



**Third wave Cognitive Therapy versus Mentalization-based Treatment for Major Depressive Disorder. A Randomised Clinical Pilot Trial**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-004903
Article Type:	Research
Date Submitted by the Author:	22-Jan-2014
Complete List of Authors:	Jakobsen, Janus; Copenhagen Trial Unit, 7812 Gluud, Christian; Copenhagen Trial Unit, 7812 Kongerslev, Mickey; Psychiatric Research Unit, Region Zealand, Roskilde, Copenhagen University Hospital, Denmark, Larsen, Kirsten; Psychiatric Clinic, Psychiatry, Roskilde;; Sørensen, Per; Department of Psychiatry, Copenhagen University Hospital, Copenhagen, Winkel, Per; Copenhagen Trial Unit, 7812 Lange, Theis; Department of Public Health, University of Copenhagen., Søgaard, Ulf; Psychiatric Clinic, Psychiatry, Roskilde;; Simonsen, Erik; Psychiatric Research Unit, Region Zealand, Roskilde, Copenhagen University Hospital, Denmark,
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Public health
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Personality disorders < PSYCHIATRY

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# Third wave Cognitive Therapy versus Mentalization-based Treatment for Major Depressive Disorder. A Randomised Clinical Pilot Trial

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## Abstract

**Background and objective:** No randomised clinical trial has compared the effects of third wave cognitive therapy and mentalization-based treatment in patients with major depression. Our objectives were (1) to compare the benefits and harms of these two interventions in a small sample of participants with major depressive disorder, and (2) to test the feasibility of the trial design. The results from this pilot trial might provide valuable information about the optimal design of a future more definitive trial.

**Design, setting, participants and measurements:** We planned to randomise 84 consecutive adult participants diagnosed with major depressive disorder to third wave cognitive therapy (n=22) versus mentalization-based treatment (n=22). The primary outcome was the Hamilton Rating Scale for Depression (HDRS) at end of treatment (18 weeks). Secondary outcomes were: remission (HDRS < 8), Beck's Depression Inventory, Symptom Checklist 90 Revised, and The World Health Organisation-Five Well-being Index 1999.

**Results:** Only 44 out of the planned 84 participants were randomised in the trial. Two participants were lost to follow-up. The unadjusted analysis showed that third wave participants compared with mentalization-based participants did not differ significantly regarding the 18 weeks HDRS score (12.9 versus 17.0; mean difference -4.14; 95% CI -8.30 to 0.03; P = 0.051). In the analysis adjusted for baseline HDRS score, the difference was significant favouring third wave cognitive therapy (P = 0.039). At 18 weeks, five of the third wave participants (22.7%) were in remission versus none of the mentalization-based participants (P = 0.049). No significant differences were found between the two intervention groups on the secondary outcomes.

1 **Conclusions:** It was much harder to recruit participants to the trial than expected. Our results  
2 suggest that third wave cognitive therapy may be more effective than mentalization-based  
3 therapy for depressive symptoms measured on the HDRS. More randomised clinical trials are  
4 needed to assess third wave cognitive therapy versus mentalization-based treatment for  
5 depression. Such trials should be multicentre trials to secure adequate enrolment.  
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14 **Trial registration:** Registered with Clinical Trials government identifier: NCT01070134  
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19 **Keywords:** Randomised clinical trial; Depression; Third wave cognitive therapy; Mentalization-  
20 based treatment  
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## Strengths and limitations of this study

- It was possible to conduct the trial with a low risk of bias, which was the primary strength of this randomised clinical pilot trial.
- The pilot trial also provided valuable information about the difficulty of recruiting eligible participants, and indications about intervention effects that may be used when estimating future sample size calculations.
- The primary limitation of this randomised clinical pilot trial was that only 44 out of the planned 84 participants were randomised in the trial.

## Introduction

Major depressive disorder afflicts an estimated 17% of individuals during their lifetimes at tremendous cost to the individual and society.<sup>1, 2</sup> Major depressive disorder has for decades been treated with many different kinds and forms of interventions. Nevertheless, roughly a third of all depressive disorders take on a chronic course,<sup>3, 4</sup> and approximately 15% of depressed patients will commit suicide over a 10 to 20 year period.<sup>5</sup> Our objectives were (1) to compare the benefits and harms of these two interventions in a small sample of participants with major depressive disorder, and (2) to test the feasibility of the trial design. The results from this pilot trial might provide valuable information about the optimal design of a future more definitive trial.

### Third wave cognitive therapy

Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of cognitive therapy versus no intervention for major depressive disorder.<sup>6</sup> We found that cognitive therapy seems to have a statistically significant beneficial effect on depressive symptoms. However, we identified only a limited number of relatively small randomised clinical trials all with a high risk of bias.<sup>6</sup> Other non-systematic reviews have concluded that cognitive therapy has large clinical effects.<sup>7</sup> Our review results showed that the effects of cognitive therapy, if any, seem to be relatively small (mean difference about three HDRS points).<sup>6</sup> During the last two decades new forms of cognitive therapy have been developed. These third wave cognitive therapies include, e.g., acceptance and commitment therapy, schema therapy, mindfulness-based cognitive therapy, and meta-cognitive therapy.<sup>8</sup> Especially mindfulness-based interventions have been implemented in numerous different clinical contexts in recent years.<sup>9-11</sup> One meta-analysis observed that third wave cognitive therapy might prevent relapse of depression,<sup>12</sup> and small trials show that third wave cognitive therapy versus no intervention or treatment as usual is effective for acutely depressed patients.<sup>13, 14</sup> One trial has shown comparable effects between cognitive

1 therapy and third wave cognitive therapy in non-melancholic depression, but the trial only  
2 included 45 participants.<sup>15</sup>  
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### 8 **Mentalization-based treatment**

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10 Mentalizing entails attending to mental states – holding ‘mind in mind’.<sup>16</sup> It is the process by which  
11 an individual explicitly and implicitly interpret the action of himself or herself and others on the  
12 basis on intentional mental states such as wishes, needs, goals, and reason.<sup>16</sup>  
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19 Mentalization-based treatment is rooted in attachment theory and developmental psychopathology  
20 and it includes essentials from psychodynamic psychotherapy in a concurrent individual and group  
21 format.<sup>16</sup> Prior to this trial we carried out a systematic review of randomised clinical trials  
22 examining the effects of psychodynamic therapy for major depressive disorder.<sup>17</sup> We found that  
23 psychodynamic therapy versus no intervention seems to have a small statistically significant effect  
24 on depressive symptoms (mean difference about three HDRS points).<sup>17</sup> However, we identified a  
25 limited number of trials, the trials were small, and all the trials had a high risk of bias so our results  
26 might be questioned.  
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40 Mentalization-based therapy was originally developed to treat borderline personality disorder but is  
41 now also used to treat various other psychiatric disorders such as depression, eating disorders,  
42 substance abuse, and personality disorders other than borderline.<sup>16, 18</sup> Mentalization-based  
43 treatment is based on the concept of mentalization as described by Fonagy and Bateman,<sup>19, 20</sup> and  
44 is different from the more strictly defined mentalization-based therapy as manualized by Karterud  
45 and Bateman.<sup>19-22</sup> In comparison with mentalization-based therapy, mentalization-based treatment  
46 used in this trial has a more open therapeutic stance — letting the patient decide the theme in an  
47 associative way. The therapist is less active in directing the theme in the dialog and uses  
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1 interpretations. Mentalizing deficits can be assumed to underlie depressive symptoms,<sup>23, 24</sup> and  
2 many depressed patients have a comorbid personality disorder.<sup>25</sup> We did not identify any trial  
3 assessing the effects of mentalization-based treatment or therapy versus no intervention for major  
4 depressive disorder.<sup>17</sup>  
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### 10 11 12 13 **Third wave cognitive therapy versus mentalization-based treatment**

14 No randomised clinical trials or systematic reviews seem to have examined the effects of third  
15 wave cognitive therapy versus mentalization-based treatment or therapy for major depression.<sup>26</sup>  
16 Our objective was to compare the benefits and harms of third wave cognitive therapy versus  
17 mentalization-based treatment in a small sample of participants with major depressive disorder, as  
18 a pilot for a more definitive randomised clinical trial.  
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## 28 **Methods**

29 In the following, we briefly describe the methodology of this trial. For details please consult our  
30 primary trial protocol (published at our website:  
31 [http://www.ctu.dk/Protocols/Mipsy\\_protocol2010.pdf](http://www.ctu.dk/Protocols/Mipsy_protocol2010.pdf) and registered at clinicaltrials.gov:  
32 NCT01070134) and our published design article.<sup>27</sup>  
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### 45 **Inclusion of participants**

46 The trial was conducted at a public psychiatric outpatient clinic only treating patients on sick leave  
47 due to a psychiatric disorder. Patients were referred from general practitioners, psychiatrists in  
48 private practice, and medical and psychiatric departments. No special announcement of the trial  
49 was made to the referrers. All patients referred to the psychiatric clinic had a full psychiatric  
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1 examination by a physician who made the preliminary psychiatric diagnoses (DSM-IV-TR).<sup>28</sup>  
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3 Eligible patients were then interviewed by the principal investigator (JCJ) who used the depression  
4 part of the structured clinical interview for DSM-IV axis I disorders (SCID I) interview<sup>29</sup> to assess  
5 whether the patient fulfilled the criteria for a major depressive disorder (DSM-IV-TR).<sup>28</sup> Before  
6 randomisation baseline assessments were carried out for all outcome measures and all eligible  
7 patients were assessed with the structured clinical Interview for DSM-IV axis II disorders (SCID  
8 II).<sup>30</sup> We chose to perform the SCID II assessments because we wanted to compare personality  
9 disorders at baseline in the two intervention groups and to exclude patients with schizotypal  
10 personality disorder.  
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24 The participant had to meet all of the inclusion criteria and none of the exclusion criteria.  
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### 28 **Inclusion criteria**

- 29 1. Age from 18 to 65 years.
- 30 2. Major depressive disorder, whether first episode or recurrent (DSM-IV-TR).<sup>29</sup>
- 31 3. Beck's Depression Inventory (BDI II) score > 13.<sup>31</sup>
- 32 4. Written informed consent.

### 33 **Exclusion criteria**

- 34 1. Current psychosis, schizophrenia, or schizotypal personality disorder (DSM-IV-TR).<sup>28</sup>
  - 35 2. A significant alcohol or substance abuse (assessed during the preliminary consultations).
  - 36 3. Initiated or changed medical anti-depressive treatment less than six weeks before  
37 randomisation.
  - 38 4. Pregnancy.
  - 39 5. No written informed consent.
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## Randomisation

Eligible patients with major depressive disorder were randomised 1:1 to third wave cognitive therapy versus mentalization-based treatment. The Copenhagen Trial Unit performed the randomisation centrally, using a computer generated block randomisation sequence that was unknown to the investigators. Participant inclusion began in February 2010 and the last patient was randomised in July 2011. Because of an unequal allocation of the trial participants to one of the two groups in the beginning of the trial (there were only a few participants in one of the groups), the block size was reduced from 12 to 4 and a stratification variable (HDRS score  $\geq 22$ ) was removed. The block sizes were at all times unknown to the trial investigators, and the Copenhagen Trial Unit performed these changes without informing the investigators of the changes. Otherwise, the methodology was not changed after trial commencement.

## Interventions

Each participant received treatment for 18 weeks. The two intervention groups were 'slow-open' (new patients entered the group continually) with a maximum of seven patients per group.

The time of each of the elements in the comprehensive treatment package (see below) was planned to be similar in the compared intervention groups.

### Shared elements for both intervention groups

All participants were, as part of the outpatient clinic's usual care, offered a communal breakfast twice a week and participated in group psycho-education for one hour a week. During the course of treatment, all participants with children were offered participation in a parent support group (four

1 weekly one-hour sessions). A psychiatric consultant (KAL), who was not otherwise involved in  
2  
3 the interventions, assessed each participant and prescribed psychopharmacological treatment  
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5 when needed. The psychiatric consultant prescribed medication according to the official  
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7 recommendations.<sup>32</sup> After the first consultation, medical consultations were offered by demand of  
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9 the participant or the therapists.  
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### 12 13 14 15 **Third wave cognitive therapy**

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17 The third wave cognitive therapy consisted of one weekly third wave cognitive individual  
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19 psychotherapy session (45-minute) and one weekly mindfulness-skills training group (1.5 hours).  
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21 Altogether the third wave cognitive therapy consisted of 18 individual psychotherapy sessions (45  
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23 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.  
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28 The weekly individual psychotherapy session included:  
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- 30 • Introduction of the cognitive model and mindfulness.
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- 32 • Exploration of thoughts, feelings, behaviour, and physical sensations.
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- 34 • Work on acceptance of difficult feelings and difficult life circumstances.
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- 36 • Work on assumptions challenged by behavioural experiments.
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- 38 • Self esteem training.
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- 40 • Tools to prevent relapse.
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47 The weekly mindfulness-skills training group included:

48 Education in the practical use of six basic mindfulness skills: focusing, acceptance, labeling  
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50 feelings, body awareness, self-esteem skills, and mindful communication. The group participants  
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52 were encouraged to practice the six mindfulness skills between sessions. The skills training group  
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1 ran in a continuous cycle of six sessions. Consequently, participants went through the skills  
2 training group's program three times during the course of the 18 weeks of treatment.  
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8 The manual for the third wave cognitive therapy was developed specifically for the trial and had  
9 not been used before in a trial setting. Details about the third wave cognitive therapy program is  
10 available elsewhere.<sup>33</sup>  
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### 14 **Mentalization-based treatment**

15 The mentalization-based treatment consisted of a weekly mentalization-based individual  
16 psychotherapy session (45-minute) and a weekly mentalization-based group therapy session (1.5  
17 hours). Altogether the mentalization-based treatment consisted of 18 individual psychotherapy  
18 sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.  
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30 Mentalization-based treatment imposes explicit attention to mentalizing in the therapeutic process.  
31 This is established by a therapeutic stance where the therapist aims at demonstrating a  
32 'mentalizing attitude', i.e., validating, 'not-knowing', and curiously questioning the patient about  
33 feelings and thoughts.<sup>16, 22, 34</sup> The therapist tries to identify and intervene when the patient is not  
34 mentalizing and assists the patient in regulating the level of the emotions so the patient is able to  
35 mentalize and to get different perspectives on life events, conflicts, etc.<sup>16, 22, 34</sup>  
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46 At the time this project was planned there was no manual available for the mentalization-based  
47 treatment. Therefore, we developed our own treatment manual based on mentalization  
48 principles.<sup>35</sup> Further details about the mentalization-based treatment is available elsewhere.<sup>35</sup>  
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### 55 **Therapists and adherence to the intervention manuals**

1 Each intervention group had two therapists. The two third wave cognitive therapists (one of  
2 these therapists was the principal investigator) and the two mentalization-based therapists had  
3 comparable psychotherapeutic education and experience.  
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10 All individual sessions were recorded on an audio recorder and all group sessions were recorded  
11 on video. An experienced external psychologist not otherwise involved in the trial assessed the  
12 degree of adherence to the manuals 0-5 (0: no adherence; 1: adherence about 20% of the time; 2:  
13 adherence about 40% of the time; 3: adherence about 60% of the time; 4: adherence about 80%  
14 of the time; 5: adherence about 100% of the time). The psychologist randomly selected 4 x 5  
15 sessions using a computer program. The results showed high adherence to the treatment manuals  
16 for both interventions. The means of the ratings were: 4.6 in five sessions of individual third wave  
17 cognitive therapy; 4.2 in five sessions of third wave cognitive group therapy; 4.2 in five sessions of  
18 individual mentalization-based treatment; and 3.8 in five sessions of mentalization-based group  
19 treatment.  
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## 35 Outcomes

### 36 Primary outcome

- 37 • Score on the Hamilton Depression Rating Scale (HDRS)<sup>36</sup> after end of treatment at week  
38 18.  
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### 40 Secondary outcomes

- 41 • The proportion of participants in remission after cessation of treatment at week 18. We  
42 defined remission as HDRS below 8.<sup>37</sup>  
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- Global Severity Index score (GSI-score)<sup>38</sup> on the Symptom Checklist 90 Revised (SCL-90-R)<sup>38</sup> after cessation of treatment at week 18.
- Score on the World Health Organisation-Five Well-being Index 1999 (WHO 5)<sup>39</sup> after cessation of treatment at week 18.
- Score on the Beck's Depression Inventory (BDI II)<sup>31</sup> after cessation of treatment at week 18.

### Reliability of the Hamilton Depression Rating Scale (HDRS) interviews

Two experienced psychologists performed the Hamilton interviews during the trial period. Prior to the trial the principal investigator and one of the psychologists both Hamilton interviewed eight patients at the same time point. The mean difference between these two HDRS ratings performed on the same patient at the same time point was -0.13 HDRS points (SD 1.25) (intra-class correlation coefficient 0.98; Spearman correlation 0.92). During the trial both psychologists Hamilton interviewed 21 patients at the same time point. The mean difference between these two HDRS ratings performed on the same patient at the same time point was 0.29 HDRS points (SD 2.21) (intra-class correlation coefficient 0.96; Spearman correlation 0.94). All these 29 interviews were performed with both HDRS-raters present simultaneously. One rater interviewed and rated the interviewee and the other rater only rated the interviewee. The interviewers were not allowed to discuss the results before each interviewer had registered the HDRS result.

### Data-management

All data were handled by research assistants not otherwise involved in the trial and was stored in the principal investigator's office and at the Copenhagen Trial Unit. Privacy of trial participants was protected in accordance with the Act on Processing of Personal Data and the Health Act. The project was notified to the Danish Data Protection Agency (no.: 2008-58-0020).

## Blinding

The Hamilton interviewers were blinded to treatment allocation and were instructed by the principal investigator to avoid questions beside the Hamilton interview. All interviewees were prior to each interview instructed by the principal investigator not to mention which treatment they were allocated to. It was not possible to blind neither the therapists nor the participants to treatment allocation.

The chief consultant performing the medical consultations was, due to practical circumstances, not blinded to treatment allocation.

A statistician at The Copenhagen Trial Unit performed the statistical analyses blinded with the two intervention groups coded as 'A' and 'B'.

## A priori sample size estimate

With a 'minimal relevant mean difference' (MIREDIFF) between the two interventions of 5 HDRS points, an alpha of 0.05 (type I error), a power of 0.90 (type II error of 10%), and a standard deviation (SD) of 7, the sample size calculation showed that a total of 84 participants would be necessary. We estimated that we would need an inclusion period of about two years to recruit 84 participants.

## Statistical analyses

The primary analyses were intention-to-treat analyses. Significance tests were two-sided at a significance level of 0.05.

1 Continuous outcomes were compared between the two intervention groups using the univariate  
2 general linear model with (ANCOVA) and without HDRS baseline value adjustment (ANOVA). The  
3 binary outcome was compared between the groups using Fisher's exact test. Logistic regression  
4 could not be used since none of the participants in the mentalization-based group obtained  
5 remission implying an infinite odds ratio.  
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14 As the trial was stopped before the sample size was reached, we post hoc decided to conduct  
15 sequential analysis to assess the results of significance testing taking sparse data and repetitive  
16 testing into consideration. We used the trial sequential analysis program for that purpose.<sup>40-43</sup>  
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## 24 **Results**

### 25 **Participants**

26 Only 44 out of the 84 planned participants were included in the trial, due to problems with  
27 enrolment. Twenty-two participants were randomised to third wave cognitive therapy versus 22  
28 participants to mentalization-based treatment. **Figure 1** details the participant flow through the  
29 phases of the trial.<sup>42</sup>  
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### 43 **Baseline characteristics of the participants**

44 The baseline characteristics regarding age, sex, number of children, score on the HDRS, baseline  
45 diagnosis of personality disorder, and psychopharmacological treatment were overall assessed as  
46 comparable between the two intervention groups. The psychopharmacological treatment and the  
47 baseline participant characteristics are described in detail in **Table 1** and **Table 2**.  
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## Treatment compliance

None of the 22 participants randomised to third wave cognitive therapy were lost to follow-up or excluded due to the fact that they participated in less than 70% of the sessions. One participant out of the 22 randomised to mentalization-based treatment was lost to follow-up and one was excluded, as she did not attend the required 70% of the sessions (**Figure 1**).

## Psychopharmacological treatment

The psychopharmacological medication varied greatly between all of the trial participants. However, we assessed the psychopharmacological medication at baseline and at cessation of treatment as being comparable in the two intervention groups. The psychopharmacological medication in the two groups is outlined in **Table 2**.

## Intervention effects

### Primary outcome

#### Mean score on the HDRS after end of interventions

Participants randomised to third wave therapy compared with participants randomised to mentalization-based treatment did not differ significantly regarding 18-week HDRS scores in the unadjusted analysis (mean 12.9, 95% CI 9.81 to 15.9 versus mean 17.0, 95% CI 14.0 to 20.0;  $P = 0.051$ ). The mean difference between the two groups was -4.14 HDRS points (95% CI -8.30 to 0.03) corresponding to a Cohen's  $D$  of -0.62. The difference was, however, significant in the analysis adjusted for baseline HDRS score ( $P = 0.039$ ) (**Table 3**).

1 Following imputation<sup>27</sup> of the two missing values in the group randomised to mentalization-  
2 based treatment the P-values were 0.064 (unadjusted analysis) and 0.041 (analysis adjusted for  
3 baseline HDRS). Histograms on the data from both intervention groups showed that the data  
4 seem to be normally distributed. Using the non-parametric test the P-value was 0.064 without  
5 imputation and 0.093 after imputation.  
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14 There was no significant interaction between the indicator of a diagnosis of a personality disorder  
15 and the intervention effects. This was also not the case when the indicator was redefined as a  
16 binary quantity defined as any kind of personality disorder (yes/no) or as a binary quantity defined  
17 as personality disorder = borderline personality disorder (yes/no).  
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26 Sequential analysis demonstrated that the observed significant findings ought to be interpreted  
27 conservatively as random errors due to sparse data cannot be excluded (**Figure 2**).  
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## 32 **Secondary outcomes**

### 33 **Participants in remission after cessation of treatment**

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38 In the third wave therapy group 22.7% (n=5) were in remission after cessation of treatment  
39 (defined as having HDRS < 8) versus 0% in the mentalization-based treatment group. This  
40 difference was significant (P = 0.049) (**Table 3**).  
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### 48 **BDI II<sup>31</sup>, SCL-90-R<sup>38</sup>, and WHO 5<sup>39</sup> after end of interventions**

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50 No significant difference was found on BDI II, SCL-90-R (GSI-scores), or WHO 5 between the two  
51 intervention groups after cessation of treatment (**Table 3**).  
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Sequential analysis demonstrated that the observed insignificant findings regarding BDI II ought to be interpreted conservatively as random errors due to sparse data cannot be excluded (**Figure 3**).

## Other outcomes

### Admissions, suicide attempts, and suicides

One of the participants randomised to third wave cognitive therapy and two of the participants randomised to mentalization-based treatment were for a short period (some days) admitted to a psychiatric hospital during the intervention period.

We recorded no suicide attempts or suicides during the intervention period in any of the 44 participants.

## Discussion

Our pilot trial results show that it was much harder than expected to recruit eligible participants to the trial. It took us longer to recruit participants than stipulated, and we had to terminate the trial due to economical and practical constraints. Basically, not enough eligible participants were referred to the clinic during the inclusion period. On the positive side, our pilot demonstrated the feasibility of conducting the trial with low risks of bias. Our preliminary results indicate that third wave cognitive therapy compared with mentalization-based treatment may be a more effective intervention for lowering depressive symptoms measured on the HDRS and may increase the

1 probability of remission (HDRS < 8). However, when only 44 out of the planned 84 participants  
2 (52%) of the projected sample size is obtained in a trial, it is necessary to evaluate the calculated  
3 p-values more conservatively. Had this been an interim analysis, any independent safety and data  
4 monitoring committee would have recommended continued randomisation and completion of the  
5 trial (**Figure 2** and **Figure 3**). Furthermore, the two interventions do not seem to have significant  
6 differential effects on BDI (subjective depressive symptoms), SCL 90-R (psychological distress),  
7 and WHO 5 (well-being).  
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10 Compared with the baseline scores, both intervention groups improved during the trial period on  
11 all continuous outcomes. However, we did not include a control group receiving no intervention so  
12 it is unclear whether it was trial intervention effects or 'regression towards the mean' effects that  
13 caused these changes.<sup>44</sup> More randomised clinical trials are needed to assess the effects of third  
14 wave cognitive therapy versus mentalization-based treatment for major depressive disorder.  
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### 33 **Strengths**

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35 First of all, we proved the feasibility of our trial design, which can be used for larger trials provided  
36 that funding can be raised. Our trial has a number of additional strengths. (1) The trial protocol  
37 was registered before randomisation began at ClinicalTrials.gov. In this protocol the outcome  
38 hierarchy and plans for analyses were presented. Our trial was altogether conducted according to  
39 good clinical research practice and therefore with low risk of bias and a high degree of external  
40 validity.<sup>45-49</sup> (2) The participants in this trial were similar to patients normally referred to a  
41 psychiatric outpatient clinic, and clinicians can therefore relate our trial results to a clinical context.  
42 (3) Both of the trial interventions were conducted using manuals and adherence to the manuals  
43 was assessed as relatively high. The manualization of the trial interventions makes it possible, to  
44 some extent, to implement the two trial interventions in clinical practice and to replicate or refute  
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our results in future trials. Both the cognitive therapists and the mentalization therapists were involved in developing the treatment manuals for the respective psychotherapeutic treatments, which might make the therapist enthusiasm and thoroughness similar in the two intervention groups. (4) We have used the most commonly used outcomes in trials assessing the effects of psychotherapeutic interventions for depression (i.e., HDRS).<sup>17, 36, 50, 51</sup> This makes it possible to relate our results to results from other trials examining the effects of interventions for depression. Moreover, using HDRS as outcome makes it possible to perform blinded objective outcome assessment, which is a further strength of our trial. (5) The baseline characteristics of the trial participants as well as the psychopharmacological medication in the two groups were comparable which indicates that the randomisation succeeded in allocating comparable participants to the two intervention groups. (6) Only 2 out of the total of 44 participants were not assessed after end of treatment, which decreases the risk of biased results. Furthermore, we imputed missing values.<sup>52</sup> (7) All outcomes suggested that the participants randomised to third wave cognitive therapy had improved more than the participants randomised to mentalization-based treatment. This supports the validity of our results, even though most of these differences were non-significant.

