relationship to efficacy parameters prior to and after the intervention.

Statistics

SPSS statistical software is used for all calculations (SPSS for Windows, version 16.0). Data are analysed based on the principles of 'intention to treat'. Parametric testing is used if the distributions are normally distributed (t-test) and otherwise non-parametric testing: McNemar test for binary observations and Wilcoxon signed rank-test for ordinal or continuous observations. Distribution of the efficacy parameters and changes are described using mean, median and SD, together with range. Changes in the 2 treatment forms are compared by testing paired observations. All tests are two-sided and use p values of <0.05.

Competing interests

The primary investigator is also a therapist in the MIBT treatment and has developed the manual for the MIBT – programe. Other authors have no competing interests.

Publication

This protocol is registered before the randomisation begins (8/2 2010).

The intention is to publish positive, neutral, and negative results of the intervention.

- The following persons will be authors of all publications: Janus Jakobsen, Erik Simonsen, Ulf Søgaard, Kirsten Åskov Larsen, Per Sørensen, Christian Gluud.

- The lead author is attributed to the person responsible for the majority part of the work.

- Publication rules comply with the Vancouver regulations.

It is planned to publish the results in major international medical journals.

Economic factors

The project has been initiated by unit consultant Janus Jakobsen. There are no commercial sponsors. There will also be an application for funds for study travel as well as study and course fees via the scientific research fund. Janus Jakobsen has no financial links with private companies, funds etc.

No expense allowance is offered to trial participants.

Information for trial participants

Participants will be informed of the trial in writing and verbally, and written informed consent will be obtained from every participant before inclusion. All trial participants may, on request, be permitted access to further information about the project. The individual therapists and the principal investigator will perform this function.

Research ethics statement

The project raises no immediate ethical problems. Two well-known forms of treatment are compared, which in the literature have never been shown to involve significant adverse effects or risks. Any adverse events of the interventions will be reported. The trial has obtained approval by the Regional Ethics Committee of Zealand (nr.: SJ-43), and is registered at the Danish Data Protection Agency (nr.: 2008-58-0020).

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