## Limitations

Our trial has a number of limitations. This pilot trial was in essence failed because we only included 44 out of the planned 84 participants. The trial inclusion lasted for about two years as planned but we had problems with recruiting participants. Basically, not enough eligible depressed patients were referred to the clinic within the planned trial period. The low number of randomised participants leads to a high risk of type I errors and type II errors.<sup>53, 54</sup> Moreover, our results do not show anything about long-term effects of the two interventions.

1 The chief consultant prescribing the psychopharmacological treatment was not blinded to  
2 intervention allocation. Although we assessed the psychopharmacological treatment to be  
3 comparable in the two randomised groups at cessation of the trial interventions (**Table 2**), the lack  
4 of blinding might have influenced the psychopharmacological treatment. The chief consultant is a  
5 mentalization-based therapist and was involved in developing the mentalization-based treatment  
6 manual. The first author and primary investigator conducted the third wave cognitive therapy and  
7 wrote the manual for the third wave cognitive therapy program, which may also raise the risks of  
8 bias.  
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10 We did not perform power calculation for the secondary outcomes before randomisation began,  
11 which is a further limitation. If an analysis of a secondary outcome has a power of less than 80%,  
12 then either the secondary outcome should be classified as an exploratory outcome or the *P*-value  
13 and the confidence interval thresholds for significance should be adjusted, just as the thresholds  
14 are adjusted if a sample size has not been reached.  
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16 Because of an unequal allocation of the trial participants to one of the two groups in the beginning  
17 of the trial, the block size was reduced from 12 to 4 (see '**Randomisation**'). The block sizes were  
18 at all times unknown to the trial investigators, and the Copenhagen Trial Unit performed these  
19 changes without informing the investigators. However, a block size of four is small making it  
20 possible to foresee which group a given eligible participant will be allocated to before  
21 randomisation. This might question whether the allocation concealment was effective.  
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23 The trial was conducted at an outpatient psychiatric clinic with special interest for treatment of  
24 personality disorders and depressive patients were not routinely referred to the clinic before the  
25 trial began randomisation. Our results showed that a high proportion of the trial participants had  
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1 comorbid personality disorder and depression. This might explain why the baseline HDRS  
2 scores indicated that the trial participants were only moderately depressed although all of the trial  
3 participants were on sick leave due to psychological problems. Some of the trial participants might  
4 suffer primarily from psychological problem other than depressive symptoms, i.e., personality  
5 related problems. We did not assess number of prior depressive episodes in the included  
6 participants, which makes it unclear whether our trial results demonstrate intervention effects in  
7 participants with a first time depression or recurrent depression. Our results can only be related to  
8 patients comparable to our trial participants, i.e., patients diagnosed with major depressive  
9 disorder on sick leave due to psychiatric problems.  
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24 Mentalization-based treatment was the primary psychotherapeutic method used at the outpatient  
25 clinic prior to the trial, and the co-interventions (communal breakfast and psycho-education) were  
26 also a part of the treatment program prior to the trial. The co-interventions were delivered  
27 similarly to both treatment groups and the possible effects of co-interventions will therefore even  
28 out between the compared intervention groups unless there are significant interactions. Due to  
29 ethical considerations it was not possible to conduct a trial comparing the psychotherapeutic  
30 interventions versus no intervention. Nevertheless, it is a clear limitation that our interventions are  
31 not and have not been compared versus no intervention.<sup>44</sup> If a trial comparing the effects of two  
32 active interventions shows no difference in effect it is not clear whether the two interventions are  
33 equally effective or equally ineffective — and if an experimental intervention seem superior  
34 compared with a control intervention then the effect size of the experimental intervention will be  
35 unclear because any beneficial or harmful effects of the control intervention might influence the  
36 trial results.<sup>44</sup> All interventions should be assessed versus no intervention before being introduced  
37 into clinical practice.<sup>44</sup>  
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## Mentalization-based treatment

We did not find any relevant treatment manual we could use for the mentalization-based treatment, and we therefore created our own manual.<sup>35</sup> The therapists in the mentalization-based treatment group were educated and experienced in psychodynamic therapy and group therapy and had undergone basic training and education in mentalization-based treatment according to Bateman and Karterud.<sup>19-22</sup> Mentalization-based treatment was originally designed to treat borderline personality.<sup>16, 18</sup> Few participants were diagnosed with borderline personality disorder (**Table 1**), and it can be argued that mentalization-based treatment was not a relevant intervention for the depressed participants of this trial. However, mentalization-based treatment is now used to treat a number of different disorders other than borderline personality disorder, including depression.<sup>16, 18</sup> Furthermore, a study has shown that female inpatients with depression showed a significantly lower capacity for mentalization compared with healthy controls — and deficits in mentalizing capacity were related to illness duration, number of admissions, and cognitive impairment.<sup>23</sup> The authors conclude that the investigation of mentalization may be of particular importance for the development of targeted psychotherapeutic interventions for depression.<sup>23</sup>

## Comorbid personality disorders

A large proportion of the included participants were diagnosed with cluster C personality disorders (anxious or fearful personality disorders).<sup>29, 30</sup> It has been debated if a diagnosis of a personality disorder is accurate when patients are acutely depressed.<sup>25</sup> Our results indicate that comorbid personality disorder and depression does not lead to a poorer outcome compared to patients with depression alone — but this could be because the diagnoses of the personality disorders in our trial are inaccurate because the depressive symptoms might mimic pathological personality traits. Furthermore, the limited number of included participants significantly reduces the power of this analysis.



## BDI compared to HDRS as outcome

It is a common belief among clinicians that BDI is a more 'reactive' outcome than HDRS,<sup>55</sup> and it might be surprising to some why we identified a borderline significant effect on the HDRS results but no significant effect on the BDI. However, two systematic reviews with meta-analysis have included trials that simultaneously used HDRS and BDI to assess the effects of the same interventions.<sup>55, 56</sup> The results showed that BDI under such circumstances shows significantly less effect sizes compared to the HDRS.<sup>55, 56</sup> A greater percentage of participants would be considered improved if ratings of change were based on the HDRS rather than BDI.<sup>55</sup> The results from these two reviews<sup>55, 56</sup> are in agreement with our present results and may explain why we found a borderline significant effect on HDRS and no significant effect on BDI. On the other hand, it is also possible that HDRS compared to BDI overestimates participant improvement.<sup>56</sup>

It was impossible to blind the participants to treatment allocation. To ensure some degree of blinding we chose HDRS over BDI because it was possible to perform objective blinded outcome assessment using the HDRS. BDI is a self-administered questionnaire, which makes blinded objective outcome assessment impossible. We therefore expected the results on HDRS to be a more clinically valid compared to the BDI results — but we cannot exclude that breaking of blinding and biased assessment of the HDRS may have occurred. In accordance with the CONSORT Statement we did not assess degree of unblinding.<sup>45</sup>

## Implications

First of all, if a larger more definitive trial has to be conducted then a more realistic estimate of the recruitment rate will be needed and more centres should be involved. On average, we recruited approximately one participant every third week and we expected to be able to recruit

1 approximately one participant every week. Before the randomisation began, we did not  
2 systematically assess how many participants it was possible to recruit. This should also be done  
3 before a larger trial is conducted so the sample size can be reached. Moreover, we did not take  
4 any specific actions promoting the trial outside the clinic. If a future trial is to be conducted it  
5 should be considered to promote the trial through advertising or use of other measures to motivate  
6 potential referrers to refer more eligible participants. Besides the problems with recruiting enough  
7 participants, it was otherwise feasible to conduct a randomised clinical trial with low risk of bias  
8 assessing the effects of third wave cognitive therapy versus mentalization-based treatment for  
9 major depressive disorder.  
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24 The apparent difference in intervention effect found on the HDRS might be caused by random  
25 error ('play of chance'), unaccounted bias, or a signal of a real effect.<sup>54</sup> The National Institute for  
26 Clinical Excellence (NICE) have suggested a mean difference between two compared  
27 interventions of three points on HDRS as a criterion for 'clinical significance'.<sup>57</sup> Most interventions  
28 for depression, both psychopharmacological as well as psychotherapeutic, rarely exceed having a  
29 beneficial effect of more than three points on the HDRS.<sup>6, 17, 58-60</sup> We found a mean difference of  
30 more than four points on the HDRS which, compared to other interventions, is relatively high.  
31 These results might be used to calculate a necessary sample size in a larger more definitive trial.  
32 However, HDRS might not at all be a clinically relevant outcome measure and other more clinically  
33 relevant outcome measures might be more valid to use in future trials. Severity of depression as  
34 measured by the total HDRS score has failed to predict suicide attempts,<sup>61, 62</sup> and some  
35 publications have questioned the usefulness of the HDRS and concluded that the scale is  
36 psychometrically and conceptually flawed.<sup>62, 63</sup>  
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## 55 Conclusions

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1 Our trial results show that it was much harder than expected to recruit eligible participants to the  
2 trial. It took us longer to recruit participants than stipulated. However, it was otherwise possible to  
3 conduct the trial with low risk of bias. Our preliminary results show that third wave cognitive  
4 therapy compared with mentalization-based treatment may be a more effective intervention for  
5 depressive symptoms measured on the HDRS. The effects of the two interventions did not seem  
6 to differ significantly regarding BDI II, SCL 90-R, and WHO 5. More randomised clinical trials are  
7 needed to assess the effects of third wave cognitive therapy versus mentalization-based treatment  
8 and versus no intervention.  
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## Acknowledgments

We would like to thank all the participants in the trial for patiently cooperating with the assessments. We would also like to thank Anita Jensen for helping with data management; Lotte Dragsted and Marianne Lyngby for performing the Hamilton interviews; Gitte Nielsen for assistance in developing the treatment manual for the third wave cognitive therapy; and Jane Lindschou for expert assistance with the randomisation. Lastly, we would like to thank all the co-workers at the psychiatric clinic in Roskilde. Without their patience and cooperation the trial would have been impossible to conduct.

## Conflicts of interest

We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors. The principal investigator was also a therapist in the third wave cognitive therapy treatment and has developed the treatment manual for the third wave cognitive therapy. The consultant performing the medical consultations during the trial period was not blinded to the treatment allocation of the participants and developed the mentalization-based treatment manual in close cooperation with the two mentalization-based therapists. Other authors have no competing interests.

## Contributors

JCJ and CG wrote the first draft. JCJ, CG, KAL, PS, US, and ES planned and designed the trial. JCJ and MK performed the reliability tests. KAL, PS, US, and ES contributed with psychiatric expertise. PW conducted the statistical analyses. TL contributed with statistical expertise. All

1 authors contributed academically to the manuscript and have accepted the manuscript for  
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3 publication.  
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## 10 **Ethical considerations and regulatory approval**

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13 There were no immediate ethical problems regarding this trial. Research has not identified any  
14 significant adverse effects or risks from either of the compared interventions. Before randomization  
15 began approval was obtained by the Regional Ethics Committee of Zealand (no: SJ-43) and the  
16 trial was registered at the Danish Data Protection Agency (no: 2008-58-0020).  
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24 All participants were informed of the trial in writing and verbally before randomization. Written  
25 informed consent was obtained from every participant before inclusion. All trial participants were,  
26 on request, permitted access to further information about the project. No expense allowance was  
27 offered to the trial participants  
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## Tables

### Table 1. Baseline characteristics

		Participants randomised to third wave cognitive therapy (n=22)	Participants randomised to mentalization-based therapy (n=22)
<b>Age</b>	mean (SD)	38.5 (8.9)	40.3 (6.8)
<b>Sex</b>	female n (%)	18 (82)	20 (91)
<b>Number of children</b>	mean (SD)	1.4 (1.2)	1.7 (1.1)
<b>Marital status</b>	n (%)		
Single		3 (14)	7 (32)
In a relationship		6 (27)	5 (23)
Married		12 (55)	8 (36)
Separated/divorced		1 (5)	2 (9)
<b>Level of education</b>	n (%)		
Only high school diploma		7 (32)	3 (14)
Medium long education		14 (64)	19 (86)
Long education		1 (5)	0 (0)
<b>Baseline HDRS** scores</b>			
	mean (SD)	22.1 (5.9)	22.5 (4.9)
	median	22.5	23.6
	range	7-30	11-29
<b>Baseline GSI scores (SCL 90-R)***</b>			
	mean (SD)	1.80 (0.59)	1.84 (0.41)
	median	1.72	1.74
	range	0.68-2.79	0.99-2.54
<b>Personality disorders</b>	n (%)		
No personality disorder		5 (23)	6 (27)
One personality disorder		11 (50)	12 (55)
Two personality disorders		4 (18)	3 (14)
Three or more personality disorders		2 (9)	1 (5)
<b>Personality disorders diagnoses</b>	n (%)		
Paranoid		1 (5)	0 (0)
Borderline		4 (18)	1 (5)
Avoidant		7 (32)	5 (23)
Obsessive-compulsive		4 (18)	3 (14)
Dependant		1 (5)	0 (0)
Depressive		7 (32)	8 (36)
Personality disorder NOS		1 (5)	4 (18)

\*SD=Standard Deviation; \*\*HDRS=17-item Hamilton Depression rating Scale; \*\*\*SCL-90-R=Global Severity Index score on the Symptom Checklist 90 Revised

**Table 2. Psychopharmacological medication**

	Participants randomised to third wave cognitive therapy		Participants randomised to mentalization-based treatment	
	At baseline (N=22)	At end of treatment (N=22)	At baseline (N=22)	At end of treatment (N=20)
No medication	3 (13%)	5 (23%)	2 (9%)	2 (10%)
SSRI*	9 (40%)	9 (41%)	13 (59%)	7 (35%)
Dual-action antidepressants**	11 (50%)	6 (27%)	4 (18%)	6 (30%)
Other antidepressants***	1 (5%)	0 (0%)	2 (9%)	2 (10%)
Pregabalin (150mg/ day)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Mood stabilizers****	2 (9%)	1 (5%)	1 (5%)	1 (5%)
Benzodiazepines*****	3 (14%)	2 (9%)	7 (32%)	5 (25%)
Antipsychotics*****	5 (23%)	4 (18%)	5 (23%)	2 (10%)
Medication for attention-deficit hyperactivity disorder*****	2 (9%)	1 (5%)	0 (0%)	0 (0%)
Disulfiram (200mg/ day)	1 (5%)	0 (0%)	1 (5%)	1 (5%)

\*SSRI (selective serotonin reuptake inhibitors): fluoxetine 20mg - 60mg/ day; sertraline 100mg-200mg/ day; citalopram 20mg-40mg/ day; escitalopram 10mg-20mg.

\*\*duloxetine (60mg-90mg/ day); venlafaxine 75mg-225mg/ day; mirtazapine 15mg-45mg/ day

\*\*\*agomelatine (50mg/ day); amitriptyline (100mg/ day).

\*\*\*\*lamotrigine (25mg-100mg/ day); valproate (600mg/ day).

\*\*\*\*\*oxazepam 15mg-45mg/ day; bromazepam 4.5mg/ day; zolpidem 5mg/ day; oxazepam 15mg/ by demand; alprazolam 0.5mg/ by demand; diazepam 5mg/ by demand; zopiclone 7.5mg/ by demand.

\*\*\*\*\*quetiapine 25-100mg/day; olanzapine 2.5mg-5mg/day; chlordiazepoxid 15-25mg/ by demand.

\*\*\*\*\*methylphenidate 36mg/ day; atomoxetine 80mg/ day.

**Table 3. Effects of third wave cognitive therapy versus mentalisation-based treatment**

Outcome measure	Group randomised to third wave cognitive therapy (N=22)		Group randomised to mentalization-based treatment (N=22)		P-value of unadjusted analysis at end of treatment	P-value of adjusted analysis* at end of treatment
	Baseline	End of treatment	Baseline	End of treatment		
<b>HDRS</b>						
N	22	22	21	20	0.051	0.039
Mean	22.1	12.9	22.5	17.0		
95%CI	19.5-24.8	9.81-15.9	20.3-24.8	14.0-20.0		
<b>Remission (HDRS&lt;8)</b>						
N/ total	0/22	5/22	0/21	0/20	0.049	Not possible to calculate
<b>BDI II</b>						
N	21	21	22	17	0.46	0.46
Mean	36.8	17.6	36.3	20.5		
95%CI	32.5-41.1	12.2-23.0	32.1-40.6	14.5-26.4		
<b>SCL 90-R (GSI score)</b>						
N	22	22	22	20	0.52	0.66
Mean	1.80	0.88	1.84	1.00		
95%CI	1.54-2.05	0.62-1.15	1.66-2.02	0.74-1.25		
<b>WHO 5</b>						
N	22	22	21	20	0.54	0.46
Mean	3.55	10.5	4.33	9.45		
95%CI	1.84-5.25	7.66-13.4	3.13-5.53	7.18-11.7		

\*= Adjusted for baseline values of each outcome

Abbreviations: HDRS=Hamilton Depression Rating Scale (17-item); N=Number of participants; CI=Confidence interval; BDI=Beck's Depression Inventory; SCL 90-R=Symptom Checklist 90 Revised; GSI=Global Severity Index score; WHO 5=World Health Organisation-Five Well-being Index 1999, a high score associates to a high level of well-being.

## Figure Legends

### Figure 1 (CONSORT flowchart)

### Figure 2

Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks. 42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.<sup>40-43</sup> These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

### Figure 3

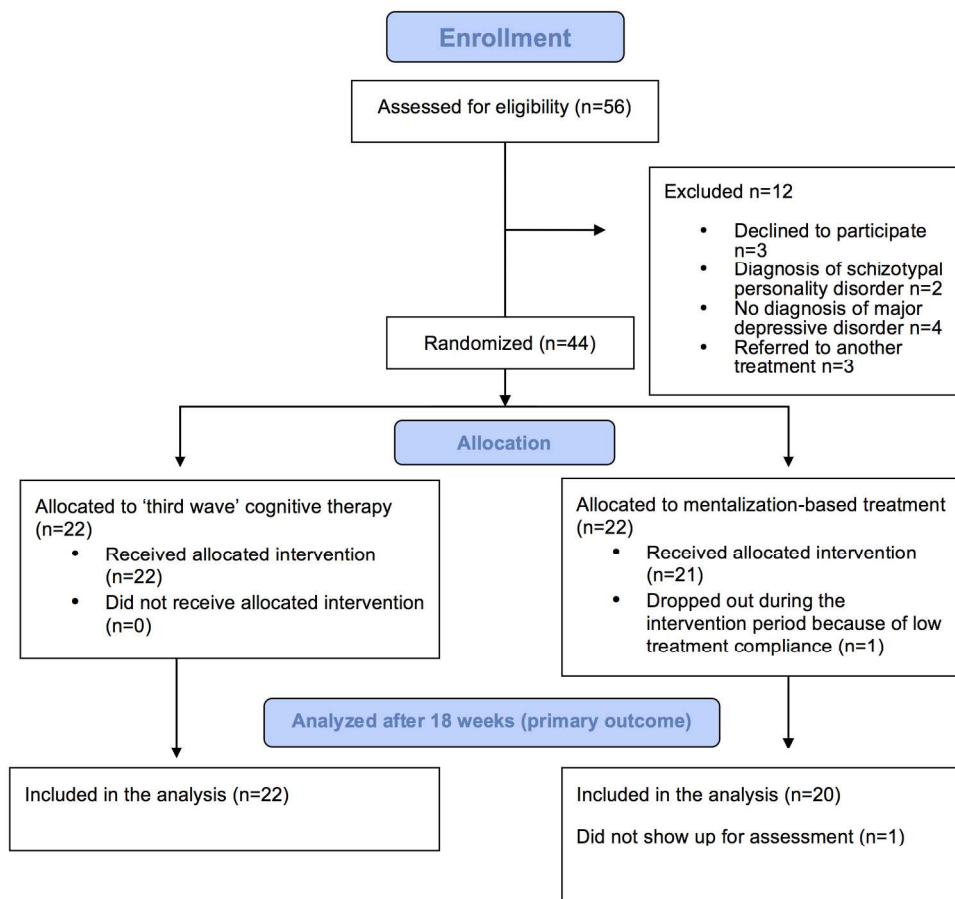
Post-hoc sequential analysis of the results on Beck's depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.<sup>40-43</sup> The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data

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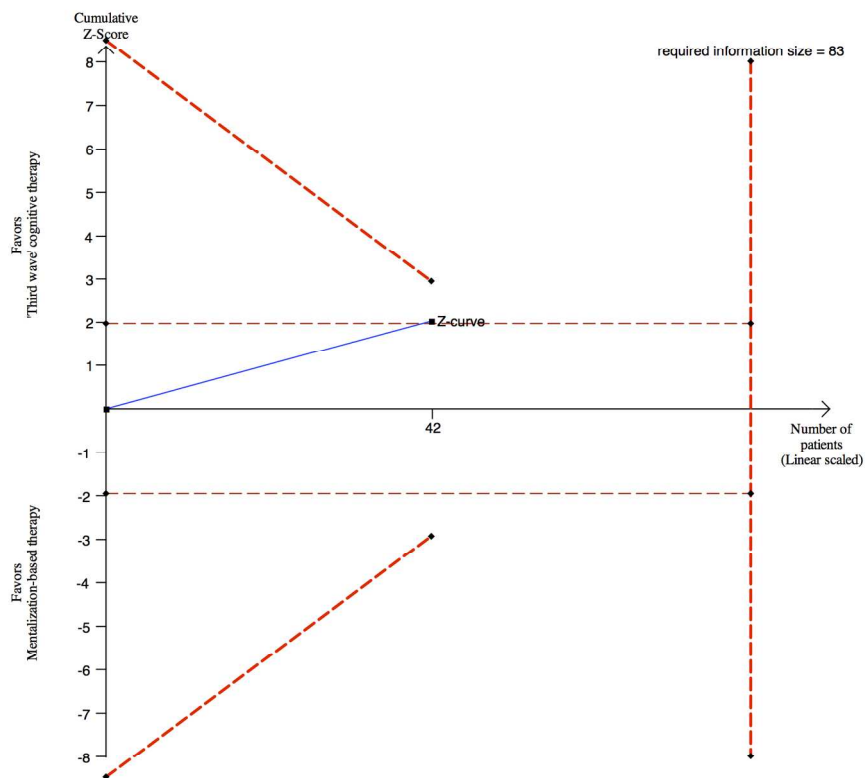
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(CONSORT flowchart)  
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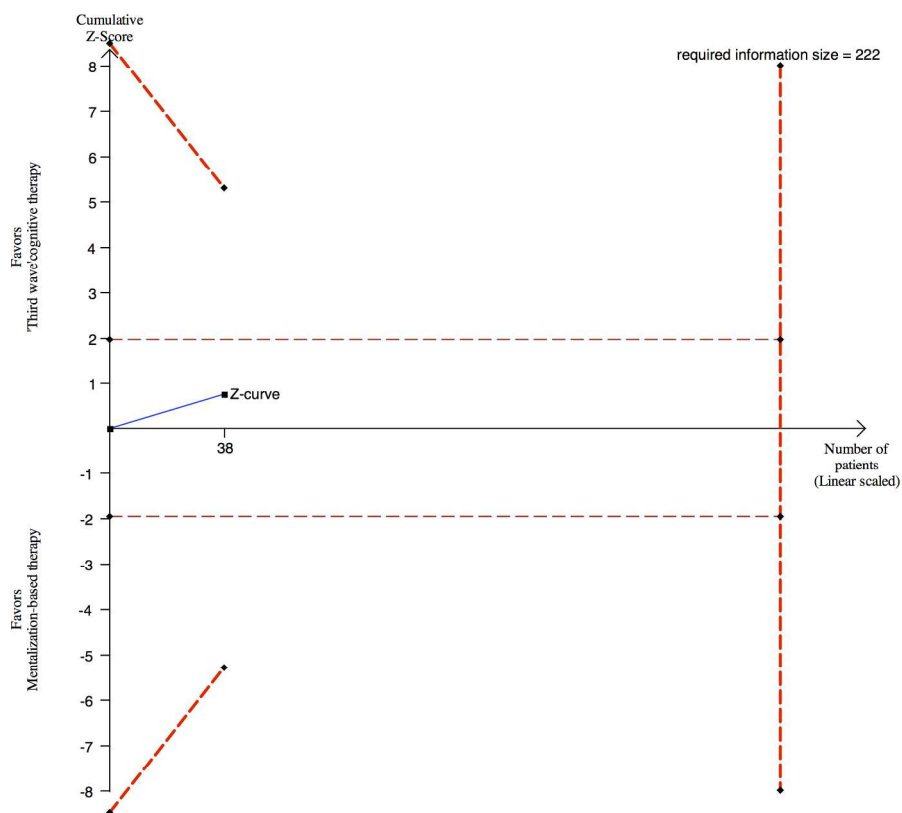


Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks.

42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.40-43. These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) does not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

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Post-hoc sequential analysis of the results on Beck’s depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.40-43 The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of no beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

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## CONSORT CHECKLIST

**Table.** CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial<sup>a</sup>

Section and Topic	Item No.	Checklist Item	Reported on Page No.
<b>Title and abstract</b>	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
<b>Introduction</b> Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
<b>Methods</b> Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	6-7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-10
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	10-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomization; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	13
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
<b>Results</b> Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	see cor 14
	13b	For each group, losses and exclusions after randomization, together with reasons	14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	17-18
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	see Tab
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Se Tabl
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	See Tal Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	26
<b>Comment</b> Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	17-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-20
<b>Other information</b> Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22

<sup>a</sup>We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see <http://www.consort-statement.org>.

# BMJ Open

## Third wave Cognitive Therapy versus Mentalization-based Treatment for Major Depressive Disorder. A Randomised Clinical Trial

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-004903.R1
Article Type:	Research
Date Submitted by the Author:	09-Jun-2014
Complete List of Authors:	Jakobsen, Janus; Copenhagen Trial Unit, 7812 Gluud, Christian; Copenhagen Trial Unit, 7812 Kongerslev, Mickey; Psychiatric Research Unit, Region Zealand, Roskilde, Copenhagen University Hospital, Denmark, Larsen, Kirsten; Psychiatric Clinic, Psychiatry, Roskilde;; Sørensen, Per; Department of Psychiatry, Copenhagen University Hospital, Copenhagen, Winkel, Per; Copenhagen Trial Unit, 7812 Lange, Theis; Department of Public Health, University of Copenhagen., Søgaard, Ulf; Psychiatric Clinic, Psychiatry, Roskilde;; Simonsen, Erik; Psychiatric Research Unit, Region Zealand, Roskilde, Copenhagen University Hospital, Denmark,
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Public health
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Personality disorders < PSYCHIATRY

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Manuscripts

# Third wave Cognitive Therapy versus Mentalization-based Treatment for Major Depressive Disorder. A Randomised Clinical Trial

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## Abstract

**Objective:** To compare the benefits and harms of third wave cognitive therapy versus mentalization-based therapy in a small sample of depressed participants.

**Design, participants, and setting:** We planned to randomise 84 consecutive adult participants diagnosed with major depressive disorder to third wave cognitive therapy (n=22) versus mentalization-based treatment (n=22) in a superiority randomised clinical trial. The outcome assessors and the statistician were blinded to treatment allocation. The trial was conducted at an outpatient psychiatric clinic for non-psychotic patients in Roskilde, Denmark.

**Outcomes:** The primary outcome was the Hamilton Rating Scale for Depression (HDRS) at end of treatment (18 weeks). Secondary outcomes were: remission (HDRS < 8), Beck's Depression Inventory, Symptom Checklist 90 Revised, and The World Health Organisation-Five Well-being Index 1999.

**Results:** The trial inclusion lasted for about two years as planned but only 44 out of the planned 84 participants were randomised. Two mentalization-based participants were lost to follow-up. The unadjusted analysis showed that third wave participants compared with mentalization-based participants did not differ significantly regarding the 18 weeks HDRS score (12.9 versus 17.0; mean difference -4.14; 95% CI -8.30 to 0.03; P = 0.051). In the analysis adjusted for baseline HDRS score, the difference was favouring third wave cognitive therapy (P = 0.039). At 18 weeks, five of the third wave participants (22.7%) were in remission versus none of the mentalization-based participants (P = 0.049). We recorded no suicide attempts or suicides during the

1 intervention period in any of the 44 participants. No significant differences were found between  
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4 the two intervention groups on the remaining secondary outcomes.  
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8 **Conclusions:** Third wave cognitive therapy may be more effective than mentalization-based  
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10 therapy for depressive symptoms measured on the HDRS. However, more randomised clinical  
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12 trials are needed to assess the effects of third wave cognitive therapy and mentalization-based  
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14 treatment for depression.  
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19 **Trial registration:** Registered with Clinical Trials government identifier: NCT01070134  
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24 **Keywords:** Randomised clinical trial; depression; third wave cognitive therapy; mentalization-  
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## Strengths and limitations of this study

- It was possible to conduct the trial with a low risk of bias, which was the primary strength of this randomised clinical trial.
- The trial also provided valuable information about possible intervention effects of third wave cognitive therapy and mentalization-based treatment. Our preliminary results may be used to design future trials including estimation of sample size calculations.
- The primary limitation of this randomised clinical trial was that only 44 out of the planned 84 participants were randomised in this small-scale trial.

## Introduction

### Third wave cognitive therapy

Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of traditional cognitive therapy versus no intervention for major depressive disorder.<sup>1</sup> We found that cognitive therapy seems to have a statistically significant beneficial effect on depressive symptoms. However, we identified only a limited number of relatively small randomised clinical trials all with a high risk of bias.<sup>1</sup> Our results are in contrast to non-systematic reviews concluding that cognitive therapy has large clinical effects.<sup>2</sup> Our review results showed that the effects of cognitive therapy, if any, seem to be relatively small (mean difference about three HDRS points).<sup>1</sup> During the last two decades new forms of cognitive therapy have been developed. These third wave cognitive therapies include, e.g., acceptance and commitment therapy, schema therapy, mindfulness-based cognitive therapy, and meta-cognitive therapy.<sup>3</sup> Especially mindfulness-based interventions have been implemented in numerous different clinical contexts in recent years.<sup>4-6</sup> One meta-analysis showed that third wave cognitive therapy might prevent relapse of depression,<sup>7</sup> and small trials show that third wave cognitive therapy versus no intervention or treatment as usual is effective for acutely depressed patients.<sup>8, 9</sup> One trial has shown comparable effects between cognitive therapy and third wave cognitive therapy in non-melancholic depression, but the trial only included 45 participants.<sup>10</sup>

### Mentalization-based treatment

Mentalizing entails attending to mental states – holding ‘mind in mind’.<sup>11</sup> It is the process by which an individual explicitly and implicitly interpret the action of himself or herself and others on the basis on intentional mental states such as wishes, needs, goals, and reason.<sup>11</sup>



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Mentalization-based treatment is rooted in attachment theory and developmental psychopathology and it includes essentials from psychodynamic psychotherapy in a concurrent individual and group format.<sup>11</sup> Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of psychodynamic therapy for major depressive disorder.<sup>12</sup> We found that psychodynamic therapy versus no intervention seems to have a small statistically significant effect on depressive symptoms (mean difference about three HDRS points).<sup>12</sup> However, we identified a limited number of trials, the trials were small, and all the trials had a high risk of bias so our results might be questioned.

Mentalization-based therapy was originally developed to treat borderline personality disorder but is now also used to treat various other psychiatric disorders such as depression, eating disorders, substance abuse, and personality disorders other than borderline.<sup>11, 13</sup> Mentalization-based treatment is based on the concept of mentalization as described by Fonagy and Bateman,<sup>14, 15</sup> and is different from the more strictly defined mentalization-based therapy as manualized by Karterud and Bateman.<sup>14-17</sup> In comparison with mentalization-based therapy, mentalization-based treatment used in this trial has a more open therapeutic stance – letting the patient decide the theme in an associative way. The therapist is less active in directing the theme in the dialog and uses interpretations. Mentalizing deficits can be assumed to underlie depressive symptoms,<sup>18, 19</sup> and many depressed patients have a comorbid personality disorder.<sup>20</sup> We did not identify any trial assessing the effects of mentalization-based treatment or therapy versus no intervention for major depressive disorder.<sup>12</sup>

### **Third wave cognitive therapy versus mentalization-based treatment**

No randomised clinical trials or systematic reviews seem to have examined the effects of third wave cognitive therapy versus mentalization-based treatment or therapy for major depression.<sup>21</sup>

## Methods

In the following, we briefly describe the methodology of this trial. For details please consult our registered (clinicaltrials.gov: NCT01070134) and published protocol.<sup>22</sup>

### Objective

Our objective was to compare the effect of third wave cognitive therapy versus mentalization-based therapy in a small sample of participants with major depressive disorder.

### Inclusion of participants

The trial was conducted at a public psychiatric outpatient clinic only treating patients on sick leave due to a psychiatric disorder. Patients were referred from general practitioners, psychiatrists in private practice, and medical and psychiatric departments. No special announcement of the trial was made to the referrers. All patients referred to the psychiatric clinic had a full psychiatric examination by a physician who made the preliminary psychiatric diagnoses (DSM-IV-TR).<sup>23</sup> Eligible patients were then interviewed by the principal investigator (JCJ) who used the depression part of the structured clinical interview for DSM-IV axis I disorders (SCID I) interview<sup>24</sup> to assess whether the patient fulfilled the criteria for a major depressive disorder (DSM-IV-TR).<sup>23</sup> Before randomisation baseline assessments were carried out for all outcome measures and all eligible patients were assessed with the structured clinical Interview for DSM-IV axis II disorders (SCID II).<sup>25</sup> We chose to perform the SCID II assessments because we wanted to compare personality disorders at baseline in the two intervention groups and to exclude patients with schizotypal personality disorder.

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4 The participant had to meet all of the inclusion criteria and none of the exclusion criteria.  
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### 8 **Inclusion criteria** 9

- 10 1. Age from 18 to 65 years.
- 11 2. Major depressive disorder, whether first episode or recurrent (DSM-IV-TR).<sup>24</sup>
- 12 3. Beck's Depression Inventory (BDI II) score >13 points.<sup>26</sup>
- 13 4. Written informed consent.
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### 21 **Exclusion criteria** 22

- 23 1. Current psychosis, schizophrenia, or schizotypal personality disorder (DSM-IV-TR).<sup>23</sup>
- 24 2. A significant alcohol or substance abuse (assessed during the preliminary consultations).
- 25 3. Initiated or changed medical anti-depressive treatment less than six weeks before  
26 randomisation.
- 27 4. Pregnancy.
- 28 5. No written informed consent.
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### 40 **Randomisation** 41

42 Eligible patients with major depressive disorder were randomised 1:1 to third wave cognitive  
43 therapy versus mentalization-based treatment. The Copenhagen Trial Unit performed the  
44 randomisation centrally, using a computer generated block randomisation sequence that was  
45 unknown to the investigators. Participant inclusion began in February 2010 and the last patient  
46 was randomised in July 2011. Because of an unequal allocation of the trial participants to one of  
47 the two groups in the beginning of the trial (there were only a few participants in one of the  
48 groups), the block size was reduced from 12 to 4 and a stratification variable (HDRS score  $\geq 22$   
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1 points) was removed. The block sizes were at all times unknown to the trial investigators, and the  
2  
3 Copenhagen Trial Unit performed these changes without informing the investigators of the  
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5 changes. Otherwise, the methodology was not changed after trial commencement.  
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## 10 11 **Interventions**

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13 Each participant received treatment for 18 weeks. The two intervention groups were 'slow-open'  
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15 (new patients entered the group continually) with a maximum of seven patients per group.  
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20 The time of each of the elements in the comprehensive treatment package (see below) was  
21  
22 planned to be similar in the compared intervention groups.  
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## 25 26 27 **Shared elements for both intervention groups**

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29 All participants were, as part of the outpatient clinic's usual care, offered a communal breakfast  
30  
31 twice a week and participated in group psycho-education for one hour a week. During the course  
32  
33 of treatment, all participants with children were offered participation in a parent support group (four  
34  
35 weekly one-hour sessions). A psychiatric consultant (KAL), who was not otherwise involved in the  
36  
37 interventions, assessed each participant and prescribed psychopharmacological treatment when  
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39 needed. The psychiatric consultant prescribed medication according to the official  
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41 recommendations.<sup>27</sup> After the first consultation, medical consultations were offered by demand of  
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43 the participant or the therapists.  
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## 49 50 **Third wave cognitive therapy**

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52 The third wave cognitive therapy consisted of one weekly third wave cognitive individual  
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54 psychotherapy session (45 minutes) and one weekly mindfulness-skills training group (1.5 hours).  
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2 Altogether the third wave cognitive therapy consisted of 18 individual psychotherapy sessions  
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4 (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.  
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8 The weekly individual psychotherapy session included:  
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- 10 • Introduction of the cognitive model and mindfulness.
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- 12 • Exploration of thoughts, feelings, behaviour, and physical sensations.
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- 14 • Work on acceptance of difficult feelings and difficult life circumstances.
- 15
- 16 • Work on assumptions challenged by behavioural experiments.
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- 18 • Self esteem training.
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- 20 • Tools to prevent relapse.
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26 The weekly mindfulness-skills training group included:  
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28 Education in the practical use of six basic mindfulness skills: focusing, acceptance, labeling  
29 feelings, body awareness, self-esteem skills, and mindful communication. The group participants  
30 were encouraged to practice the six mindfulness skills between sessions. The participants went  
31 through the complete skills training group's program three times during the course of the 18 weeks  
32 of treatment.  
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41 The manual for the third wave cognitive therapy was developed specifically for the trial and had  
42 not been used before in a trial setting. Details about the third wave cognitive therapy program is  
43 available elsewhere.<sup>28</sup>  
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## 49 50 51 **Mentalization-based treatment**

52 The mentalization-based treatment consisted of a weekly mentalization-based individual  
53 psychotherapy session (45 minutes) and a weekly mentalization-based group therapy session (1.5  
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1 hours). Altogether the mentalization-based treatment consisted of 18 individual psychotherapy  
2 sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.  
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8 Mentalization-based treatment imposes explicit attention to mentalizing in the therapeutic process.  
9 This is established by a therapeutic stance where the therapist aims at demonstrating a  
10 'mentalizing attitude', i.e., validating, 'not-knowing', and curiously questioning the patient about  
11 feelings and thoughts.<sup>11, 17, 29</sup> The therapist tries to identify and intervene when the patient is not  
12 mentalizing and assists the patient in regulating the level of the emotions so the patient is able to  
13 mentalize and to get different perspectives on life events, conflicts, etc.<sup>11, 17, 29</sup>  
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24 At the time this project was planned there was no manual available for the mentalization-based  
25 treatment. Therefore, we developed our own treatment manual based on mentalization  
26 principles.<sup>30</sup> Further details about the mentalization-based treatment is available elsewhere.<sup>30</sup>  
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### 33 **Therapists and adherence to the intervention manuals**

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35 Each intervention group had two therapists. The two third wave cognitive therapists (one of these  
36 therapists was the principal investigator) and the two mentalization-based therapists had  
37 comparable psychotherapeutic education and experience.  
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44 All individual sessions were recorded on an audio recorder and all group sessions were recorded  
45 on video. An experienced external psychologist not otherwise involved in the trial assessed the  
46 degree of adherence to the manuals 0-5 (0: no adherence; 1: adherence about 20% of the time; 2:  
47 adherence about 40% of the time; 3: adherence about 60% of the time; 4: adherence about 80%  
48 of the time; 5: adherence about 100% of the time). The psychologist randomly selected 4 x 5  
49 sessions using a computer program. The results showed high adherence to the treatment manuals  
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2 for both interventions. The means of the ratings were: 4.6 in five sessions of individual third  
3 wave cognitive therapy; 4.2 in five sessions of third wave cognitive group therapy; 4.2 in five  
4 sessions of individual mentalization-based treatment; and 3.8 in five sessions of mentalization-  
5 based group treatment.  
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## 10 11 12 13 **Outcomes**

### 14 15 16 17 **Primary outcome**

- 18 • Score on the Hamilton Depression Rating Scale (HDRS)<sup>31</sup> after end of treatment at week  
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### 24 25 26 27 **Secondary outcomes**

- 28 • The proportion of participants in remission after cessation of treatment at week 18. We  
29 defined remission as HDRS below 8.<sup>32</sup>  
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- 33 • Global Severity Index score (GSI-score)<sup>33</sup> on the Symptom Checklist 90 Revised (SCL-90-  
34 R)<sup>33</sup> after cessation of treatment at week 18.  
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- 37 • Score on the World Health Organisation-Five Well-being Index 1999 (WHO 5)<sup>34</sup> after  
38 cessation of treatment at week 18.  
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- 42 • Score on the Beck's Depression Inventory (BDI II)<sup>26</sup> after cessation of treatment at week 18.  
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### 46 47 **Reliability of the Hamilton Depression Rating Scale (HDRS) interviews**

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49 Two experienced psychologists performed the Hamilton interviews during the trial period. Prior to  
50 the trial, the principal investigator and one of the psychologists both Hamilton interviewed eight  
51 patients at the same time point. The mean difference between these two HDRS ratings performed  
52 on the same patient at the same time point was -0.13 points (SD 1.25) (intra-class correlation  
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1 coefficient 0.98; Spearman correlation 0.92). During the trial both psychologists Hamilton  
2 interviewed 21 patients at the same time point. The mean difference between these two HDRS  
3 ratings performed on the same patient at the same time point was 0.29 points (SD 2.21) (intra-  
4 class correlation coefficient 0.96; Spearman correlation 0.94). All these 29 interviews were  
5 performed with both HDRS-raters present simultaneously. One rater interviewed and rated the  
6 interviewee and the other rater only rated the interviewee. The interviewers were not allowed to  
7 discuss the results before each interviewer had registered the HDRS result.  
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## 20 **Data-management**

21 All data were handled by research assistants not otherwise involved in the trial and was stored in  
22 the principal investigator's office and later at the Copenhagen Trial Unit. Privacy of trial  
23 participants was protected in accordance with the Act on Processing of Personal Data and the  
24 Health Act. The project was notified to the Danish Data Protection Agency (no.: 2008-58-0020).  
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## 33 **Blinding**

34 The Hamilton interviewers were blinded to treatment allocation and were instructed by the  
35 principal investigator to avoid questions beside the Hamilton interview. All interviewees were prior  
36 to each interview instructed by the principal investigator not to mention which treatment they were  
37 allocated to. It was not possible to blind neither the therapists nor the participants to treatment  
38 allocation.  
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49 The chief consultant performing the medical consultations was, due to practical circumstances, not  
50 blinded to treatment allocation.  
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1 A statistician at The Copenhagen Trial Unit performed the statistical analyses blinded with the  
2 two intervention groups coded as 'A' and 'B'.  
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### 8 **A priori sample size estimate**

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10 With a 'minimal relevant mean difference' (MIREDIF) between the two interventions of 5 HDRS  
11 points, an alpha of 0.05 (type I error), a power of 0.90 (type II error of 10%), and a standard  
12 deviation (SD) of 7 HDRS points, the sample size calculation showed that a total of 84 participants  
13 would be necessary. We estimated that we would need an inclusion period of about two years to  
14 recruit 84 participants.  
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### 24 **Statistical analyses**

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26 The primary analyses were intention-to-treat analyses. Significance tests were two-sided at a  
27 significance level of 0.05.  
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33 Continuous outcomes were compared between the two intervention groups using the univariate  
34 general linear model with (ANCOVA) and without HDRS baseline value adjustment (ANOVA). The  
35 binary outcome was compared between the groups using Fisher's exact test. Logistic regression  
36 could not be used since none of the participants in the mentalization-based group obtained  
37 remission implying an infinite odds ratio.  
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47 As the trial was stopped before the sample size was reached, we *post hoc* decided to conduct  
48 sequential analysis to assess the results of significance testing taking sparse data and repetitive  
49 testing into consideration.<sup>35</sup> We used the trial sequential analysis program for that purpose.<sup>36-39</sup>  
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## Results

### Participants

Only 44 out of the 84 planned participants were included in the trial. Twenty-two participants were randomised to third wave cognitive therapy versus 22 participants to mentalization-based treatment. **Figure 1** details the participant flow through the phases of the trial.

### Baseline characteristics of the participants

The baseline characteristics regarding age, sex, number of children, score on the HDRS, baseline diagnosis of personality disorder, and psychopharmacological treatment were overall assessed as being comparable between the two intervention groups. The baseline participant characteristics are described in detail in **Table 1** and the psychopharmacological treatment in **Supplementary material 1**.

### Treatment compliance

None of the 22 participants randomised to third wave cognitive therapy were lost to follow-up or excluded due to the fact that they participated in less than 70% of the sessions. One participant out of the 22 randomised to mentalization-based treatment was lost to follow-up and one was excluded, as she did not attend the required 70% of the sessions (**Figure 1**). The excluded participant was not assessed on any of the outcomes at end of treatment.

## Intervention effects

### Primary outcome

### Mean score on the HDRS after end of interventions

Participants randomised to third wave therapy compared with participants randomised to mentalization-based treatment did not differ significantly regarding the 18-week HDRS scores in the unadjusted analysis (mean 12.9, 95% CI 9.81 to 15.9 versus mean 17.0, 95% CI 14.0 to 20.0;  $P = 0.051$ ). The mean difference between the two groups was -4.14 HDRS points (95% CI -8.30 to 0.03) corresponding to a Cohen's D of -0.62. The difference was, however, significant in the analysis adjusted for baseline HDRS score ( $P = 0.039$ ) (**Table 2**).

Sequential analysis demonstrated that the observed significant findings ought to be interpreted conservatively as random errors due to sparse data cannot be excluded (**Figure 2**).

We did not impute missing values because only 2 out of 44 (4.5%) participants had missing values.

Histograms on the data from both intervention groups showed that the data seem to be normally distributed. Using the non-parametric test the P-value was 0.064.

There was no significant interaction between the indicator of a diagnosis of a personality disorder and the intervention effects. This was also the case when the indicator was redefined as a binary quantity defined as any kind of personality disorder (yes/no) or as a binary quantity defined as personality disorder = borderline personality disorder (yes/no).

### Secondary outcomes

### Participants in remission after cessation of treatment

In the third wave cognitive therapy group 22.7% (n=5) were in remission after cessation of treatment (defined as having HDRS <8 points) versus 0% in the mentalization-based treatment group. This difference was significant (P = 0.049) (**Table 2**).

### BDI II<sup>26</sup>, SCL-90-R<sup>33</sup>, and WHO 5<sup>34</sup> after end of interventions

No significant difference was found on BDI II, SCL-90-R (GSI-scores), or WHO 5 between the two intervention groups after cessation of treatment (**Table 2**). Sequential analysis demonstrated that the observed insignificant findings ought to be interpreted conservatively as random errors due to sparse data cannot be excluded (see **Figure 3** regarding BDI II).

### Other outcomes

#### Admissions, suicide attempts, and suicides

One of the participants randomised to third wave cognitive therapy and two of the participants randomised to mentalization-based treatment were for a short period (some days) admitted to a psychiatric hospital during the intervention period.

We recorded no suicide attempts or suicides during the intervention period in any of the 44 participants.

### Discussion

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4 Our preliminary results indicate that third wave cognitive therapy compared with mentalization-  
5 based treatment may be a more effective intervention for lowering depressive symptoms  
6 measured on the HDRS and may increase the probability of remission (HDRS <8 points).  
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8 Furthermore, our trial demonstrated the feasibility of conducting the trial with low risks of bias.  
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10 However, when only 44 out of the planned 84 participants (52%) of the projected sample size is  
11 obtained in a trial, it is necessary to interpret the results cautiously. Had this been an interim  
12 analysis, any independent safety and data monitoring committee would have recommended  
13 continued randomisation and completion of the trial (**Figure 2** and **Figure 3**).<sup>35</sup> Furthermore, the  
14 two interventions do not seem to have significant differential effects on BDI (subjective depressive  
15 symptoms), SCL 90-R (psychological distress), and WHO 5 (well-being).  
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28 Compared with the baseline scores, both intervention groups improved during the trial period on  
29 all continuous outcomes. However, we did not include a control group receiving no intervention in  
30 this head-to-head trial so it is unclear whether it was trial intervention effects or 'regression  
31 towards the mean' effects that caused these changes.<sup>40</sup> More randomised clinical trials are  
32 needed to assess the effects of third wave cognitive therapy and mentalization-based treatment  
33 for major depressive disorder.  
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## 44 **Strengths**

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46 First of all, the trial was conducted with an overall high level of methodological quality and we  
47 assessed the validity of the trial results according to the procedure proposed by Jakobsen et al.<sup>35</sup>  
48 including adjusting the thresholds for significance according to the number of randomised  
49 participants and the planned sample size.<sup>35</sup> We also proved the feasibility of our trial design, which  
50 can be used for larger trials provided that funding can be raised. Our trial has a number of  
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1 additional strengths: (1) The trial protocol was registered before randomisation began at  
2 ClinicalTrials.gov. In this protocol the outcome hierarchy and plans for analyses were presented.  
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4 Our trial was altogether conducted according to good clinical research practice and therefore with  
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6 low risk of bias and a high degree of external validity.<sup>41-45</sup> (2) Both of the trial interventions were  
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8 conducted using manuals and adherence to the manuals was assessed as relatively high. The  
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10 manualization of the trial interventions makes it possible, to some extent, to implement the two trial  
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12 interventions in clinical practice and to replicate or refute our results in future trials. Both the  
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14 cognitive therapists and the mentalization therapists were involved in developing the treatment  
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16 manuals for the respective psychotherapeutic treatments, which might make the therapist  
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18 enthusiasm and thoroughness similar in the two intervention groups. (3) We have used the most  
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20 commonly used outcomes in trials assessing the effects of psychotherapeutic interventions for  
21  
22 depression (i.e., HDRS and BDI).<sup>12, 31, 46, 47</sup> This makes it possible to relate our results to results  
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24 from other trials examining the effects of interventions for depression. Moreover, using HDRS as  
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26 outcome makes it possible to perform blinded objective outcome assessment, which is a further  
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28 strength of our trial. (4) The baseline characteristics of the trial participants as well as the  
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30 psychopharmacological medication in the two groups were comparable which indicates that the  
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32 randomisation succeeded in allocating comparable participants to the two intervention groups. (5)  
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34 Only 2 out of the total of 44 participants were not assessed after end of treatment, which  
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36 decreases the risk of biased results.<sup>48</sup> (6) All outcomes suggested that the participants randomised  
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38 to third wave cognitive therapy had improved more than the participants randomised to  
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40 mentalization-based treatment. This supports the validity of our results, even though most of these  
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42 differences were non-significant.  
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## 53 Limitations

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1 Our trial has a number of limitations. This small-scale trial was in essence failed because we  
2 only included 44 out of the planned 84 participants. The trial inclusion lasted for about two years  
3 as planned but we had problems with recruiting participants. Basically, not enough eligible  
4 depressed patients were referred to the clinic within the planned trial period. The great advantage  
5 of the randomised clinical trial in general is that all known and unknown participant characteristics  
6 will be similar at baseline in compared intervention groups.<sup>40</sup> However, even though our baseline  
7 characteristics indicate similarity between the two groups on assessed baseline characteristics, it  
8 is unlikely that all baseline characteristics will be similar when only 44 participants are randomised.  
9 The low number of randomised participants in this small-scale trial increases the risks of wrong  
10 results due to type I errors, and type II errors,<sup>49, 50</sup> and our adequate trial methodology cannot  
11 necessarily compensate for these increased risks. Moreover, our results do not show anything  
12 about long-term effects of the two interventions.

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31 The chief consultant prescribing the psychopharmacological treatment was not blinded to  
32 intervention allocation. Although we assessed the psychopharmacological treatment to be  
33 comparable in the two randomised groups at cessation of the trial interventions (**Supplementary**  
34 **material 1**), the lack of blinding might have influenced the psychopharmacological treatment. The  
35 chief consultant is a mentalization-based therapist and was involved in developing the  
36 mentalization-based treatment manual. The first author and primary investigator conducted the  
37 third wave cognitive therapy and wrote the manual for the third wave cognitive therapy program,  
38 which may also increase the risks of bias.

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50 We did not perform power calculations for the secondary outcomes before randomisation began,  
51 which is a further limitation. If an analysis of a secondary outcome has a power of less than 80%,  
52 then either the secondary outcome should be classified as an exploratory outcome or the *P*-value  
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1 and the confidence interval thresholds for significance should be adjusted, just as the thresholds  
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3 are adjusted if a sample size has not been reached.<sup>35</sup>  
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8 Because of an unequal allocation of the trial participants to one of the two groups in the beginning  
9 of the trial, the block size was reduced from 12 to 4 (see '**Randomisation**'). The block sizes were  
10 at all times unknown to the trial investigators, and the Copenhagen Trial Unit performed these  
11 changes without informing the investigators. However, a block size of four is small making it  
12 possible to foresee which group a given eligible participant will be allocated to before  
13 randomisation. This might question whether the allocation concealment was effective.  
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22 The trial was conducted at an outpatient psychiatric clinic with special interest for treatment of  
23 personality disorders and depressive patients were not routinely referred to the clinic before the  
24 trial began randomisation. Our results showed that a high proportion of the trial participants had  
25 comorbid personality disorder and depression. This might explain why the baseline HDRS scores  
26 indicated that the trial participants were only moderately depressed although all of the trial  
27 participants were on sick leave due to psychological problems. Some of the trial participants might  
28 suffer primarily from psychological problem other than depressive symptoms, i.e., personality  
29 related problems. We did not assess number of prior depressive episodes in the included  
30 participants, which makes it unclear whether our trial results demonstrate intervention effects in  
31 participants with a first time depression or recurrent depression. Our results can only be related to  
32 patients comparable to our trial participants, i.e., patients diagnosed with major depressive  
33 disorder on sick leave due to psychiatric problems.  
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52 Highly specialised mentalization-based treatment was the primary psychotherapeutic method used  
53 at the outpatient clinic prior to the trial, the co-interventions (communal breakfast and psycho-  
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1 education) were also a part of the treatment program prior to the trial, and experienced and  
2 specialised third wave cognitive therapists were members of the staff at the psychiatric clinic  
3 where the trial was conducted. Furthermore, all patients referred to the psychiatric clinic were on  
4 sick leave due to psychiatric problems, and even though the evidence behind the specialised  
5 treatments is lacking we considered that some form of specialised treatment was needed for all  
6 patients at the psychiatric clinic. We did, therefore, not consider it ethically justifiable to use a  
7 control group receiving no intervention, placebo, or only the co-interventions. All these  
8 considerations and practical circumstances led to the choice of the psychotherapeutic  
9 interventions and the design of this head-to-head trial comparing third wave cognitive therapy and  
10 co-interventions versus mentalization-based therapy and co-interventions. The co-interventions  
11 were delivered similarly to both treatment groups and the possible effects of co-interventions will  
12 therefore even out between the compared intervention groups unless there are significant  
13 interactions. Nevertheless, it is a clear limitation that our interventions are not and have not been  
14 compared versus no intervention or a more simple and basic form of psychotherapy plus co-  
15 interventions.<sup>40</sup> If a trial comparing the effects of two active interventions shows no difference in  
16 effect it is not clear whether the two interventions are equally effective or equally ineffective – and  
17 if an experimental intervention seem superior compared with a control intervention then the effect  
18 size of the experimental intervention will be unclear because any beneficial or harmful effects of  
19 the control intervention might influence the trial results.<sup>40</sup> All interventions should be assessed  
20 versus no intervention before being introduced into clinical practice.<sup>40</sup> Furthermore, the  
21 combination of specialised psychotherapy and co-interventions constitute a relatively  
22 comprehensive treatment, which might not always be accessible to psychiatric patients in clinical  
23 practice – this might limit the generalizability of our results.

## 55 **Mentalization-based treatment**

1 We did not find any relevant treatment manual we could use for the mentalization-based  
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3 treatment, and we therefore created our own manual.<sup>30</sup> The therapists in the mentalization-based  
4  
5 treatment group were educated and experienced in psychodynamic therapy and group therapy  
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7 and had underwent basic training and education in mentalization-based treatment according to  
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9 Bateman and Karterud.<sup>14-17</sup> Mentalization-based treatment was originally designed to treat  
10  
11 borderline personality.<sup>11, 13</sup> Few participants were diagnosed with borderline personality disorder  
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13 **(Table 1)**, and it can be argued that mentalization-based treatment was not a relevant intervention  
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15 for the depressed participants of this trial. However, mentalization-based treatment is now used to  
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17 treat a number of different disorders other than borderline personality disorder, including  
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19 depression.<sup>11, 13</sup> Furthermore, a study has shown that female inpatients with depression showed a  
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21 significantly lower capacity for mentalization compared with healthy controls – and deficits in  
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23 mentalizing capacity were related to illness duration, number of admissions, and cognitive  
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25 impairment.<sup>18</sup> The authors conclude that the investigation of mentalization may be of particular  
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27 importance for the development of targeted psychotherapeutic interventions for depression.<sup>18</sup>  
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### 35 **Comorbid personality disorders**

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37 A large proportion of the included participants were diagnosed with cluster C personality disorders  
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39 (anxious or fearful personality disorders).<sup>24, 25</sup> It has been debated if a diagnosis of a personality  
40  
41 disorder is accurate when patients are acutely depressed.<sup>20</sup> Our results indicate that comorbid  
42  
43 personality disorder and depression does not lead to a poorer outcome compared to patients with  
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45 depression alone – but this could be because the diagnoses of the personality disorders in our trial  
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47 are inaccurate because the depressive symptoms might mimic pathological personality traits.  
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49 Furthermore, the limited number of included participants significantly reduces the power of this  
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51 analysis.  
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## BDI compared to HDRS as outcome

It is a common belief among clinicians that BDI is a more 'reactive' outcome than HDRS,<sup>51</sup> and it might be surprising to some why we identified a borderline significant effect on the HDRS results but no significant effect on the BDI. However, two systematic reviews with meta-analysis have included trials that simultaneously used HDRS and BDI to assess the effects of the same interventions.<sup>51, 52</sup> The results showed that BDI under such circumstances shows significantly less effect sizes compared to the HDRS.<sup>51, 52</sup> A greater percentage of participants would be considered improved if ratings of change were based on the HDRS rather than BDI.<sup>51</sup> The results from these two reviews<sup>51, 52</sup> are in agreement with our present results and may explain why we found a borderline significant effect on HDRS and no significant effect on BDI. On the other hand, it is also possible that HDRS compared to BDI overestimates participant improvement.<sup>52</sup>

It was impossible to blind the participants to treatment allocation. To ensure some degree of blinding we chose HDRS over BDI because it was possible to perform objective blinded outcome assessment using the HDRS. BDI is a self-administered questionnaire, which makes blinded objective outcome assessment impossible. We therefore expected the results on HDRS to be a more clinically valid compared to the BDI results – but we cannot exclude that breaking of blinding and biased assessment of the HDRS may have occurred. In accordance with the CONSORT Statement we did not assess degree of unblinding.<sup>41</sup>

## Implications

First of all, if a larger more definitive trial has to be conducted then a more realistic estimate of the recruitment rate will be needed and more centres should be involved. On average, we recruited approximately one participant every third week and we expected to be able to recruit approximately one participant every week. Basically, not enough eligible participants were referred

1 to the clinic during the inclusion period and we had to terminate the trial due to economical and  
2 practical constraints – this was the primary reason why we did not randomise more participants.  
3  
4 Before the randomisation began, we did not systematically assess how many participants it was  
5 possible to recruit. This should also be done before a larger trial is conducted so the sample size  
6 can be reached. Moreover, we did not take any specific actions promoting the trial outside the  
7 clinic. If a future trial is to be conducted it should be considered to promote the trial through  
8 advertising or use of other measures to motivate potential referrers to refer more eligible  
9 participants. Besides the problems with recruiting enough participants, it was otherwise feasible to  
10 conduct a randomised clinical trial with low risk of bias assessing the effects of third wave  
11 cognitive therapy versus mentalization-based treatment for major depressive disorder.  
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26 The apparent difference in intervention effect found on the HDRS might be caused by random  
27 error ('play of chance'), unaccounted bias, or a signal of a real effect.<sup>50</sup> The National Institute for  
28 Clinical Excellence (NICE) have suggested a mean difference between two compared  
29 interventions of three HDRS points as a criterion for 'clinical significance'.<sup>53</sup> Most interventions for  
30 depression, both psychopharmacological as well as psychotherapeutic, rarely exceed having a  
31 beneficial effect of more than three HDRS points.<sup>1, 12, 54-56</sup> We used an anticipated intervention  
32 effect of five HDRS points to estimate the necessary sample size and this anticipated intervention  
33 effect was optimistic. Calculating Bayes factor based on the anticipated intervention effect, the  
34 observed intervention effect, and the standard error of the observed intervention effect shows a  
35 Bayes factor of 0.14, which is above the recommended threshold for significance of 0.1.<sup>35</sup> This  
36 underlines that our results should be regarded as insignificant and that an anticipated intervention  
37 effect lower than five HDRS points ought to be used in sample size calculations in future trials  
38 assessing the effects of third wave cognitive therapy and mentalization-based therapy. We found a  
39 mean difference of more than four HDRS points which, compared to other interventions, is  
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1 relatively high. These results might be used to calculate a necessary sample size in a larger  
2 more definitive trial. However, HDRS might not at all be a clinically relevant outcome and other  
3 more clinically relevant outcomes might be more valid to use in future trials. Severity of depression  
4 as measured by the total HDRS score has failed to predict suicide attempts,<sup>57, 58</sup> and some  
5 publications have questioned the usefulness of the HDRS and concluded that the scale is  
6 psychometrically and conceptually flawed.<sup>58, 59</sup>  
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## 15 **Conclusions**

16  
17 Our preliminary results show that third wave cognitive therapy compared with mentalization-based  
18 treatment may be a more effective intervention for depressive symptoms measured on the HDRS.  
19 The effects of the two interventions did not seem to differ significantly regarding BDI II, SCL 90-R,  
20 and WHO 5. More randomised clinical trials are needed to assess the effects of third wave  
21 cognitive therapy and mentalization-based treatment.  
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## Acknowledgments

We would like to thank all the participants in the trial for patiently cooperating with the assessments. We would also like to thank Anita Jensen for helping with data management; Lotte Dragsted and Marianne Lyngby for performing the Hamilton interviews; Gitte Nielsen for assistance in developing the treatment manual for the third wave cognitive therapy; and Jane Lindschou for expert assistance with the randomisation. Lastly, we would like to thank all the co-workers at the psychiatric clinic in Roskilde. Without their patience and cooperation the trial would have been impossible to conduct.

## Funding

We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors.

## Conflicts of interest

We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors. The principal investigator was also a therapist in the third wave cognitive therapy treatment and has developed the treatment manual for the third wave cognitive therapy. The consultant performing the medical consultations during the trial period was not blinded to the treatment allocation of the participants and developed the mentalization-based treatment manual in close cooperation with the two mentalization-based therapists. Other authors have no competing interests.

## Contributors

JCJ and CG wrote the first draft. JCJ, CG, KAL, PS, US, and ES planned and designed the trial. JCJ and MK performed the reliability tests. KAL, PS, US, and ES contributed with psychiatric expertise. PW conducted the statistical analyses. TL contributed with statistical expertise. All authors contributed academically to the manuscript and have accepted the manuscript for publication.

## Data Sharing Statement

Technical appendix, statistical code, and dataset available from the corresponding author at Dryad repository, who will provide a permanent, citable and open access home for the dataset

## Ethical considerations and regulatory approval

There were no immediate ethical problems regarding this trial. Research has not identified any significant adverse effects or risks from either of the compared interventions. Before randomization began approval was obtained by the Regional Ethics Committee of Zealand (no: SJ-43) and the trial was registered at the Danish Data Protection Agency (no: 2008-58-0020).

All participants were informed of the trial in writing and verbally before randomization. Written informed consent was obtained from every participant before inclusion. All trial participants were, on request, permitted access to further information about the project. No expense allowance was offered to the trial participants

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## Tables

### Table 1. Baseline characteristics

		Participants randomised to third wave cognitive therapy (n=22)	Participants randomised to mentalization-based therapy (n=22)
<b>Age</b>	mean (SD)	38.5 (8.9)	40.3 (6.8)
<b>Sex</b>	female n (%)	18 (82)	20 (91)
<b>Number of children</b>	mean (SD)	1.4 (1.2)	1.7 (1.1)
<b>Marital status</b>	n (%)		
Single		3 (14)	7 (32)
In a relationship		6 (27)	5 (23)
Married		12 (55)	8 (36)
Separated/divorced		1 (5)	2 (9)
<b>Level of education</b>	n (%)		
Only high school diploma		7 (32)	3 (14)
Medium long education		14 (64)	19 (86)
Long education		1 (5)	0 (0)
<b>Baseline HDRS** scores</b>			
	mean (SD)	22.1 (5.9)	22.5 (4.9)
	median	22.5	23.6
	range	7-30	11-29
<b>Baseline GSI scores (SCL 90-R)***</b>			
	mean (SD)	1.80 (0.59)	1.84 (0.41)
	median	1.72	1.74
	range	0.68-2.79	0.99-2.54
<b>Personality disorders</b>	n (%)		
No personality disorder		5 (23)	6 (27)
One personality disorder		11 (50)	12 (55)
Two personality disorders		4 (18)	3 (14)
Three or more personality disorders		2 (9)	1 (5)
<b>Personality disorders diagnoses</b>	n (%)		
Paranoid		1 (5)	0 (0)
Borderline		4 (18)	1 (5)
Avoidant		7 (32)	5 (23)
Obsessive-compulsive		4 (18)	3 (14)
Dependant		1 (5)	0 (0)
Depressive		7 (32)	8 (36)
Personality disorder NOS		1 (5)	4 (18)

\*SD=Standard Deviation; \*\*HDRS=17-item Hamilton Depression rating Scale; \*\*\*SCL-90-R=Global Severity Index score on the Symptom Checklist 90 Revised

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**Table 2. Effects of third wave cognitive therapy versus mentalisation-based treatment**

Outcome measure	Group randomised to third wave cognitive therapy (N=22)		Group randomised to mentalization-based treatment (N=22)		P-value of unadjusted analysis at end of treatment	P-value of adjusted analysis* at end of treatment
	Baseline	End of treatment	Baseline	End of treatment		
<b>HDRS</b>						
N	22	22	21	20	0.051	0.039
Mean	22.1	12.9	22.5	17.0		
95%CI	19.5-24.8	9.81-15.9	20.3-24.8	14.0-20.0		
<b>Remission (HDRS&lt;8)</b>						
N/ total	0/22	5/22	0/21	0/20	0.049	Not possible to calculate
<b>BDI II</b>						
N	21	21	22	17	0.46	0.46
Mean	36.8	17.6	36.3	20.5		
95%CI	32.5-41.1	12.2-23.0	32.1-40.6	14.5-26.4		
<b>SCL 90-R (GSI score)</b>						
N	22	22	22	20	0.52	0.66
Mean	1.80	0.88	1.84	1.00		
95%CI	1.54-2.05	0.62-1.15	1.66-2.02	0.74-1.25		
<b>WHO 5</b>						
N	22	22	21	20	0.54	0.46
Mean	3.55	10.5	4.33	9.45		
95%CI	1.84-5.25	7.66-13.4	3.13-5.53	7.18-11.7		

\*= Adjusted for baseline values of each outcome

Abbreviations: HDRS=Hamilton Depression Rating Scale (17-item); N=Number of participants; CI=Confidence interval; BDI=Beck's Depression Inventory; SCL 90-R=Symptom Checklist 90 Revised; GSI=Global Severity Index score; WHO 5=World Health Organisation-Five Well-being Index 1999, a high score associates to a high level of well-being.

## Figure Legends

### Figure 1 (CONSORT flowchart)

### Figure 2

Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks. 42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.<sup>36-39</sup> These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

### Figure 3

Post-hoc sequential analysis of the results on Beck's depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.<sup>36-39</sup> The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data

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7 **Third wave Cognitive Therapy versus Mentalization-based**  
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9 **Treatment for Major Depressive Disorder. A Randomised Clinical**  
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11 **Pilot Trial**  
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## Abstract

**Background and Objective:** ~~No randomised clinical trial has compared the effects of third wave cognitive therapy and mentalization based treatment in patients with major depression. Our objectives were (1) to compare the benefits and harms of third wave cognitive therapy versus mentalization-based therapy these two interventions in a small sample of depressed participants with major depressive disorder, and (2) to test the feasibility of the trial design. The results from this pilot trial might provide valuable information about the optimal design of a future more definitive trial.~~

**Design, setting, participants, and setting: and measurements:** We planned to randomise 84 consecutive adult participants diagnosed with major depressive disorder to third wave cognitive therapy (n=22) versus mentalization-based treatment (n=22) in a superiority randomised clinical trial. The outcome assessors and the statistician were blinded to treatment allocation. The trial was conducted at an outpatient psychiatric clinic for non-psychotic patients in Roskilde, Denmark.

**Outcomes:** The primary outcome was the Hamilton Rating Scale for Depression (HDRS) at end of treatment (18 weeks). Secondary outcomes were: remission (HDRS < 8), Beck's Depression Inventory, Symptom Checklist 90 Revised, and The World Health Organisation-Five Well-being Index 1999.

**Results:** The trial inclusion lasted for about two years as planned but only 44 out of the planned 84 participants were randomised in the trial. Two mentalization-based participants were lost to follow-up. The unadjusted analysis showed that third wave participants compared with mentalization-based participants did not differ significantly regarding the 18 weeks HDRS score

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(12.9 versus 17.0; mean difference -4.14; 95% CI -8.30 to 0.03; P = 0.051). In the analysis adjusted for baseline HDRS score, the difference was ~~significant~~ favouring third wave cognitive therapy (P = 0.039). At 18 weeks, five of the third wave participants (22.7%) were in remission versus none of the mentalization-based participants (P = 0.049). ~~One of the participants randomised to third wave cognitive therapy and two of the participants randomised to mentalization-based treatment were for a short period (some days) admitted to a psychiatric hospital during the intervention period. We recorded no suicide attempts or suicides during the intervention period in any of the 44 participants.~~ No significant differences were found between the two intervention groups on the remaining secondary outcomes.

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**Conclusions:** ~~It was much harder to recruit participants to the trial than expected. Our results suggest that t~~ third wave cognitive therapy may be more effective than mentalization-based therapy for depressive symptoms measured on the HDRS. ~~However, M~~ more randomised clinical trials are needed to assess the effects of third wave cognitive therapy ~~and versus~~ mentalization-based treatment for depression. ~~Such trials should be multicentre trials to secure adequate enrolment.~~

**Funding:** ~~We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors.~~

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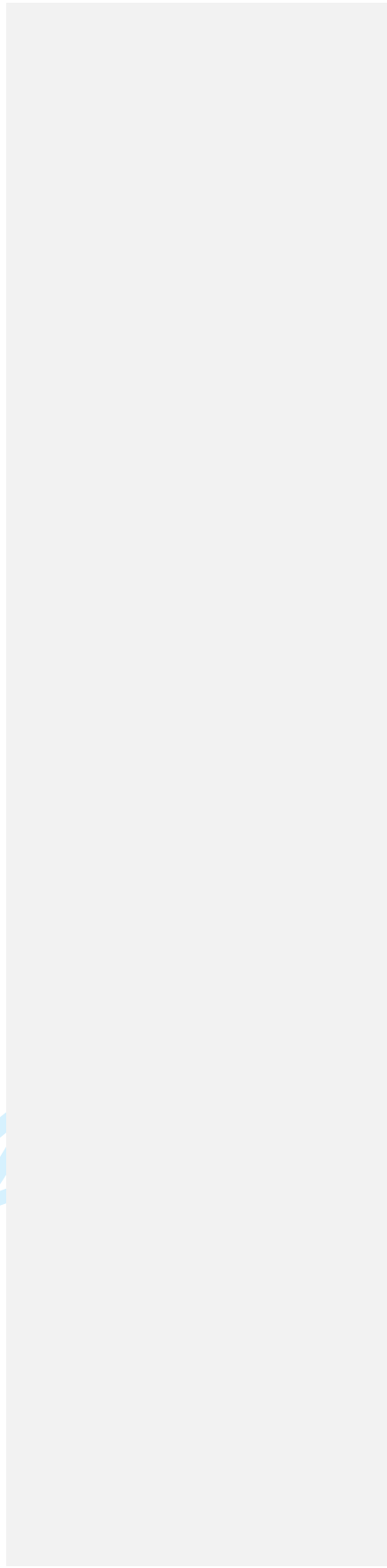
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**Keywords:** Randomised clinical trial; dDepression; tThird wave cognitive therapy; mMentalization-based treatment

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## Strengths and limitations of this study

- It was possible to conduct the trial with a low risk of bias, which was the primary strength of this randomised clinical ~~pilot~~ trial.
- The ~~pilot~~ trial also provided valuable information about possible in the difficulty of recruiting eligible participants, and indications about intervention effects of third wave cognitive therapy and mentalization-based treatment. Our preliminary results that may be used to design future trials including when estimation of ing future sample size calculations.
- The primary limitation of this randomised clinical ~~pilot~~ trial was that only 44 out of the planned 84 participants were randomised in this small-scale e trial.

## Introduction

~~Major depressive disorder afflicts an estimated 17% of individuals during their lifetimes at tremendous cost to the individual and society.<sup>1,2</sup> Major depressive disorder has for decades been treated with many different kinds and forms of interventions. Nevertheless, roughly a third of all depressive disorders take on a chronic course,<sup>3,4</sup> and approximately 15% of depressed patients will commit suicide over a 10 to 20 year period.<sup>5</sup> Our objectives were (1) to compare the benefits and harms of these two interventions in a small sample of participants with major depressive disorder, and (2) to test the feasibility of the trial design. The results from this pilot trial might provide valuable information about the optimal design of a future more definitive trial.~~

### Third wave cognitive therapy

<sup>6</sup>Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of traditional cognitive therapy versus no intervention for major depressive disorder.<sup>1</sup> We found that cognitive therapy seems to have a statistically significant beneficial effect on depressive symptoms. However, we identified only a limited number of relatively small randomised clinical trials all with a high risk of bias.<sup>1</sup> ~~Our results are in contrast to other~~ non-systematic reviews ~~have~~ concludinged that cognitive therapy has large clinical effects.<sup>2</sup> Our review results showed that the effects of cognitive therapy, if any, seem to be relatively small (mean difference about three HDRS points).<sup>1</sup> During the last two decades new forms of cognitive therapy have been developed. These third wave cognitive therapies include, e.g., acceptance and commitment therapy, schema therapy, mindfulness-based cognitive therapy, and meta-cognitive therapy.<sup>3</sup> Especially mindfulness-based interventions have been implemented in numerous different clinical contexts in recent years.<sup>4,6</sup> One meta-analysis ~~showed observed~~ that third wave cognitive therapy might

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7 prevent relapse of depression,<sup>7</sup> and small trials show that third wave cognitive therapy versus no  
8 intervention or treatment as usual is effective for acutely depressed patients.<sup>8, 9</sup> One trial has  
9 shown comparable effects between cognitive therapy and third wave cognitive therapy in non-  
10 melancholic depression, but the trial only included 45 participants.<sup>10</sup>  
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### 15 16 **Mentalization-based treatment**

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18 Mentalizing entails attending to mental states – holding ‘mind in mind’.<sup>11</sup> It is the process by which  
19 an individual explicitly and implicitly interpret the action of himself or herself and others on the  
20 basis on intentional mental states such as wishes, needs, goals, and reason.<sup>11</sup>  
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25 Mentalization-based treatment is rooted in attachment theory and developmental psychopathology  
26 and it includes essentials from psychodynamic psychotherapy in a concurrent individual and group  
27 format.<sup>11</sup> Prior to this trial we carried out a systematic review of randomised clinical trials  
28 examining the effects of psychodynamic therapy for major depressive disorder.<sup>12</sup> We found that  
29 psychodynamic therapy versus no intervention seems to have a small statistically significant effect  
30 on depressive symptoms (mean difference about three HDRS points).<sup>12</sup> However, we identified a  
31 limited number of trials, the trials were small, and all the trials had a high risk of bias so our results  
32 might be questioned.  
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41 Mentalization-based therapy was originally developed to treat borderline personality disorder but is  
42 now also used to treat various other psychiatric disorders such as depression, eating disorders,  
43 substance abuse, and personality disorders other than borderline.<sup>11, 13</sup> Mentalization-based  
44 treatment is based on the concept of mentalization as described by Fonagy and Bateman,<sup>14, 15</sup> and  
45 is different from the more strictly defined mentalization-based therapy as manualized by Karterud  
46 and Bateman.<sup>14-17</sup> In comparison with mentalization-based therapy, mentalization-based treatment  
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used in this trial has a more open therapeutic stance — letting the patient decide the theme in an associative way. The therapist is less active in directing the theme in the dialog and uses interpretations. Mentalizing deficits can be assumed to underlie depressive symptoms,<sup>18, 19</sup> and many depressed patients have a comorbid personality disorder.<sup>20</sup> We did not identify any trial assessing the effects of mentalization-based treatment or therapy versus no intervention for major depressive disorder.<sup>12</sup>

### Third wave cognitive therapy versus mentalization-based treatment

No randomised clinical trials or systematic reviews seem to have examined the effects of third wave cognitive therapy versus mentalization-based treatment or therapy for major depression.<sup>21</sup>

~~Our objective was to compare the benefits and harms of third wave cognitive therapy versus mentalization-based treatment in a small sample of a small sample of participants with major depressive disorder, as a pilot for a more definitive randomised clinical trial.~~

## Methods

In the following, we briefly describe the methodology of this trial. For details please consult our ~~registered (clinicaltrials.gov: NCT01070134) and published protocol, primary trial protocol (published at our website: [http://www.ctu.dk/Protocols/Mipsy\\_protocol2010.pdf](http://www.ctu.dk/Protocols/Mipsy_protocol2010.pdf) and registered at clinicaltrials.gov: NCT01070134) and our published design article.~~<sup>22</sup>

### Objective



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Our objective was to compare the effect of third wave cognitive therapy versus mentalization-based therapy in a small sample of participants with major depressive disorder.

### **Inclusion of participants**

The trial was conducted at a public psychiatric outpatient clinic only treating patients on sick leave due to a psychiatric disorder. Patients were referred from general practitioners, psychiatrists in private practice, and medical and psychiatric departments. No special announcement of the trial was made to the referrers. All patients referred to the psychiatric clinic had a full psychiatric examination by a physician who made the preliminary psychiatric diagnoses (DSM-IV-TR).<sup>23</sup> Eligible patients were then interviewed by the principal investigator (JCJ) who used the depression part of the structured clinical interview for DSM-IV axis I disorders (SCID I) interview<sup>24</sup> to assess whether the patient fulfilled the criteria for a major depressive disorder (DSM-IV-TR).<sup>23</sup> Before randomisation baseline assessments were carried out for all outcome measures and all eligible patients were assessed with the structured clinical Interview for DSM-IV axis II disorders (SCID II).<sup>25</sup> We chose to perform the SCID II assessments because we wanted to compare personality disorders at baseline in the two intervention groups and to exclude patients with schizotypal personality disorder.

The participant had to meet all of the inclusion criteria and none of the exclusion criteria.

### **Inclusion criteria**

1. Age from 18 to 65 years.
2. Major depressive disorder, whether first episode or recurrent (DSM-IV-TR).<sup>24</sup>
3. Beck's Depression Inventory (BDI II) score >-13 points.<sup>26</sup>
4. Written informed consent.

### Exclusion criteria

1. Current psychosis, schizophrenia, or schizotypal personality disorder (DSM-IV-TR).<sup>23</sup>
2. A significant alcohol or substance abuse (assessed during the preliminary consultations).
3. Initiated or changed medical anti-depressive treatment less than six weeks before randomisation.
4. Pregnancy.
5. No written informed consent.

### Randomisation

Eligible patients with major depressive disorder were randomised 1:1 to third wave cognitive therapy versus mentalization-based treatment. The Copenhagen Trial Unit performed the randomisation centrally, using a computer generated block randomisation sequence that was unknown to the investigators. Participant inclusion began in February 2010 and the last patient was randomised in July 2011. Because of an unequal allocation of the trial participants to one of the two groups in the beginning of the trial (there were only a few participants in one of the groups), the block size was reduced from 12 to 4 and a stratification variable (HDRS score  $\geq$ -22 points) was removed. The block sizes were at all times unknown to the trial investigators, and the Copenhagen Trial Unit performed these changes without informing the investigators of the changes. Otherwise, the methodology was not changed after trial commencement.

### Interventions

Each participant received treatment for 18 weeks. The two intervention groups were 'slow-open' (new patients entered the group continually) with a maximum of seven patients per group.

The time of each of the elements in the comprehensive treatment package (see below) was planned to be similar in the compared intervention groups.

#### **Shared elements for both intervention groups**

All participants were, as part of the outpatient clinic's usual care, offered a communal breakfast twice a week and participated in group psycho-education for one hour a week. During the course of treatment, all participants with children were offered participation in a parent support group (four weekly one-hour sessions). A psychiatric consultant (KAL), who was not otherwise involved in the interventions, assessed each participant and prescribed psychopharmacological treatment when needed. The psychiatric consultant prescribed medication according to the official recommendations.<sup>27</sup> After the first consultation, medical consultations were offered by demand of the participant or the therapists.

#### **Third wave cognitive therapy**

The third wave cognitive therapy consisted of one weekly third wave cognitive individual psychotherapy session (45 minutes) and one weekly mindfulness-skills training group (1.5 hours). Altogether the third wave cognitive therapy consisted of 18 individual psychotherapy sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.

The weekly individual psychotherapy session included:

- Introduction of the cognitive model and mindfulness.
- Exploration of thoughts, feelings, behaviour, and physical sensations.
- Work on acceptance of difficult feelings and difficult life circumstances.
- Work on assumptions challenged by behavioural experiments.

- Self esteem training.
- Tools to prevent relapse.

The weekly mindfulness-skills training group included:

Education in the practical use of six basic mindfulness skills: focusing, acceptance, labeling feelings, body awareness, self-esteem skills, and mindful communication. The group participants were encouraged to practice the six mindfulness skills between sessions. ~~The skills training group ran in a continuous cycle of six sessions. Consequently,~~ participants went through the complete skills training group's program three times during the course of the 18 weeks of treatment.

The manual for the third wave cognitive therapy was developed specifically for the trial and had not been used before in a trial setting. Details about the third wave cognitive therapy program is available elsewhere.<sup>28</sup>

### **Mentalization-based treatment**

The mentalization-based treatment consisted of a weekly mentalization-based individual psychotherapy session (45 minutes) and a weekly mentalization-based group therapy session (1.5 hours). Altogether the mentalization-based treatment consisted of 18 individual psychotherapy sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.

Mentalization-based treatment imposes explicit attention to mentalizing in the therapeutic process.

This is established by a therapeutic stance where the therapist aims at demonstrating a 'mentalizing attitude', i.e., validating, 'not-knowing', and curiously questioning the patient about feelings and thoughts.<sup>11, 17, 29</sup> The therapist tries to identify and intervene when the patient is not

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7 mentalizing and assists the patient in regulating the level of the emotions so the patient is able  
8 to mentalize and to get different perspectives on life events, conflicts, etc.<sup>11, 17, 29</sup>  
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12 At the time this project was planned there was no manual available for the mentalization-based  
13 treatment. Therefore, we developed our own treatment manual based on mentalization  
14 principles.<sup>30</sup> Further details about the mentalization-based treatment is available elsewhere.<sup>30</sup>  
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### 18 19 20 **Therapists and adherence to the intervention manuals**

21 Each intervention group had two therapists. The two third wave cognitive therapists (one of these  
22 therapists was the principal investigator) and the two mentalization-based therapists had  
23 comparable psychotherapeutic education and experience.  
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29 All individual sessions were recorded on an audio recorder and all group sessions were recorded  
30 on video. An experienced external psychologist not otherwise involved in the trial assessed the  
31 degree of adherence to the manuals 0-5 (0: no adherence; 1: adherence about 20% of the time; 2:  
32 adherence about 40% of the time; 3: adherence about 60% of the time; 4: adherence about 80%  
33 of the time; 5: adherence about 100% of the time). The psychologist randomly selected 4 x 5  
34 sessions using a computer program. The results showed high adherence to the treatment manuals  
35 for both interventions. The means of the ratings were: 4.6 in five sessions of individual third wave  
36 cognitive therapy; 4.2 in five sessions of third wave cognitive group therapy; 4.2 in five sessions of  
37 individual mentalization-based treatment; and 3.8 in five sessions of mentalization-based group  
38 treatment.  
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### 49 **Outcomes**

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**Primary outcome**

- Score on the Hamilton Depression Rating Scale (HDRS)<sup>31</sup> after end of treatment at week 18.

**Secondary outcomes**

- The proportion of participants in remission after cessation of treatment at week 18. We defined remission as HDRS below 8.<sup>32</sup>
- Global Severity Index score (GSI-score)<sup>33</sup> on the Symptom Checklist 90 Revised (SCL-90-R)<sup>33</sup> after cessation of treatment at week 18.
- Score on the World Health Organisation-Five Well-being Index 1999 (WHO 5)<sup>34</sup> after cessation of treatment at week 18.
- Score on the Beck's Depression Inventory (BDI II)<sup>26</sup> after cessation of treatment at week 18.

**Reliability of the Hamilton Depression Rating Scale (HDRS) interviews**

Two experienced psychologists performed the Hamilton interviews during the trial period. Prior to the trial, the principal investigator and one of the psychologists both interviewed eight patients at the same time point. The mean difference between these two HDRS ratings performed on the same patient at the same time point was -0.13 HDRS-points (SD 1.25) (intra-class correlation coefficient 0.98; Spearman correlation 0.92). During the trial both psychologists interviewed 21 patients at the same time point. The mean difference between these two HDRS ratings performed on the same patient at the same time point was 0.29 HDRS-points (SD 2.21) (intra-class correlation coefficient 0.96; Spearman correlation 0.94). All these 29 interviews were performed with both HDRS-raters present simultaneously. One rater interviewed and rated the interviewee and the other rater only rated the interviewee. The interviewers were not allowed to discuss the results before each interviewer had registered the HDRS result.

### Data-management

All data were handled by research assistants not otherwise involved in the trial and was stored in the principal investigator's office and later at the Copenhagen Trial Unit. Privacy of trial participants was protected in accordance with the Act on Processing of Personal Data and the Health Act. The project was notified to the Danish Data Protection Agency (no.: 2008-58-0020).

### Blinding

The Hamilton interviewers were blinded to treatment allocation and were instructed by the principal investigator to avoid questions beside the Hamilton interview. All interviewees were prior to each interview instructed by the principal investigator not to mention which treatment they were allocated to. It was not possible to blind neither the therapists nor the participants to treatment allocation.

The chief consultant performing the medical consultations was, due to practical circumstances, not blinded to treatment allocation.

A statistician at The Copenhagen Trial Unit performed the statistical analyses blinded with the two intervention groups coded as 'A' and 'B'.

### A priori sample size estimate

With a 'minimal relevant mean difference' (MIREDIF) between the two interventions of 5 HDRS points, an alpha of 0.05 (type I error), a power of 0.90 (type II error of 10%), and a standard deviation (SD) of 7 HDRS points, the sample size calculation showed that a total of 84 participants

would be necessary. We estimated that we would need an inclusion period of about two years to recruit 84 participants.

## Statistical analyses

The primary analyses were intention-to-treat analyses. Significance tests were two-sided at a significance level of 0.05.

Continuous outcomes were compared between the two intervention groups using the univariate general linear model with (ANCOVA) and without HDRS baseline value adjustment (ANOVA). The binary outcome was compared between the groups using Fisher's exact test. Logistic regression could not be used since none of the participants in the mentalization-based group obtained remission implying an infinite odds ratio.

As the trial was stopped before the sample size was reached, we *post hoc* decided to conduct sequential analysis to assess the results of significance testing taking sparse data and repetitive testing into consideration.<sup>35</sup> We used the trial sequential analysis program for that purpose.<sup>36-39</sup>

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## Results

### Participants

Only 44 out of the 84 planned participants were included in the trial, ~~due to problems with enrolment.~~ Twenty-two participants were randomised to third wave cognitive therapy versus 22 participants to mentalization-based treatment. **Figure 1** details the participant flow through the phases of the trial.<sup>42</sup>



### Baseline characteristics of the participants

The baseline characteristics regarding age, sex, number of children, score on the HDRS, baseline diagnosis of personality disorder, and psychopharmacological treatment were overall assessed as being comparable between the two intervention groups. The baseline participant characteristics are described in detail in Table 1 and the psychopharmacological treatment ~~and the baseline participant characteristics are described in detail in Table 1 and in~~ Supplementary material Table 21.

### Treatment compliance

None of the 22 participants randomised to third wave cognitive therapy were lost to follow-up or excluded due to the fact that they participated in less than 70% of the sessions. One participant out of the 22 randomised to mentalization-based treatment was lost to follow-up and one was excluded, as she did not attend the required 70% of the sessions (**Figure 1**). The excluded participant was not assessed on any of the outcomes at end of treatment.

### ~~Psychopharmacological treatment~~

~~The psychopharmacological medication varied greatly between all of the trial participants. However, we assessed the psychopharmacological medication at baseline and at cessation of treatment as being comparable in the two intervention groups. The psychopharmacological medication in the two groups is outlined in Table 2.~~

### Intervention effects

#### Primary outcome

### Mean score on the HDRS after end of interventions

Participants randomised to third wave therapy compared with participants randomised to mentalization-based treatment did not differ significantly regarding the 18-week HDRS scores in the unadjusted analysis (mean 12.9, 95% CI 9.81 to 15.9 versus mean 17.0, 95% CI 14.0 to 20.0;  $P = 0.051$ ). The mean difference between the two groups was -4.14 HDRS points (95% CI -8.30 to 0.03) corresponding to a Cohen's D of -0.62. The difference was, however, significant in the analysis adjusted for baseline HDRS score ( $P = 0.039$ ) (Table 32).

Sequential analysis demonstrated that the observed significant findings ought to be interpreted conservatively as random errors due to sparse data cannot be excluded (Figure 2).

We did not impute missing values because only 2 out of 44 (4.5%) participants had missing values.

~~Following imputation<sup>28</sup> of the two missing values in the group randomised to mentalization-based treatment the P-values were 0.064 (unadjusted analysis) and 0.041 (analysis adjusted for baseline HDRS). Histograms on the data from both intervention groups showed that the data seem to be normally distributed. Using the non-parametric test the P-value was 0.064, without imputation and 0.093 after imputation.~~

There was no significant interaction between the indicator of a diagnosis of a personality disorder and the intervention effects. This was also not the case when the indicator was redefined as a binary quantity defined as any kind of personality disorder (yes/no) or as a binary quantity defined as personality disorder = borderline personality disorder (yes/no).

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~~Sequential analysis demonstrated that the observed significant findings ought to be interpreted conservatively as random errors due to sparse data cannot be excluded (Figure 2).~~

## Secondary outcomes

### Participants in remission after cessation of treatment

In the third wave [cognitive](#) therapy group 22.7% (n=5) were in remission after cessation of treatment (defined as having HDRS <-8 [points](#)) versus 0% in the mentalization-based treatment group. This difference was significant (P = 0.049) (Table 32).

### BDI II<sup>26</sup>, SCL-90-R<sup>33</sup>, and WHO 5<sup>34</sup> after end of interventions

No significant difference was found on BDI II, SCL-90-R (GSI-scores), or WHO 5 between the two intervention groups after cessation of treatment (Table 32).

Sequential analysis demonstrated that the observed insignificant findings [regarding BDI II](#) ought to be interpreted conservatively as random errors due to sparse data cannot be excluded ([see Figure 3 regarding BDI II](#)).

## Other outcomes

### Admissions, suicide attempts, and suicides

One of the participants randomised to third wave cognitive therapy and two of the participants randomised to mentalization-based treatment were for a short period (some days) admitted to a psychiatric hospital during the intervention period.

We recorded no suicide attempts or suicides during the intervention period in any of the 44 participants.

## Discussion

~~Our pilot trial results show that it was much harder than expected to recruit eligible participants to the trial. It took us longer to recruit participants than stipulated, and we had to terminate the trial due to economical and practical constraints. Basically, not enough eligible participants were referred to the clinic during the inclusion period. On the positive side, our pilot demonstrated the feasibility of conducting the trial with low risks of bias.~~ Our preliminary results indicate that third wave cognitive therapy compared with mentalization-based treatment may be a more effective intervention for lowering depressive symptoms measured on the HDRS and may increase the probability of remission (HDRS  $< -8$  points). Furthermore, our trial demonstrated the feasibility of conducting the trial with low risks of bias. However, when only 44 out of the planned 84 participants (52%) of the projected sample size is obtained in a trial, it is necessary to interpret the results cautiously~~evaluate the calculated p-values more conservatively~~. Had this been an interim analysis, any independent safety and data monitoring committee would have recommended continued randomisation and completion of the trial (**Figure 2** and **Figure 3**).<sup>35</sup> Furthermore, the two interventions do not seem to have significant differential effects on BDI (subjective depressive symptoms), SCL 90-R (psychological distress), and WHO 5 (well-being).

Compared with the baseline scores, both intervention groups improved during the trial period on all continuous outcomes. However, we did not include a control group receiving no intervention in

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this head-to-head trial so it is unclear whether it was trial intervention effects or 'regression towards the mean' effects that caused these changes.<sup>40</sup> More randomised clinical trials are needed to assess the effects of third wave cognitive therapy and versus mentalization-based treatment for major depressive disorder.

## Strengths

First of all, the trial was conducted with an overall high level of methodological quality and we assessed the validity of the trial results according to the procedure proposed by Jakobsen et al.<sup>35</sup> including adjusting the thresholds for significance according to the number of randomised participants and the planned sample size.<sup>35</sup> ~~We also~~ proved the feasibility of our trial design, which can be used for larger trials provided that funding can be raised. Our trial has a number of additional strengths: (1) The trial protocol was registered before randomisation began at ClinicalTrials.gov. In this protocol the outcome hierarchy and plans for analyses were presented. Our trial was altogether conducted according to good clinical research practice and therefore with low risk of bias and a high degree of external validity.<sup>41-45</sup> ~~(2) The participants in this trial were similar to patients normally referred to a psychiatric outpatient clinic, and clinicians can therefore relate our trial results to a clinical context.~~ (23) Both of the trial interventions were conducted using manuals and adherence to the manuals was assessed as relatively high. The manualization of the trial interventions makes it possible, to some extent, to implement the two trial interventions in clinical practice and to replicate or refute our results in future trials. Both the cognitive therapists and the mentalization therapists were involved in developing the treatment manuals for the respective psychotherapeutic treatments, which might make the therapist enthusiasm and thoroughness similar in the two intervention groups. (34) We have used the most commonly used outcomes in trials assessing the effects of psychotherapeutic interventions for depression (i.e., HDRS and BDI).<sup>12, 31, 46, 47</sup> This makes it possible to relate our results to results from other trials

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examining the effects of interventions for depression. Moreover, using HDRS as outcome makes it possible to perform blinded objective outcome assessment, which is a further strength of our trial. (45) The baseline characteristics of the trial participants as well as the psychopharmacological medication in the two groups were comparable which indicates that the randomisation succeeded in allocating comparable participants to the two intervention groups. (56) Only 2 out of the total of 44 participants were not assessed after end of treatment, which decreases the risk of biased results. ~~Furthermore, we imputed missing values.~~<sup>48</sup> (67) All outcomes suggested that the participants randomised to third wave cognitive therapy had improved more than the participants randomised to mentalization-based treatment. This supports the validity of our results, even though most of these differences were non-significant.

## Limitations

Our trial has a number of limitations. This ~~pilot-small-scale~~ trial was in essence failed because we only included 44 out of the planned 84 participants. The trial inclusion lasted for about two years as planned but we had problems with recruiting participants. Basically, not enough eligible depressed patients were referred to the clinic within the planned trial period. The great advantage of the randomised clinical trial in general is that all known and unknown participant characteristics will be similar at baseline in compared intervention groups.<sup>40</sup> However, even though our baseline characteristics indicate similarity between the two groups on assessed baseline characteristics, it is unlikely that all baseline characteristics will be similar when only 44 participants are randomised. The low number of randomised participants in this small-scale trial increases the risks of wrong biased results leads to a high risk of due to type I errors, and type II errors,<sup>49, 50</sup> and our high level of the adequate trial methodology cannot necessarily sufficiently compensate for these increased risks. Moreover, our results do not show anything about long-term effects of the two interventions.

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8 The chief consultant prescribing the psychopharmacological treatment was not blinded to  
9 intervention allocation. Although we assessed the psychopharmacological treatment to be  
10 comparable in the two randomised groups at cessation of the trial interventions (**Supplementary**  
11 **material Table 21**), the lack of blinding might have influenced the psychopharmacological  
12 treatment. The chief consultant is a mentalization-based therapist and was involved in developing  
13 the mentalization-based treatment manual. The first author and primary investigator conducted the  
14 third wave cognitive therapy and wrote the manual for the third wave cognitive therapy program,  
15 which may also **increase** raise the risks of bias.  
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25 We did not perform power calculations for the secondary outcomes before randomisation began,  
26 which is a further limitation. If an analysis of a secondary outcome has a power of less than 80%,  
27 then either the secondary outcome should be classified as an exploratory outcome or the *P*-value  
28 and the confidence interval thresholds for significance should be adjusted, just as the thresholds  
29 are adjusted if a sample size has not been reached.<sup>35</sup>  
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36 Because of an unequal allocation of the trial participants to one of the two groups in the beginning  
37 of the trial, the block size was reduced from 12 to 4 (see '**Randomisation**'). The block sizes were  
38 at all times unknown to the trial investigators, and the Copenhagen Trial Unit performed these  
39 changes without informing the investigators. However, a block size of four is small making it  
40 possible to foresee which group a given eligible participant will be allocated to before  
41 randomisation. This might question whether the allocation concealment was effective.  
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49 The trial was conducted at an outpatient psychiatric clinic with special interest for treatment of  
50 personality disorders and depressive patients were not routinely referred to the clinic before the  
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7 trial began randomisation. Our results showed that a high proportion of the trial participants had  
8 comorbid personality disorder and depression. This might explain why the baseline HDRS scores  
9 indicated that the trial participants were only moderately depressed although all of the trial  
10 participants were on sick leave due to psychological problems. Some of the trial participants might  
11 suffer primarily from psychological problem other than depressive symptoms, i.e., personality  
12 related problems. We did not assess number of prior depressive episodes in the included  
13 participants, which makes it unclear whether our trial results demonstrate intervention effects in  
14 participants with a first time depression or recurrent depression. Our results can only be related to  
15 patients comparable to our trial participants, i.e., patients diagnosed with major depressive  
16 disorder on sick leave due to psychiatric problems.  
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27 Highly specialised mentalization-based treatment was the primary psychotherapeutic method  
28 used at the outpatient clinic prior to the trial, and the co-interventions (communal breakfast and  
29 psycho-education) were also a part of the treatment program prior to the trial, and experienced  
30 and specialised third wave cognitive therapists were members of the staff at the psychiatric clinic  
31 where the trial was conducted. Furthermore, all patients referred to the psychiatric clinic were on  
32 sick leave due to psychiatric problems, and even though the evidence behind the specialised  
33 treatments is lacking so we considered that some form of specialised treatment was needed for all  
34 patients at the psychiatric clinic even though the evidence behind the specialised treatments is  
35 lacking. We did, therefore, not consider it ethically justifiable to use a control group receiving no  
36 intervention, placebo, or only the co-interventions. All these considerations and practical  
37 circumstances led to the choice of the psychotherapeutic interventions and the design of this  
38 head-to-head trial comparing third wave cognitive therapy and co-interventions versus  
39 mentalization-based therapy and co-interventions. The co-interventions were delivered similarly  
40 to both treatment groups and the possible effects of co-interventions will therefore even out  
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between the compared intervention groups unless there are significant interactions.

~~Nevertheless, Due to ethical considerations it was not possible to conduct a trial comparing the psychotherapeutic interventions versus no intervention. Nevertheless, it~~ is a clear limitation that our interventions are not and have not been compared versus no intervention or a more simple and basic form of psychotherapy plus co-interventions.<sup>40</sup> If a trial comparing the effects of two active interventions shows no difference in effect it is not clear whether the two interventions are equally effective or equally ineffective — and if an experimental intervention seem superior compared with a control intervention then the effect size of the experimental intervention will be unclear because any beneficial or harmful effects of the control intervention might influence the trial results.<sup>40</sup> All interventions should be assessed versus no intervention before being introduced into clinical practice.<sup>40</sup> ~~Furthermore, the combination of specialised psychotherapy and co-interventions constitute a relatively comprehensive treatment, which might not always be accessible to psychiatric patients in clinical practice – this might limit the generalizability of our results.~~

### **Mentalization-based treatment**

We did not find any relevant treatment manual we could use for the mentalization-based treatment, and we therefore created our own manual.<sup>30</sup> The therapists in the mentalization-based treatment group were educated and experienced in psychodynamic therapy and group therapy and had underwent basic training and education in mentalization-based treatment according to Bateman and Karterud.<sup>14-17</sup> Mentalization-based treatment was originally designed to treat borderline personality.<sup>11, 13</sup> Few participants were diagnosed with borderline personality disorder (**Table 1**), and it can be argued that mentalization-based treatment was not a relevant intervention for the depressed participants of this trial. However, mentalization-based treatment is now used to treat a number of different disorders other than borderline personality disorder, including

depression.<sup>11, 13</sup> Furthermore, a study has shown that female inpatients with depression showed a significantly lower capacity for mentalization compared with healthy controls — and deficits in mentalizing capacity were related to illness duration, number of admissions, and cognitive impairment.<sup>18</sup> The authors conclude that the investigation of mentalization may be of particular importance for the development of targeted psychotherapeutic interventions for depression.<sup>18</sup>

### Comorbid personality disorders

A large proportion of the included participants were diagnosed with cluster C personality disorders (anxious or fearful personality disorders).<sup>24, 25</sup> It has been debated if a diagnosis of a personality disorder is accurate when patients are acutely depressed.<sup>20</sup> Our results indicate that comorbid personality disorder and depression does not lead to a poorer outcome compared to patients with depression alone — but this could be because the diagnoses of the personality disorders in our trial are inaccurate because the depressive symptoms might mimic pathological personality traits. Furthermore, the limited number of included participants significantly reduces the power of this analysis.

### BDI compared to HDRS as outcome

It is a common belief among clinicians that BDI is a more 'reactive' outcome than HDRS,<sup>51</sup> and it might be surprising to some why we identified a borderline significant effect on the HDRS results but no significant effect on the BDI. However, two systematic reviews with meta-analysis have included trials that simultaneously used HDRS and BDI to assess the effects of the same interventions.<sup>51, 52</sup> The results showed that BDI under such circumstances shows significantly less effect sizes compared to the HDRS.<sup>51, 52</sup> A greater percentage of participants would be considered improved if ratings of change were based on the HDRS rather than BDI.<sup>51</sup> The results from these two reviews<sup>51, 52</sup> are in agreement with our present results and may explain why we found a

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borderline significant effect on HDRS and no significant effect on BDI. On the other hand, it is also possible that HDRS compared to BDI overestimates participant improvement.<sup>52</sup>

It was impossible to blind the participants to treatment allocation. To ensure some degree of blinding we chose HDRS over BDI because it was possible to perform objective blinded outcome assessment using the HDRS. BDI is a self-administered questionnaire, which makes blinded objective outcome assessment impossible. We therefore expected the results on HDRS to be a more clinically valid compared to the BDI results — but we cannot exclude that breaking of blinding and biased assessment of the HDRS may have occurred. In accordance with the CONSORT Statement we did not assess degree of unblinding.<sup>41</sup>

## Implications

First of all, if a larger more definitive trial has to be conducted then a more realistic estimate of the recruitment rate will be needed and more centres should be involved. On average, we recruited approximately one participant every third week and we expected to be able to recruit approximately one participant every week. Basically, not enough eligible participants were referred to the clinic during the inclusion period and we had to terminate the trial due to economical and practical constraints – this was the primary reason why we did not randomise more participants.

Before the randomisation began, we did not systematically assess how many participants it was possible to recruit. This should also be done before a larger trial is conducted so the sample size can be reached. Moreover, we did not take any specific actions promoting the trial outside the clinic. If a future trial is to be conducted it should be considered to promote the trial through advertising or use of other measures to motivate potential referrers to refer more eligible participants. Besides the problems with recruiting enough participants, it was otherwise feasible to

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7 conduct a randomised clinical trial with low risk of bias assessing the effects of third wave  
8 cognitive therapy versus mentalization-based treatment for major depressive disorder.  
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12 The apparent difference in intervention effect found on the HDRS might be caused by random  
13 error ('play of chance'), unaccounted bias, or a signal of a real effect.<sup>50</sup> The National Institute for  
14 Clinical Excellence (NICE) have suggested a mean difference between two compared  
15 interventions of three HDRS points ~~on HDRS~~ as a criterion for 'clinical significance'.<sup>53</sup> Most  
16 interventions for depression, both psychopharmacological as well as psychotherapeutic, rarely  
17 exceed having a beneficial effect of more than three HDRS points ~~on the HDRS~~.<sup>1, 12, 54-56</sup> We used  
18 an anticipated intervention effect of five HDRS points to estimate the necessary sample size and  
19 this anticipated intervention effect was optimistic. Calculating Bayes factor based on the  
20 anticipated intervention effect, the observed intervention effect, and the standard error of the  
21 observed intervention effect shows a Bayes factor of 0.14, which is above the recommended  
22 threshold for significance of 0.1.<sup>35</sup> This underlines that our results should be regarded as  
23 insignificant and that an anticipated intervention effect lower than five HDRS points ought to be  
24 used in sample size calculations in future trials assessing the effects of third wave cognitive  
25 therapy and mentalization-based therapy. We found a mean difference of more than four HDRS  
26 points ~~on the HDRS~~ which, compared to other interventions, is relatively high. These results might  
27 be used to calculate a necessary sample size in a larger more definitive trial. However, HDRS  
28 might not at all be a clinically relevant outcome ~~measure~~ and other more clinically relevant  
29 outcomes ~~measures~~ might be more valid to use in future trials. Severity of depression as  
30 measured by the total HDRS score has failed to predict suicide attempts,<sup>57, 58</sup> and some  
31 publications have questioned the usefulness of the HDRS and concluded that the scale is  
32 psychometrically and conceptually flawed.<sup>58, 59</sup>  
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## Conclusions

~~Our trial results show that it was much harder than expected to recruit eligible participants to the trial. It took us longer to recruit participants than stipulated. However, it was otherwise possible to conduct the trial with low risk of bias.~~ Our preliminary results show that third wave cognitive therapy compared with mentalization-based treatment may be a more effective intervention for depressive symptoms measured on the HDRS. The effects of the two interventions did not seem to differ significantly regarding BDI II, SCL 90-R, and WHO 5. More randomised clinical trials are needed to assess the effects of third wave cognitive therapy and versus mentalization-based treatment ~~and versus no intervention~~.

## Acknowledgments

We would like to thank all the participants in the trial for patiently cooperating with the assessments. We would also like to thank Anita Jensen for helping with data management; Lotte Dragsted and Marianne Lyngby for performing the Hamilton interviews; Gitte Nielsen for assistance in developing the treatment manual for the third wave cognitive therapy; and Jane Lindschou for expert assistance with the randomisation. Lastly, we would like to thank all the co-workers at the psychiatric clinic in Roskilde. Without their patience and cooperation the trial would have been impossible to conduct.

## Conflicts of interest

We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors. The principal investigator was also a therapist in the third wave cognitive therapy treatment and has developed the treatment manual for the third wave cognitive therapy. The consultant performing the medical consultations during the trial period was not blinded to the treatment allocation of the participants and developed the mentalization-based treatment manual in close cooperation with the two mentalization-based therapists. Other authors have no competing interests.

## Contributors

JCJ and CG wrote the first draft. JCJ, CG, KAL, PS, US, and ES planned and designed the trial. JCJ and MK performed the reliability tests. KAL, PS, US, and ES contributed with psychiatric

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expertise. PW conducted the statistical analyses. TL contributed with statistical expertise. All authors contributed academically to the manuscript and have accepted the manuscript for publication.

### **Ethical considerations and regulatory approval**

There were no immediate ethical problems regarding this trial. Research has not identified any significant adverse effects or risks from either of the compared interventions. Before randomization began approval was obtained by the Regional Ethics Committee of Zealand (no: SJ-43) and the trial was registered at the Danish Data Protection Agency (no: 2008-58-0020).

All participants were informed of the trial in writing and verbally before randomization. Written informed consent was obtained from every participant before inclusion. All trial participants were, on request, permitted access to further information about the project. No expense allowance was offered to the trial participants

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## Tables

### Table 1. Baseline characteristics

		Participants randomised to third wave cognitive therapy (n=22)	Participants randomised to mentalization-based therapy (n=22)
<b>Age</b>	mean (SD)	38.5 (8.9)	40.3 (6.8)
<b>Sex</b>	female n (%)	18 (82)	20 (91)
<b>Number of children</b>	mean (SD)	1.4 (1.2)	1.7 (1.1)
<b>Marital status</b>	n (%)		
Single		3 (14)	7 (32)
In a relationship		6 (27)	5 (23)
Married		12 (55)	8 (36)
Separated/divorced		1 (5)	2 (9)
<b>Level of education</b>	n (%)		
Only high school diploma		7 (32)	3 (14)
Medium long education		14 (64)	19 (86)
Long education		1 (5)	0 (0)
<b>Baseline HDRS** scores</b>			
mean (SD)		22.1 (5.9)	22.5 (4.9)
median		22.5	23.6
range		7-30	11-29
<b>Baseline GSI scores (SCL 90-R)***</b>			
mean (SD)		1.80 (0.59)	1.84 (0.41)
median		1.72	1.74
range		0.68-2.79	0.99-2.54
<b>Personality disorders</b>	n (%)		
No personality disorder		5 (23)	6 (27)
One personality disorder		11 (50)	12 (55)
Two personality disorders		4 (18)	3 (14)
Three or more personality disorders		2 (9)	1 (5)
<b>Personality disorders diagnoses</b>	n (%)		
Paranoid		1 (5)	0 (0)
Borderline		4 (18)	1 (5)
Avoidant		7 (32)	5 (23)
Obsessive-compulsive		4 (18)	3 (14)
Dependant		1 (5)	0 (0)
Depressive		7 (32)	8 (36)
Personality disorder NOS		1 (5)	4 (18)

\*SD=Standard Deviation; \*\*HDRS=17-item Hamilton Depression rating Scale; \*\*\*SCL-90-R=Global Severity Index score on the Symptom Checklist 90 Revised

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**Table 2. Psychopharmacological medication**

	Participants randomised to third-wave cognitive therapy		Participants randomised to mentalization-based treatment	
	At baseline (N=22)	At end of treatment (N=22)	At baseline (N=22)	At end of treatment (N=20)
No medication	3 (13%)	5 (23%)	2 (9%)	2 (10%)
SSRI*	9 (40%)	9 (41%)	13 (59%)	7 (35%)
Dual-action antidepressants**	11 (50%)	6 (27%)	4 (18%)	6 (30%)
Other antidepressants***	1 (5%)	0 (0%)	2 (9%)	2 (10%)
Pregabalin (150mg/ day)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Mood stabilizers****	2 (9%)	1 (5%)	1 (5%)	1 (5%)
Benzodiazepines*****	3 (14%)	2 (9%)	7 (32%)	5 (25%)
Antipsychotics*****	5 (23%)	4 (18%)	5 (23%)	2 (10%)
Medication for attention-deficit hyperactivity disorder*****	2 (9%)	1 (5%)	0 (0%)	0 (0%)
Disulfiram (200mg/ day)	1 (5%)	0 (0%)	1 (5%)	1 (5%)

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~~\*SSRI (selective serotonin reuptake inhibitors): fluoxetine 20mg–60mg/ day; sertraline 100mg–200mg/ day;  
citalopram 20mg–40mg/ day; escitalopram 10mg–20mg.  
\*\*duloxetine (60mg–90mg/ day); venlafaxine 75mg–225mg/ day; mirtazapine 15mg–45mg/ day  
\*\*\*agomelatine (50mg/ day); amitriptyline (100mg/ day).  
\*\*\*\*lamotrigine (25mg–100mg/ day); valproate (600mg/ day).  
\*\*\*\*\*oxazepam 15mg–45mg/ day; bromazepam 4.5mg/ day; zolpidem 5mg/ day; oxazepam 15mg/ by demand;  
alprazolam 0.5mg/ by demand; diazepam 5mg/ by demand; zopiclone 7.5mg/ by demand.  
\*\*\*\*\*quetiapine 25–100mg/day; olanzapine 2.5mg–5mg/day; chlordiazepoxid 15–25mg/ by demand.  
\*\*\*\*\*methylphenidate 36mg/ day; atomoxetine 80mg/ day.~~

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**Table 32. Effects of third wave cognitive therapy versus mentalisation-based treatment**

Outcome measure	Group randomised to third wave cognitive therapy (N=22)		Group randomised to mentalization-based treatment (N=22)		P-value of unadjusted analysis at end of treatment	P-value of adjusted analysis* at end of treatment
	Baseline	End of treatment	Baseline	End of treatment		
<b>HDRS</b>						
N	22	22	21	20	0.051	0.039
Mean	22.1	12.9	22.5	17.0		
95%CI	19.5-24.8	9.81-15.9	20.3-24.8	14.0-20.0		
<b>Remission (HDRS&lt;8)</b>						
N/ total	0/22	5/22	0/21	0/20	0.049	Not possible to calculate
<b>BDI II</b>						
N	21	21	22	17	0.46	0.46
Mean	36.8	17.6	36.3	20.5		
95%CI	32.5-41.1	12.2-23.0	32.1-40.6	14.5-26.4		
<b>SCL 90-R (GSI score)</b>						
N	22	22	22	20	0.52	0.66
Mean	1.80	0.88	1.84	1.00		
95%CI	1.54-2.05	0.62-1.15	1.66-2.02	0.74-1.25		
<b>WHO 5</b>						
N	22	22	21	20	0.54	0.46
Mean	3.55	10.5	4.33	9.45		
95%CI	1.84-5.25	7.66-13.4	3.13-5.53	7.18-11.7		

\*= Adjusted for baseline values of each outcome

Abbreviations: HDRS=Hamilton Depression Rating Scale (17-item); N=Number of participants; CI=Confidence interval; BDI=Beck's Depression Inventory; SCL 90-R=Symptom Checklist 90 Revised; GSI=Global Severity Index score; WHO 5=World Health Organisation-Five Well-being Index 1999, a high score associates to a high level of well-being.

## Figure Legends

### Figure 1 (CONSORT flowchart)

### Figure 2

Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks. 42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.<sup>36-39</sup> These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

### Figure 3

Post-hoc sequential analysis of the results on Beck's depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.<sup>36-39</sup> The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data



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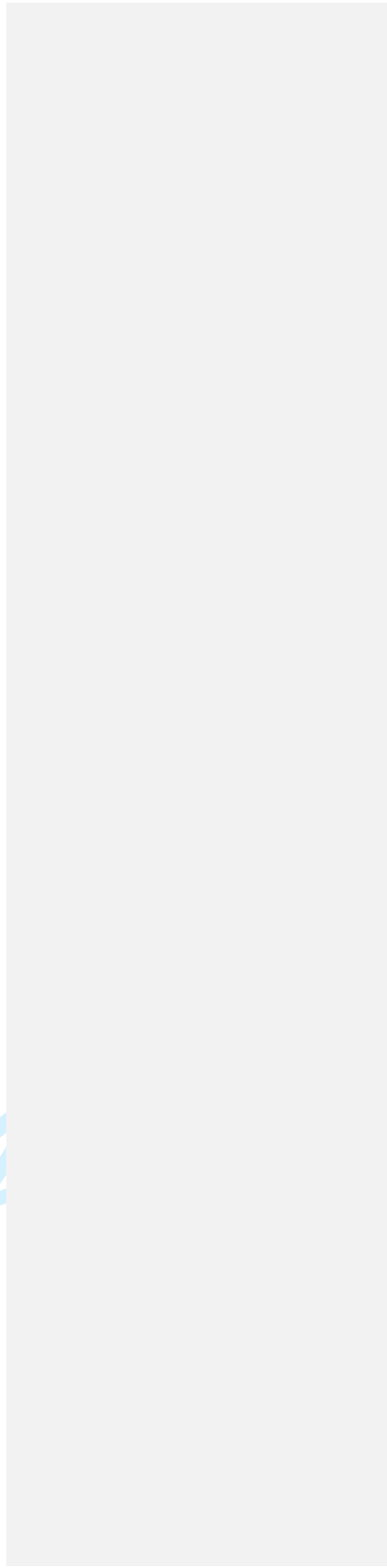
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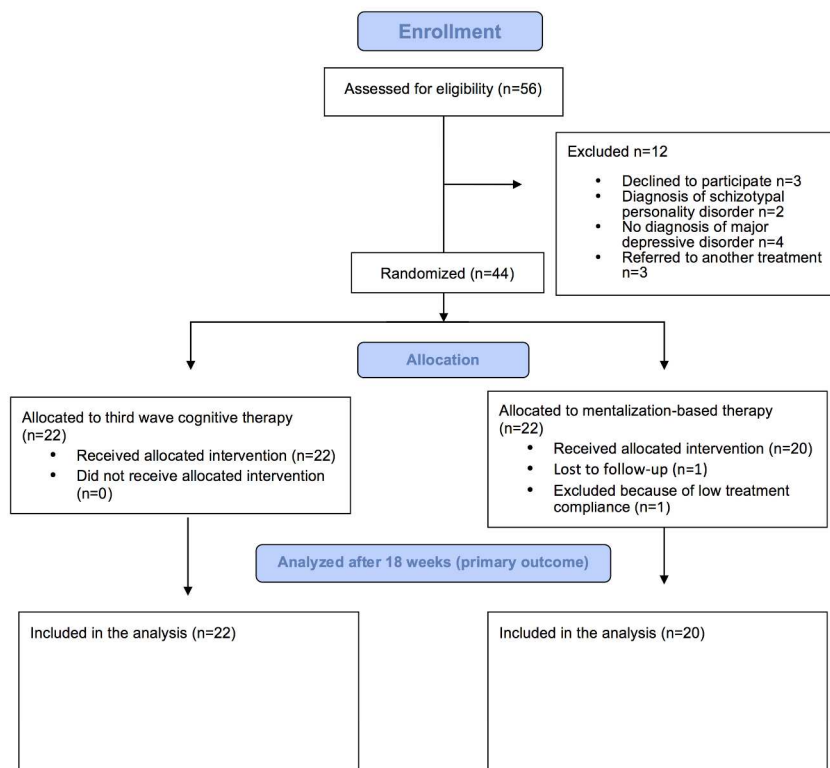
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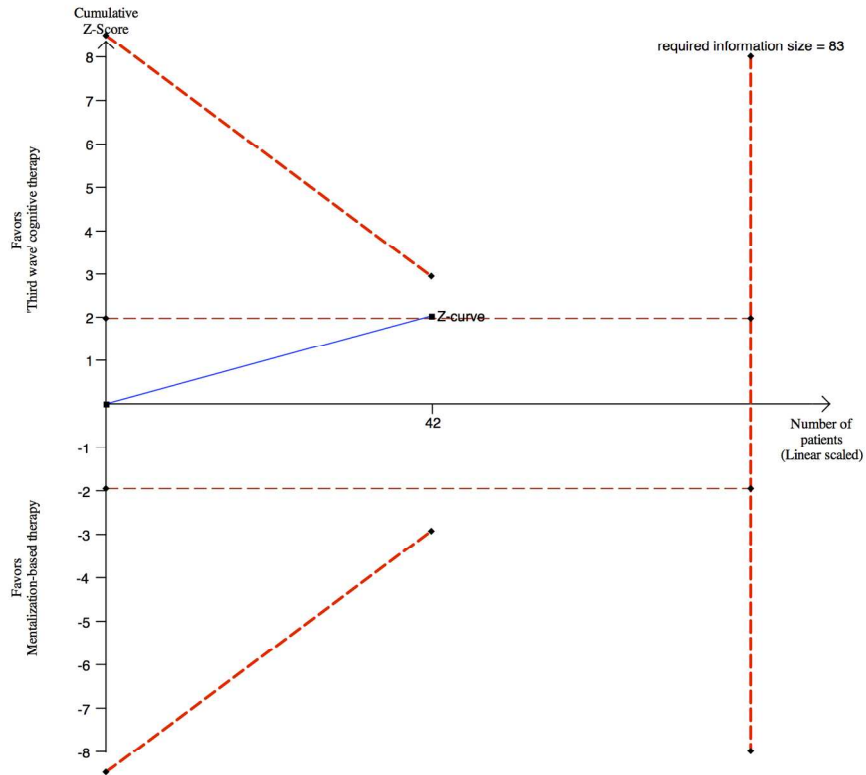
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CONSORT 2010 Flow Diagram



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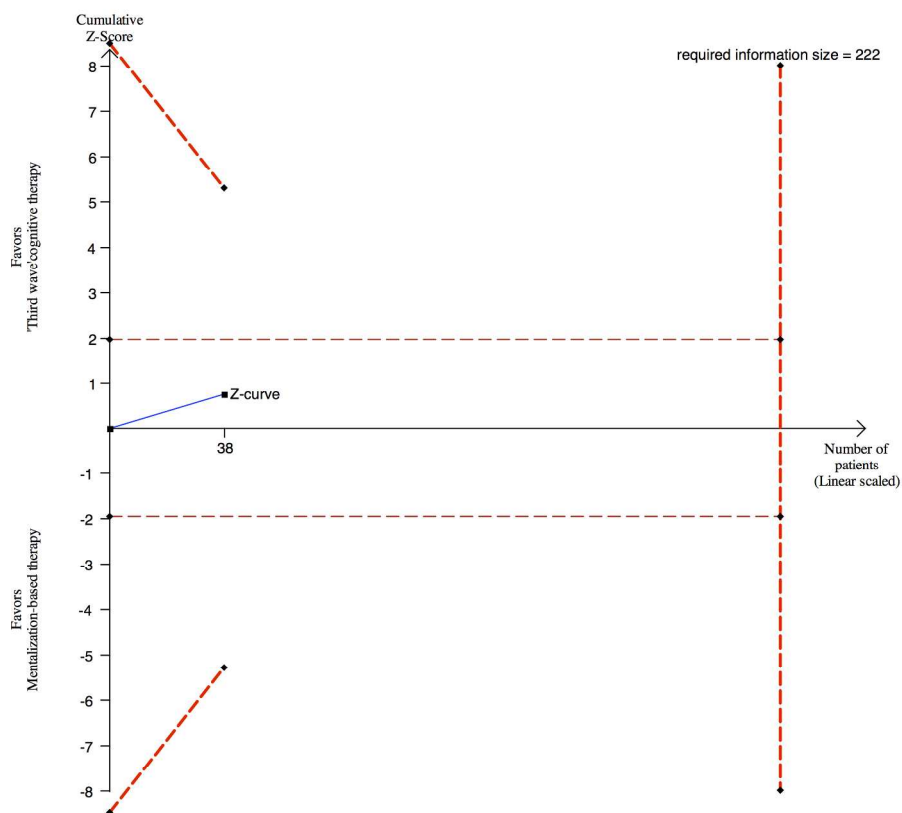
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Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks. 42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.40-43. These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) does not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

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Post-hoc sequential analysis of the results on Beck's depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.40-43 The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of no beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

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## Supplementary material 1. Psychopharmacological medication

	Participants randomised to third wave cognitive therapy		Participants randomised to mentalization-based treatment	
	At baseline (N=22)	At end of treatment (N=22)	At baseline (N=22)	At end of treatment (N=20)
No medication	3 (13%)	5 (23%)	2 (9%)	2 (10%)
SSRI*	9 (40%)	9 (41%)	13 (59%)	7 (35%)
Dual-action antidepressants**	11 (50%)	6 (27%)	4 (18%)	6 (30%)
Other antidepressants***	1 (5%)	0 (0%)	2 (9%)	2 (10%)
Pregabalin (150mg/ day)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Mood stabilizers****	2 (9%)	1 (5%)	1 (5%)	1 (5%)
Benzodiazepines*****	3 (14%)	2 (9%)	7 (32%)	5 (25%)
Antipsychotics*****	5 (23%)	4 (18%)	5 (23%)	2 (10%)
Medication for attention-deficit hyperactivity disorder*****	2 (9%)	1 (5%)	0 (0%)	0 (0%)
Disulfiram (200mg/ day)	1 (5%)	0 (0%)	1 (5%)	1 (5%)

\*SSRI (selective serotonin reuptake inhibitors): fluoxetine 20mg - 60mg/ day; sertraline 100mg-200mg/ day; citalopram 20mg-40mg/ day; escitalopram 10mg-20mg.

\*\*duloxetine (60mg-90mg/ day); venlafaxine 75mg-225mg/ day; mirtazapine 15mg-45mg/ day

\*\*\*agomelatine (50mg/ day); amitriptyline (100mg/ day).

\*\*\*\*lamotrigine (25mg-100mg/ day); valproate (600mg/ day).

\*\*\*\*\*oxazepam 15mg-45mg/ day; bromazepam 4.5mg/ day; zolpidem 5mg/ day; oxazepam 15mg/ by demand; alprazolam 0.5mg/ by demand; diazepam 5mg/ by demand; zopiclone 7.5mg/ by demand.

\*\*\*\*\*quetiapine 25-100mg/day; olanzapine 2.5mg-5mg/day; chlordiazepoxid 15-25mg/ by demand.

\*\*\*\*\*methylphenidate 36mg/ day; atomoxetine 80mg/ day.

## CONSORT CHECKLIST

**Table.** CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial<sup>a</sup>

Section and Topic	Item No.	Checklist Item	Reported on Page No.
<b>Title and abstract</b>	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
<b>Introduction</b> Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
<b>Methods</b> Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	6-7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-10
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	10-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomization; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	13
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
<b>Results</b> Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	see cor 14
	13b	For each group, losses and exclusions after randomization, together with reasons	14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	17-18
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	see Tab
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Se Tabl
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	See Tal Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	26
<b>Comment</b> Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	17-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-20
<b>Other information</b> Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22

<sup>a</sup>We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see <http://www.consort-statement.org>.

# BMJ Open

## Third wave Cognitive Therapy versus Mentalization-based Treatment for Major Depressive Disorder. A Randomised Clinical Trial

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-004903.R2
Article Type:	Research
Date Submitted by the Author:	22-Jul-2014
Complete List of Authors:	Jakobsen, Janus; Psychiatric Research Unit, Region Zealand, Roskilde, Copenhagen University Hospital, Denmark, Gluud, Christian; Copenhagen Trial Unit, 7812 Kongerslev, Mickey; Psychiatric Research Unit, Region Zealand, Roskilde, Copenhagen University Hospital, Denmark, Larsen, Kirsten; Psychiatric Clinic, Psychiatry, Roskilde;, Sørensen, Per; Department of Psychiatry, Copenhagen University Hospital, Copenhagen, Winkel, Per; Copenhagen Trial Unit, 7812 Lange, Theis; Department of Public Health, University of Copenhagen., Søgaard, Ulf; Psychiatric Clinic, Psychiatry, Roskilde;, Simonsen, Erik; Psychiatric Research Unit, Region Zealand, Roskilde, Copenhagen University Hospital, Denmark,
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Public health
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Personality disorders < PSYCHIATRY

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Manuscripts



# Third wave Cognitive Therapy versus Mentalization-based Treatment for Major Depressive Disorder. A Randomised Clinical Trial

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**Keywords:** Randomised clinical trial; depression; third wave cognitive therapy; mindfulness, mentalization-based treatment

## Abstract

**Objective:** To compare the benefits and harms of third wave cognitive therapy versus mentalization-based therapy in a small sample of depressed participants.

**Setting:** The trial was conducted at an outpatient psychiatric clinic for non-psychotic patients in Roskilde, Denmark.

**Participants:** 44 consecutive adult participants diagnosed with major depressive disorder.

**Interventions:** 18 weeks of third wave cognitive therapy (n=22) versus 18 weeks of mentalization-based treatment (n=22).

**Outcomes:** The primary outcome was the Hamilton Rating Scale for Depression (HDRS) at end of treatment (18 weeks). Secondary outcomes were: remission (HDRS < 8), Beck's Depression Inventory, Symptom Checklist 90 Revised, and The World Health Organisation-Five Well-being Index 1999.

**Results:** The trial inclusion lasted for about two years as planned but only 44 out of the planned 84 participants were randomised. Two mentalization-based participants were lost to follow-up. The unadjusted analysis showed that third wave participants compared with mentalization-based participants did not differ significantly regarding the 18 weeks HDRS score (12.9 versus 17.0; mean difference -4.14; 95% CI -8.30 to 0.03; P = 0.051). In the analysis adjusted for baseline HDRS score, the difference was favouring third wave cognitive therapy (P = 0.039). At 18 weeks, five of the third wave participants (22.7%) were in remission versus none of the mentalization-

1 based participants ( $P = 0.049$ ). We recorded no suicide attempts or suicides during the  
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4 intervention period in any of the 44 participants. No significant differences were found between the  
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6 two intervention groups on the remaining secondary outcomes.  
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10 **Conclusions:** Third wave cognitive therapy may be more effective than mentalization-based  
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12 therapy for depressive symptoms measured on the HDRS. However, more randomised clinical  
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14 trials are needed to assess the effects of third wave cognitive therapy and mentalization-based  
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16 treatment for depression.  
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21 **Trial registration:** Registered with Clinical Trials government identifier: NCT01070134  
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## Strengths and limitations of this study

- It was possible to conduct the trial with a low risk of bias (adequate allocation sequence generation, adequate allocation concealment, adequate blinding, no risk of selective outcome reporting, low risk of incomplete outcome data bias, no risk of 'for profit' bias), which was the primary strength of this randomised clinical trial.
- The trial also provided valuable information about possible intervention effects of third wave cognitive therapy and mentalization-based treatment. Our preliminary results may be used to design future trials including estimation of sample size calculations.
- The primary limitation of this randomised clinical trial was that only 44 out of the planned 84 participants were randomised in this small-scale trial.

## Introduction

### Third wave cognitive therapy

Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of traditional cognitive therapy versus no intervention for major depressive disorder.<sup>1</sup> We found that cognitive therapy compared with no intervention seems to have a small statistically significant beneficial effect on depressive symptoms. However, we identified only a limited number of relatively small randomised clinical trials all with a high risk of bias.<sup>1</sup> During the last two decades new forms of cognitive therapy have been developed. These third wave cognitive therapies include, e.g., acceptance and commitment therapy, schema therapy, mindfulness-based cognitive therapy, and meta-cognitive therapy.<sup>2</sup> Especially mindfulness-based interventions have been implemented in numerous different clinical contexts in recent years.<sup>3-5</sup> One meta-analysis showed that third wave cognitive therapy might prevent relapse of depression,<sup>6</sup> and small trials show that third wave cognitive therapy versus no intervention or treatment as usual is effective for acutely depressed patients.<sup>7, 8</sup> One trial has shown comparable effects between cognitive therapy and third wave cognitive therapy in non-melancholic depression, but the trial only included 45 participants.<sup>9</sup>

### Mentalization-based treatment

Mentalizing entails attending to mental states – holding ‘mind in mind’.<sup>10</sup> It is the process by which an individual explicitly and implicitly interpret the action of himself or herself and others on the basis on intentional mental states such as wishes, needs, goals, and reason.<sup>10</sup>

Mentalization-based treatment is rooted in attachment theory and developmental psychopathology and it includes essentials from psychodynamic psychotherapy in a concurrent individual and group

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format.<sup>10</sup> Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of psychodynamic therapy for major depressive disorder.<sup>11</sup> We found that psychodynamic therapy versus no intervention seems to have a small statistically significant effect on depressive symptoms (mean difference about three HDRS points).<sup>11</sup> However, we identified a limited number of trials, the trials were small, and all the trials had a high risk of bias so our results might be questioned.

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Mentalization-based therapy was originally developed to treat borderline personality disorder but is now also used to treat various other psychiatric disorders such as depression, eating disorders, substance abuse, and personality disorders other than borderline.<sup>10, 12</sup> Mentalization-based treatment is based on the concept of mentalization as described by Fonagy and Bateman,<sup>13, 14</sup> and is different from the more strictly defined mentalization-based therapy as manualized by Karterud and Bateman.<sup>13-16</sup> In comparison with mentalization-based therapy, mentalization-based treatment used in this trial has a more open therapeutic stance – letting the patient decide the theme in an associative way. The therapist is less active in directing the theme in the dialog and uses interpretations. Mentalizing deficits can be assumed to underlie depressive symptoms,<sup>17, 18</sup> and many depressed patients have a comorbid personality disorder.<sup>19</sup> We did not identify any trial assessing the effects of mentalization-based treatment or therapy versus no intervention for major depressive disorder.<sup>11</sup>

### 46 47 48 49 50 51 52 53 54 **Third wave cognitive therapy versus mentalization-based treatment**

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No randomised clinical trials or systematic reviews seem to have examined the effects of third wave cognitive therapy versus mentalization-based treatment or therapy for major depression.<sup>20</sup>

## 55 56 57 58 59 60 **Methods**

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4 In the following, we briefly describe the methodology of this trial. For details please consult our  
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6 registered (clinicaltrials.gov: NCT01070134) and published protocol.<sup>21</sup>  
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## 10 **Objective**

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12 Our objective was to compare the effect of third wave cognitive therapy versus mentalization-  
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14 based therapy in a small sample of participants with major depressive disorder.  
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## 18 **Inclusion of participants**

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20 The trial was conducted at a public psychiatric outpatient clinic only treating patients on sick leave  
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22 due to a psychiatric disorder. Patients were referred from general practitioners, psychiatrists in  
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24 private practice, and medical and psychiatric departments. No special announcement of the trial  
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26 was made to the referrers. All patients referred to the psychiatric clinic had a full psychiatric  
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28 examination by a physician who made the preliminary psychiatric diagnoses (DSM-IV-TR).<sup>22</sup>  
29  
30 Eligible patients were then interviewed by the principal investigator (JCJ) who used the depression  
31  
32 part of the structured clinical interview for DSM-IV axis I disorders (SCID I) interview<sup>23</sup> to assess  
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34 whether the patient fulfilled the criteria for a major depressive disorder (DSM-IV-TR).<sup>22</sup> Before  
35  
36 randomisation baseline assessments were carried out for all outcome measures and all eligible  
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38 patients were assessed with the structured clinical Interview for DSM-IV axis II disorders (SCID  
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40 II).<sup>24</sup> We chose to perform the SCID II assessments because we wanted to compare personality  
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42 disorders at baseline in the two intervention groups and to exclude patients with schizotypal  
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44 personality disorder.  
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54 The participant had to meet all of the inclusion criteria and none of the exclusion criteria.  
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### Inclusion criteria

1. Age from 18 to 65 years.
2. Major depressive disorder, whether first episode or recurrent (DSM-IV-TR).<sup>23</sup>
3. Beck's Depression Inventory (BDI II) score >13 points.<sup>25</sup>
4. Written informed consent.

### Exclusion criteria

1. Current psychosis, schizophrenia, or schizotypal personality disorder (DSM-IV-TR).<sup>22</sup>
2. A significant alcohol or substance abuse (assessed during the preliminary consultations).
3. Initiated or changed medical anti-depressive treatment less than six weeks before randomisation.
4. Pregnancy.
5. No written informed consent.

### Randomisation

Eligible patients with major depressive disorder were randomised 1:1 to third wave cognitive therapy versus mentalization-based treatment. The Copenhagen Trial Unit performed the randomisation centrally, using a computer generated block randomisation sequence that was unknown to the investigators. Participant inclusion began in February 2010 and the last patient was randomised in July 2011. Because of an unequal allocation of the trial participants to one of the two groups in the beginning of the trial (there were only a few participants in one of the groups), the block size was reduced from 12 to 4 and a stratification variable (HDRS score  $\geq 22$  points) was removed. The block sizes were at all times unknown to the trial investigators, and the



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Copenhagen Trial Unit performed these changes without informing the investigators of the changes. Otherwise, the methodology was not changed after trial commencement.

## Interventions

Each participant received treatment for 18 weeks. The two intervention groups were 'slow-open' (new patients entered the group continually) with a maximum of seven patients per group.

The time of each of the elements in the comprehensive treatment package (see below) was planned to be similar in the compared intervention groups.

### Shared elements for both intervention groups

All participants were, as part of the outpatient clinic's usual care, offered a communal breakfast twice a week and participated in group psycho-education for one hour a week. During the course of treatment, all participants with children were offered participation in a parent support group (four weekly one-hour sessions). A psychiatric consultant (KAL), who was not otherwise involved in the interventions, assessed each participant and prescribed psychopharmacological treatment when needed. The psychiatric consultant prescribed medication according to the official recommendations.<sup>26</sup> After the first consultation, medical consultations were offered by demand of the participant or the therapists.

### Third wave cognitive therapy

The third wave cognitive therapy consisted of one weekly third wave cognitive individual psychotherapy session (45 minutes) and one weekly mindfulness-skills training group (1.5 hours).

Altogether the third wave cognitive therapy consisted of 18 individual psychotherapy sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.

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4 The weekly individual psychotherapy session included:

- 5  
6 • Introduction of the cognitive model and mindfulness.  
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8 • Exploration of thoughts, feelings, behaviour, and physical sensations.  
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10 • Work on acceptance of difficult feelings and difficult life circumstances.  
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12 • Work on assumptions challenged by behavioural experiments.  
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14 • Self esteem training.  
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16 • Tools to prevent relapse.  
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22 The weekly mindfulness-skills training group included:

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24 Education in the practical use of six basic mindfulness skills: focusing, acceptance, labeling  
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26 feelings, body awareness, self-esteem skills, and mindful communication. The group participants  
27  
28 were encouraged to practice the six mindfulness skills between sessions. The participants went  
29  
30 through the complete skills training group's program three times during the course of the 18 weeks  
31  
32 of treatment.  
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38 The manual for the third wave cognitive therapy was developed specifically for the trial and had  
39  
40 not been used before in a trial setting. Details about the third wave cognitive therapy program is  
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42 available elsewhere (<http://ctu.dk/publications/supplementary-material.aspx>).<sup>27</sup>  
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### 46 **Mentalization-based treatment**

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48 The mentalization-based treatment consisted of a weekly mentalization-based individual  
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50 psychotherapy session (45 minutes) and a weekly mentalization-based group therapy session (1.5  
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52 hours). Altogether the mentalization-based treatment consisted of 18 individual psychotherapy  
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54 sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.  
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4 Mentalization-based treatment imposes explicit attention to mentalizing in the therapeutic process.  
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6 This is established by a therapeutic stance where the therapist aims at demonstrating a  
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8 'mentalizing attitude', i.e., validating, 'not-knowing', and curiously questioning the patient about  
9  
10 feelings and thoughts.<sup>10, 16, 28</sup> The therapist tries to identify and intervene when the patient is not  
11  
12 mentalizing and assists the patient in regulating the level of the emotions so the patient is able to  
13  
14 mentalize and to get different perspectives on life events, conflicts, etc.<sup>10, 16, 28</sup>  
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20 At the time this project was planned there was no manual available for the mentalization-based  
21  
22 treatment. Therefore, we developed our own treatment manual based on mentalization  
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24 principles.<sup>29</sup> Further details about the mentalization-based treatment is available elsewhere  
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26 (<http://ctu.dk/publications/supplementary-material.aspx>).<sup>29</sup>  
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### 30 **Therapists and adherence to the intervention manuals**

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33 Each intervention group had two therapists. The two third wave cognitive therapists (one of these  
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35 therapists was the principal investigator) and the two mentalization-based therapists had  
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37 comparable psychotherapeutic education and experience.  
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42 All individual sessions were recorded on an audio recorder and all group sessions were recorded  
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44 on video. An experienced external psychologist not otherwise involved in the trial assessed the  
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46 degree of adherence to the manuals 0-5 (0: no adherence; 1: adherence about 20% of the time; 2:  
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48 adherence about 40% of the time; 3: adherence about 60% of the time; 4: adherence about 80%  
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50 of the time; 5: adherence about 100% of the time). The psychologist randomly selected 4 x 5  
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52 sessions using a computer program. The results showed high adherence to the treatment manuals  
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54 for both interventions. The means of the ratings were: 4.6 in five sessions of individual third wave  
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cognitive therapy; 4.2 in five sessions of third wave cognitive group therapy; 4.2 in five sessions of individual mentalization-based treatment; and 3.8 in five sessions of mentalization-based group treatment.

## Outcomes

### Primary outcome

- Score on the Hamilton Depression Rating Scale (HDRS)<sup>30</sup> after end of treatment at week 18.

### Secondary outcomes

- The proportion of participants in remission after cessation of treatment at week 18. We defined remission as HDRS below 8.<sup>31</sup>
- Global Severity Index score (GSI-score)<sup>32</sup> on the Symptom Checklist 90 Revised (SCL-90-R)<sup>32</sup> after cessation of treatment at week 18.
- Score on the World Health Organisation-Five Well-being Index 1999 (WHO 5)<sup>33</sup> after cessation of treatment at week 18.
- Score on the Beck's Depression Inventory (BDI II)<sup>25</sup> after cessation of treatment at week 18.

### Reliability of the Hamilton Depression Rating Scale (HDRS) interviews

Two experienced psychologists performed the Hamilton interviews during the trial period. Prior to the trial, the principal investigator and one of the psychologists both Hamilton interviewed eight patients at the same time point. The mean difference between these two HDRS ratings performed on the same patient at the same time point was -0.13 points (SD 1.25) (intra-class correlation coefficient 0.98; Spearman correlation 0.92). During the trial both psychologists Hamilton

1 interviewed 21 patients at the same time point. The mean difference between these two HDRS  
2 ratings performed on the same patient at the same time point was 0.29 points (SD 2.21) (intra-  
3 class correlation coefficient 0.96; Spearman correlation 0.94). All these 29 interviews were  
4 performed with both HDRS-raters present simultaneously. One rater interviewed and rated the  
5 interviewee and the other rater only rated the interviewee. The interviewers were not allowed to  
6 discuss the results before each interviewer had registered the HDRS result.  
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## 14 **Data-management**

15 All data were handled by research assistants not otherwise involved in the trial and was stored in  
16 the principal investigator's office and later at the Copenhagen Trial Unit. Privacy of trial  
17 participants was protected in accordance with the Act on Processing of Personal Data and the  
18 Health Act. The project was notified to the Danish Data Protection Agency (no.: 2008-58-0020).  
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## 31 **Blinding**

32 The Hamilton interviewers were blinded to treatment allocation and were instructed by the  
33 principal investigator to avoid questions beside the Hamilton interview. All interviewees were prior  
34 to each interview instructed by the principal investigator not to mention which treatment they were  
35 allocated to. It was not possible to blind neither the therapists nor the participants to treatment  
36 allocation.  
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47 The chief consultant performing the medical consultations was, due to practical circumstances, not  
48 blinded to treatment allocation.  
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53 A statistician at The Copenhagen Trial Unit performed the statistical analyses blinded with the two  
54 intervention groups coded as 'A' and 'B'.  
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## A priori sample size estimate

With a 'minimal relevant mean difference' (MIREDIF) between the two interventions of 5 HDRS points, an alpha of 0.05 (type I error), a power of 0.90 (type II error of 10%), and a standard deviation (SD) of 7 HDRS points, the sample size calculation showed that a total of 84 participants would be necessary. We estimated that we would need an inclusion period of about two years to recruit 84 participants.

## Statistical analyses

The primary analyses were intention-to-treat analyses. Significance tests were two-sided at a significance level of 0.05.

Continuous outcomes were compared between the two intervention groups using the univariate general linear model with (ANCOVA) and without HDRS baseline value adjustment (ANOVA). The binary outcome was compared between the groups using Fisher's exact test. Logistic regression could not be used since none of the participants in the mentalization-based group obtained remission implying an infinite odds ratio.

As the trial was stopped before the sample size was reached, we *post hoc* decided to conduct sequential analysis to assess the results of significance testing taking sparse data and repetitive testing into consideration.<sup>34</sup> We used the trial sequential analysis program for that purpose.<sup>35-38</sup>

## Results

## Participants

Only 44 out of the 84 planned participants were included in the trial. Twenty-two participants were randomised to third wave cognitive therapy versus 22 participants to mentalization-based treatment. **Figure 1** details the participant flow through the phases of the trial.

## Baseline characteristics of the participants

The baseline characteristics regarding age, sex, number of children, score on the HDRS, baseline diagnosis of personality disorder, and psychopharmacological treatment were overall assessed as being comparable between the two intervention groups. The baseline participant characteristics are described in detail in **Table 1** and the psychopharmacological treatment in **Supplementary material 1**.

## Treatment compliance

None of the 22 participants randomised to third wave cognitive therapy were lost to follow-up or excluded due to the fact that they participated in less than 70% of the sessions. One participant out of the 22 randomised to mentalization-based treatment was lost to follow-up and one was excluded, as she did not attend the required 70% of the sessions (**Figure 1**). The excluded participant was not assessed on any of the outcomes at end of treatment.

## Intervention effects

### Primary outcome

#### Mean score on the HDRS after end of interventions

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Participants randomised to third wave therapy compared with participants randomised to mentalization-based treatment did not differ significantly regarding the 18-week HDRS scores in the unadjusted analysis (mean 12.9, 95% CI 9.81 to 15.9 versus mean 17.0, 95% CI 14.0 to 20.0;  $P = 0.051$ ). The mean difference between the two groups was -4.14 HDRS points (95% CI -8.30 to 0.03) corresponding to a Cohen's D of -0.62. The difference was, however, significant in the analysis adjusted for baseline HDRS score ( $P = 0.039$ ) (**Table 2**).

Sequential analysis demonstrated that the observed significant findings ought to be interpreted conservatively as random errors due to sparse data cannot be excluded (**Figure 2**).

We did not impute missing values because only 2 out of 44 (4.5%) participants had missing values.

Histograms on the data from both intervention groups showed that the data seem to be normally distributed. Using the non-parametric test the P-value was 0.064.

There was no significant interaction between the indicator of a diagnosis of a personality disorder and the intervention effects. This was also the case when the indicator was redefined as a binary quantity defined as any kind of personality disorder (yes/no) or as a binary quantity defined as personality disorder = borderline personality disorder (yes/no).

## Secondary outcomes

### Participants in remission after cessation of treatment



1 In the third wave cognitive therapy group 22.7% (n=5) were in remission after cessation of  
2 treatment (defined as having HDRS <8 points) versus 0% in the mentalization-based treatment  
3 group. This difference was significant (P = 0.049) (**Table 2**).  
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### 9 **BDI II<sup>25</sup>, SCL-90-R<sup>32</sup>, and WHO 5<sup>33</sup> after end of interventions**

10 No significant difference was found on BDI II, SCL-90-R (GSI-scores), or WHO 5 between the two  
11 intervention groups after cessation of treatment (**Table 2**). Sequential analysis demonstrated that  
12 the observed insignificant findings ought to be interpreted conservatively as random errors due to  
13 sparse data cannot be excluded (see **Figure 3** regarding BDI II).  
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### 24 **Other outcomes**

#### 25 **Admissions, suicide attempts, and suicides**

26 One of the participants randomised to third wave cognitive therapy and two of the participants  
27 randomised to mentalization-based treatment were for a short period (some days) admitted to a  
28 psychiatric hospital during the intervention period.  
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39 We recorded no suicide attempts or suicides during the intervention period in any of the 44  
40 participants.  
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### 49 **Discussion**

1 Our preliminary results indicate that third wave cognitive therapy compared with mentalization-  
2 based treatment may be a more effective intervention for lowering depressive symptoms  
3 measured on the HDRS and may increase the probability of remission (HDRS <8 points).  
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5 Furthermore, our trial demonstrated the feasibility of conducting the trial with low risks of bias.  
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7 However, when only 44 out of the planned 84 participants (52%) of the projected sample size is  
8 obtained in a trial, it is necessary to interpret the results cautiously. Had this been an interim  
9 analysis, any independent safety and data monitoring committee would have recommended  
10 continued randomisation and completion of the trial (**Figure 2** and **Figure 3**).<sup>34</sup> Furthermore, the  
11 two interventions do not seem to have significant differential effects on BDI (subjective depressive  
12 symptoms), SCL 90-R (psychological distress), and WHO 5 (well-being).  
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26 Compared with the baseline scores, both intervention groups improved during the trial period on  
27 all continuous outcomes. We did not include a control group receiving no intervention in this head-  
28 to-head trial so it is unclear whether it was trial intervention effects, regression towards the mean,  
29 or the natural progression of the disorder in this sample which was responsible for these  
30 changes.<sup>39</sup> More randomised clinical trials are needed to assess the effects of third wave cognitive  
31 therapy and mentalization-based treatment for major depressive disorder.  
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## 41 **Strengths**

42 First of all, the trial was conducted with an overall high level of methodological quality and we  
43 assessed the validity of the trial results according to the procedure proposed by Jakobsen et al.,  
44 including adjusting the thresholds for significance according to the number of randomised  
45 participants and the planned sample size.<sup>34</sup> We also proved the feasibility of our trial design, which  
46 can be used for larger trials provided that funding can be raised. Our trial has a number of  
47 additional strengths: (1) The trial protocol was registered before randomisation began at  
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1 ClinicalTrials.gov. In this protocol the outcome hierarchy and plans for analyses were  
2 presented. Our trial was altogether conducted according to good clinical research practice, with  
3 low risk of bias (adequate allocation sequence generation, adequate allocation concealment,  
4 adequate blinding, no risk of selective outcome reporting, low risk of incomplete outcome data  
5 bias, no risk of 'for profit' bias), and a high degree of external validity.<sup>40-44</sup> (2) Both of the trial  
6 interventions were conducted using manuals (available at [http://ctu.dk/publications/supplementary-](http://ctu.dk/publications/supplementary-material.aspx)  
7 [material.aspx](http://ctu.dk/publications/supplementary-material.aspx)) and adherence to the manuals was assessed as relatively high by an independent  
8 Danish psychologist trained both in mentalization-based therapy and third wave cognitive therapy.  
9 The manualization of the trial interventions makes it possible, to some extent, to implement the  
10 two trial interventions in clinical practice and to replicate or refute our results in future trials, but  
11 both treatment manuals are currently only available in Danish, which limits the possibility for non-  
12 Danish speakers to assess the quality of the treatment manuals. We are in the process of  
13 translating the third wave cognitive manual, which will be published at a later time point. The  
14 mentalization-based treatment is described thoroughly elsewhere.<sup>13-16</sup> Nevertheless, it is a clear  
15 limitation that the manuals are not currently available in English. Both the cognitive therapists and  
16 the mentalization therapists were involved in developing the treatment manuals for the respective  
17 psychotherapeutic treatments, which might make the therapist enthusiasm and thoroughness  
18 similar in the two intervention groups. (3) We have used the most commonly used outcomes in  
19 trials assessing the effects of psychotherapeutic interventions for depression (i.e., HDRS and  
20 BDI).<sup>11, 30, 45, 46</sup> This makes it possible to relate our results to results from other trials examining the  
21 effects of interventions for depression. Moreover, using HDRS as outcome makes it possible to  
22 perform blinded objective outcome assessment, which is a further strength of our trial. (4) The  
23 baseline characteristics of the trial participants as well as the psychopharmacological medication  
24 in the two groups were comparable which indicates that the randomisation succeeded in allocating  
25 comparable participants to the two intervention groups. (5) Only 2 out of the total of 44 participants  
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1 were not assessed after end of treatment, which decreases the risk of biased results.<sup>47</sup> (6) All  
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4 outcomes suggested that the participants randomised to third wave cognitive therapy had  
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6 improved more than the participants randomised to mentalization-based treatment. This supports  
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8 the validity of our results, even though most of these differences were non-significant.  
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## 10 11 12 13 **Limitations**

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15 Our trial has a number of limitations. This small-scale trial was in essence failed because we only  
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17 included 44 out of the planned 84 participants. The trial inclusion lasted for about two years as  
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19 planned but we had problems with recruiting participants. Basically, not enough eligible depressed  
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21 patients were referred to the clinic within the planned trial period. The great advantage of the  
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23 randomised clinical trial in general is that all known and unknown participant characteristics will be  
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25 similar at baseline in compared intervention groups.<sup>39</sup> However, even though our baseline  
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27 characteristics indicate similarity between the two groups on assessed baseline characteristics, it  
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29 is unlikely that all baseline characteristics will be similar when only 44 participants are randomised.  
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31 The low number of randomised participants in this small-scale trial increases the risks of wrong  
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33 results due to type I errors, and type II errors,<sup>48, 49</sup> and our adequate trial methodology cannot  
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35 necessarily compensate for these increased risks. Moreover, our results do not show anything  
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37 about long-term effects of the two interventions.  
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45 The chief consultant prescribing the psychopharmacological treatment was not blinded to  
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47 intervention allocation. Although we assessed the psychopharmacological treatment to be  
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49 comparable in the two randomised groups at cessation of the trial interventions (**Supplementary**  
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51 **material 1**), the lack of blinding might have influenced the psychopharmacological treatment. The  
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53 chief consultant is a mentalization-based therapist and was involved in developing the  
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55 mentalization-based treatment manual. The first author and primary investigator conducted the  
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1 third wave cognitive therapy and wrote the manual for the third wave cognitive therapy program,  
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3 which may also increase the risks of bias.  
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8 We did not perform power calculations for the secondary outcomes before randomisation began,  
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10 which is a further limitation. If an analysis of a secondary outcome has a power of less than 80%,  
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12 then either the secondary outcome should be classified as an exploratory outcome or the *P*-value  
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14 and the confidence interval thresholds for significance should be adjusted, just as the thresholds  
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16 are adjusted if a sample size has not been reached.<sup>34</sup>  
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21 Because of an unequal allocation of the trial participants to one of the two groups in the beginning  
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23 of the trial, the block size was reduced from 12 to 4 (see '**Randomisation**'). The block sizes were  
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25 at all times unknown to the trial investigators, and the Copenhagen Trial Unit performed these  
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27 changes without informing the investigators. However, a block size of four is small making it  
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29 possible to foresee which group a given eligible participant will be allocated to before  
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31 randomisation. This might question whether the allocation concealment was effective.  
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37 The trial was conducted at an outpatient psychiatric clinic with special interest for treatment of  
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39 personality disorders and depressive patients were not routinely referred to the clinic before the  
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41 trial began randomisation. Our results showed that a high proportion of the trial participants had  
42  
43 comorbid personality disorder and depression. This might explain why the baseline HDRS scores  
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45 indicated that the trial participants were only moderately depressed although all of the trial  
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47 participants were on sick leave due to psychological problems. Some of the trial participants might  
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49 suffer primarily from psychological problem other than depressive symptoms, i.e., personality  
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51 related problems. We did not assess number of prior depressive episodes in the included  
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53 participants, which makes it unclear whether our trial results demonstrate intervention effects in  
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1 participants with a first time depression or recurrent depression. Our results can only be related  
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3 to patients comparable to our trial participants, i.e., patients diagnosed with major depressive  
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5 disorder on sick leave due to psychiatric problems.  
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10 Highly specialised mentalization-based treatment was the primary psychotherapeutic method used  
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12 at the outpatient clinic prior to the trial, the co-interventions (communal breakfast and psycho-  
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14 education) were also a part of the treatment program prior to the trial, and experienced and  
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16 specialised third wave cognitive therapists were members of the staff at the psychiatric clinic  
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18 where the trial was conducted. Furthermore, all patients referred to the psychiatric clinic were on  
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20 sick leave due to psychiatric problems, and even though the evidence behind the specialised  
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22 treatments is lacking we considered that some form of specialised treatment was needed for all  
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24 patients at the psychiatric clinic. We did, therefore, not consider it ethically justifiable to use a  
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26 control group receiving no intervention, placebo, or only the co-interventions. All these  
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28 considerations and practical circumstances led to the choice of the psychotherapeutic  
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30 interventions and the design of this head-to-head trial comparing third wave cognitive therapy and  
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32 co-interventions versus mentalization-based therapy and co-interventions. The co-interventions  
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34 were delivered similarly to both treatment groups and the possible effects of co-interventions will  
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36 therefore even out between the compared intervention groups unless there are significant  
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38 interactions. Nevertheless, it is a clear limitation that our interventions are not and have not been  
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40 compared versus no intervention or a more simple and basic form of psychotherapy plus co-  
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42 interventions.<sup>39</sup> If a trial comparing the effects of two active interventions shows no difference in  
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44 effect it is not clear whether the two interventions are equally effective or equally ineffective – and  
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46 if an experimental intervention seem superior compared with a control intervention then the effect  
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48 size of the experimental intervention will be unclear because any beneficial or harmful effects of  
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50 the control intervention might influence the trial results.<sup>39</sup> All interventions should be assessed  
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versus no intervention before being introduced into clinical practice.<sup>39</sup> Furthermore, the combination of specialised psychotherapy and co-interventions constitute a relatively comprehensive treatment, which might not always be accessible to psychiatric patients in clinical practice – this might limit the generalizability of our results.

## Mentalization-based treatment

We did not find any relevant treatment manual we could use for the mentalization-based treatment, and we therefore created our own manual (<http://ctu.dk/publications/supplementary-material.aspx>).<sup>29</sup> The therapists in the mentalization-based treatment group were educated and experienced in psychodynamic therapy and group therapy and had underwent basic training and education in mentalization-based treatment according to Bateman and Karterud.<sup>13-16</sup> Mentalization-based treatment was originally designed to treat borderline personality.<sup>10, 12</sup> Few participants were diagnosed with borderline personality disorder (**Table 1**), and it can be argued that mentalization-based treatment was not a relevant intervention for the depressed participants of this trial. However, mentalization-based treatment is now used to treat a number of different disorders other than borderline personality disorder, including depression.<sup>10, 12</sup> Furthermore, a study has shown that female inpatients with depression showed a significantly lower capacity for mentalization compared with healthy controls – and deficits in mentalizing capacity were related to illness duration, number of admissions, and cognitive impairment.<sup>17</sup> The authors conclude that the investigation of mentalization may be of particular importance for the development of targeted psychotherapeutic interventions for depression.<sup>17</sup>

## Comorbid personality disorders

A large proportion of the included participants were diagnosed with cluster C personality disorders (anxious or fearful personality disorders).<sup>23, 24</sup> It has been debated if a diagnosis of a personality

1 disorder is accurate when patients are acutely depressed.<sup>19</sup> Our results indicate that comorbid  
2 personality disorder and depression does not lead to a poorer outcome compared to patients with  
3 depression alone – but this could be because the diagnoses of the personality disorders in our trial  
4 are inaccurate because the depressive symptoms might mimic pathological personality traits.  
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6 Furthermore, the limited number of included participants significantly reduces the power of this  
7 analysis.  
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### 10 **BDI compared to HDRS as outcome**

11 It is a common belief among clinicians that BDI is a more ‘reactive’ outcome than HDRS,<sup>50</sup> and it  
12 might be surprising to some why we identified a borderline significant effect on the HDRS results  
13 but no significant effect on the BDI. However, two systematic reviews with meta-analysis have  
14 included trials that simultaneously used HDRS and BDI to assess the effects of the same  
15 interventions.<sup>50, 51</sup> The results showed that BDI under such circumstances shows significantly less  
16 effect sizes compared to the HDRS.<sup>50, 51</sup> A greater percentage of participants would be considered  
17 improved if ratings of change were based on the HDRS rather than BDI.<sup>50</sup> The results from these  
18 two reviews<sup>50, 51</sup> are in agreement with our present results and may explain why we found a  
19 borderline significant effect on HDRS and no significant effect on BDI. On the other hand, it is also  
20 possible that HDRS compared to BDI overestimates participant improvement.<sup>51</sup>  
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44 It was impossible to blind the participants to treatment allocation. To ensure some degree of  
45 blinding we chose HDRS over BDI because it was possible to perform objective blinded outcome  
46 assessment using the HDRS. BDI is a self-administered questionnaire, which makes blinded  
47 objective outcome assessment impossible. We therefore expected the results on HDRS to be a  
48 more clinically valid compared to the BDI results – but we cannot exclude that breaking of blinding  
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1 and biased assessment of the HDRS may have occurred. In accordance with the CONSORT  
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4 Statement we did not assess degree of unblinding.<sup>40</sup>  
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## 8 **Implications**

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11 First of all, if a larger more definitive trial has to be conducted then a more realistic estimate of the  
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13 recruitment rate will be needed and more centres should be involved. On average, we recruited  
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15 approximately one participant every third week and we expected to be able to recruit  
16  
17 approximately one participant every week. Basically, not enough eligible participants were referred  
18  
19 to the clinic during the inclusion period and we had to terminate the trial due to economical and  
20  
21 practical constraints – this was the primary reason why we did not randomise more participants.  
22  
23 Before the randomisation began, we did not systematically assess how many participants it was  
24  
25 possible to recruit. This should also be done before a larger trial is conducted so the sample size  
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27 can be reached. Moreover, we did not take any specific actions promoting the trial outside the  
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29 clinic. If a future trial is to be conducted it should be considered to promote the trial through  
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31 advertising or use of other measures to motivate potential referrers to refer more eligible  
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33 participants. Besides the problems with recruiting enough participants, it was otherwise feasible to  
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35 conduct a randomised clinical trial with low risk of bias assessing the effects of third wave  
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37 cognitive therapy versus mentalization-based treatment for major depressive disorder.  
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44 The apparent difference in intervention effect found on the HDRS might be caused by random  
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46 error ('play of chance'), unaccounted bias, or a signal of a real effect.<sup>49</sup> The National Institute for  
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48 Clinical Excellence (NICE) have suggested a mean difference between two compared  
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50 interventions of three HDRS points as a criterion for 'clinical significance'.<sup>52</sup> Most interventions for  
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52 depression, both psychopharmacological as well as psychotherapeutic, rarely exceed having a  
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54 beneficial effect of more than three HDRS points.<sup>1, 11, 53-55</sup> We used an anticipated intervention  
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1 effect of five HDRS points to estimate the necessary sample size and this anticipated  
2 intervention effect was optimistic. Calculating Bayes factor based on the anticipated intervention  
3 effect, the observed intervention effect, and the standard error of the observed intervention effect  
4 shows a Bayes factor of 0.14, which is above the recommended threshold for significance of 0.1.<sup>34</sup>  
5  
6 This underlines that our results should be regarded as insignificant and that an anticipated  
7 intervention effect lower than five HDRS points ought to be used in sample size calculations in  
8 future trials assessing the effects of third wave cognitive therapy and mentalization-based therapy.  
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10 We found a mean difference of more than four HDRS points which, compared to other  
11 interventions, is relatively high. These results might be used to calculate a necessary sample size  
12 in a larger more definitive trial. However, HDRS might not at all be a clinically relevant outcome  
13 and other more clinically relevant outcomes might be more valid to use in future trials. Severity of  
14 depression as measured by the total HDRS score has failed to predict suicide attempts,<sup>56, 57</sup> and  
15 some publications have questioned the usefulness of the HDRS and concluded that the scale is  
16 psychometrically and conceptually flawed.<sup>57, 58</sup>  
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## 35 Conclusions

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37 Our preliminary results show that third wave cognitive therapy compared with mentalization-based  
38 treatment may be a more effective intervention for depressive symptoms measured on the HDRS.  
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40 The effects of the two interventions did not seem to differ significantly regarding BDI II, SCL 90-R,  
41 and WHO 5. More randomised clinical trials are needed to assess the effects of third wave  
42 cognitive therapy and mentalization-based treatment.  
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## Acknowledgments

We would like to thank all the participants in the trial for patiently cooperating with the assessments. We would also like to thank Anita Jensen for helping with data management; Lotte Dragsted and Marianne Lyngby for performing the Hamilton interviews; Gitte Nielsen for assistance in developing the treatment manual for the third wave cognitive therapy; and Jane Lindschou for expert assistance with the randomisation. Lastly, we would like to thank all the co-workers at the psychiatric clinic in Roskilde. Without their patience and cooperation the trial would have been impossible to conduct.

## Funding

We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors.

## Contributors

JCJ and CG wrote the first draft. JCJ, CG, KAL, PS, US, and ES planned and designed the trial. JCJ and MK performed the reliability tests. KAL, PS, US, and ES contributed with psychiatric expertise. PW conducted the statistical analyses. TL contributed with statistical expertise. All authors contributed academically to the manuscript and have accepted the manuscript for publication.

## Competing interests

The principal investigator was also a therapist in the third wave cognitive therapy treatment and has developed the treatment manual for the third wave cognitive therapy. The consultant performing the medical consultations during the trial period was not blinded to the treatment allocation of the participants and developed the mentalization-based treatment manual in close

1 cooperation with the two mentalization-based therapists. Other authors have no competing  
2 interests.  
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### 5 **Data sharing**

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8 No additional data available.  
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### 10 **Ethical considerations and regulatory approval**

11  
12 There were no immediate ethical problems regarding this trial. Research has not identified any  
13 significant adverse effects or risks from either of the compared interventions. Before randomization  
14 began approval was obtained by the Regional Ethics Committee of Zealand (no: SJ-43) and the  
15 trial was registered at the Danish Data Protection Agency (no: 2008-58-0020).  
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26 All participants were informed of the trial in writing and verbally before randomization. Written  
27 informed consent was obtained from every participant before inclusion. All trial participants were,  
28 on request, permitted access to further information about the project. No expense allowance was  
29 offered to the trial participants  
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For peer review only



## Tables

### Table 1. Baseline characteristics

		Participants randomised to third wave cognitive therapy (n=22)	Participants randomised to mentalization-based therapy (n=22)
<b>Age</b>	mean (SD)	38.5 (8.9)	40.3 (6.8)
<b>Sex</b>	female n (%)	18 (82)	20 (91)
<b>Number of children</b>	mean (SD)	1.4 (1.2)	1.7 (1.1)
<b>Marital status</b>	n (%)		
Single		3 (14)	7 (32)
In a relationship		6 (27)	5 (23)
Married		12 (55)	8 (36)
Separated/divorced		1 (5)	2 (9)
<b>Level of education</b>	n (%)		
Only high school diploma		7 (32)	3 (14)
Medium long education		14 (64)	19 (86)
Long education		1 (5)	0 (0)
<b>Baseline HDRS** scores</b>			
	mean (SD)	22.1 (5.9)	22.5 (4.9)
	median	22.5	23.6
	range	7-30	11-29
<b>Baseline GSI scores (SCL 90-R)***</b>			
	mean (SD)	1.80 (0.59)	1.84 (0.41)
	median	1.72	1.74
	range	0.68-2.79	0.99-2.54
<b>Personality disorders</b>	n (%)		
No personality disorder		5 (23)	6 (27)
One personality disorder		11 (50)	12 (55)
Two personality disorders		4 (18)	3 (14)
Three or more personality disorders		2 (9)	1 (5)
<b>Personality disorders diagnoses</b>	n (%)		
Paranoid		1 (5)	0 (0)
Borderline		4 (18)	1 (5)
Avoidant		7 (32)	5 (23)
Obsessive-compulsive		4 (18)	3 (14)
Dependant		1 (5)	0 (0)
Depressive		7 (32)	8 (36)
Personality disorder NOS		1 (5)	4 (18)

\*SD=Standard Deviation; \*\*HDRS=17-item Hamilton Depression rating Scale; \*\*\*SCL-90-R=Global Severity Index score on the Symptom Checklist 90 Revised

**Table 2. Effects of third wave cognitive therapy versus mentalisation-based treatment**

Outcome measure	Group randomised to third wave cognitive therapy (N=22)		Group randomised to mentalization-based treatment (N=22)		P-value of unadjusted analysis at end of treatment	P-value of adjusted analysis* at end of treatment
	Baseline	End of treatment	Baseline	End of treatment		
<b>HDRS</b>						
N	22	22	21	20	0.051	0.039
Mean	22.1	12.9	22.5	17.0		
95%CI	19.5-24.8	9.81-15.9	20.3-24.8	14.0-20.0		
<b>Remission (HDRS&lt;8)</b>						
N/ total	0/22	5/22	0/21	0/20	0.049	Not possible to calculate
<b>BDI II</b>						
N	21	21	22	17	0.46	0.46
Mean	36.8	17.6	36.3	20.5		
95%CI	32.5-41.1	12.2-23.0	32.1-40.6	14.5-26.4		
<b>SCL 90-R (GSI score)</b>						
N	22	22	22	20	0.52	0.66
Mean	1.80	0.88	1.84	1.00		
95%CI	1.54-2.05	0.62-1.15	1.66-2.02	0.74-1.25		
<b>WHO 5</b>						
N	22	22	21	20	0.54	0.46
Mean	3.55	10.5	4.33	9.45		
95%CI	1.84-5.25	7.66-13.4	3.13-5.53	7.18-11.7		

\*= Adjusted for baseline values of each outcome

Abbreviations: HDRS=Hamilton Depression Rating Scale (17-item); N=Number of participants; CI=Confidence interval; BDI=Beck's Depression Inventory; SCL 90-R=Symptom Checklist 90 Revised; GSI=Global Severity Index score; WHO 5=World Health Organisation-Five Well-being Index 1999, a high score associates to a high level of well-being.

## Figure Legends

### Figure 1 (CONSORT flowchart)

### Figure 2

Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks. 42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.<sup>35-38</sup> These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

### Figure 3

Post-hoc sequential analysis of the results on Beck's depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.<sup>35-38</sup> The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of no beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

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7 **Third wave Cognitive Therapy versus Mentalization-based**  
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9 **Treatment for Major Depressive Disorder. A Randomised Clinical**  
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11 **Trial**

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16 Janus Christian Jakobsen,<sup>1,2\*</sup> Christian Gluud,<sup>2</sup> Mickey Kongerslev,<sup>1</sup> Kirsten Aaskov Larsen,<sup>3</sup> Per  
17 Sørensen,<sup>4</sup> Per Winkel,<sup>2</sup> Theis Lange,<sup>5</sup> Ulf Søgaaard,<sup>3</sup> Erik Simonsen<sup>1</sup>

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## Abstract

**Objective:** To compare the benefits and harms of third wave cognitive therapy versus mentalization-based therapy in a small sample of depressed participants.

**Design, participants, and setting:** The trial was conducted at an outpatient psychiatric clinic for non-psychotic patients in Roskilde, Denmark.

**Participants:** ~~44~~~~We planned to randomise 84~~ consecutive adult participants diagnosed with major depressive disorder.

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**Interventions:** ~~18 weeks of~~ third wave cognitive therapy (n=22) versus 18 weeks of mentalization-based treatment (n=22). ~~in a superiority randomised clinical trial. The outcome assessors and the statistician were blinded to treatment allocation. The trial was conducted at an outpatient psychiatric clinic for non-psychotic patients in Roskilde, Denmark.~~

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**Outcomes:** The primary outcome was the Hamilton Rating Scale for Depression (HDRS) at end of treatment (18 weeks). Secondary outcomes were: remission (HDRS < 8), Beck's Depression Inventory, Symptom Checklist 90 Revised, and The World Health Organisation-Five Well-being Index 1999.

**Results:** The trial inclusion lasted for about two years as planned but only 44 out of the planned 84 participants were randomised. Two mentalization-based participants were lost to follow-up. The unadjusted analysis showed that third wave participants compared with mentalization-based participants did not differ significantly regarding the 18 weeks HDRS score (12.9 versus 17.0;

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mean difference -4.14; 95% CI -8.30 to 0.03; P = 0.051). In the analysis adjusted for baseline HDRS score, the difference was favouring third wave cognitive therapy (P = 0.039). At 18 weeks, five of the third wave participants (22.7%) were in remission versus none of the mentalization-based participants (P = 0.049). We recorded no suicide attempts or suicides during the intervention period in any of the 44 participants. No significant differences were found between the two intervention groups on the remaining secondary outcomes.

**Conclusions:** Third wave cognitive therapy may be more effective than mentalization-based therapy for depressive symptoms measured on the HDRS. However, more randomised clinical trials are needed to assess the effects of third wave cognitive therapy and mentalization-based treatment for depression.

~~**Funding:** We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors.~~

**Trial registration:** Registered with Clinical Trials government identifier: NCT01070134

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**Keywords:** Randomised clinical trial; depression; third wave cognitive therapy; mindfulness, mentalization-based treatment

For peer review only

## Strengths and limitations of this study

- It was possible to conduct the trial with a low risk of bias (adequate allocation sequence generation, adequate allocation concealment, adequate blinding, no risk of selective outcome reporting, low risk of incomplete outcome data bias, no risk of 'for profit' bias), which was the primary strength of this randomised clinical trial.
- The trial also provided valuable information about possible intervention effects of third wave cognitive therapy and mentalization-based treatment. Our preliminary results may be used to design future trials including estimation of sample size calculations.
- The primary limitation of this randomised clinical trial was that only 44 out of the planned 84 participants were randomised in this small-scale trial.



## Introduction

### Third wave cognitive therapy

Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of traditional cognitive therapy versus no intervention for major depressive disorder.<sup>1</sup> We found that cognitive therapy compared with no intervention seems to have a small statistically significant beneficial effect on depressive symptoms. However, we identified only a limited number of relatively small randomised clinical trials all with a high risk of bias.<sup>1</sup> During the last two decades new forms of cognitive therapy have been developed. These third wave cognitive therapies include, e.g., acceptance and commitment therapy, schema therapy, mindfulness-based cognitive therapy, and meta-cognitive therapy.<sup>2</sup> Especially mindfulness-based interventions have been implemented in numerous different clinical contexts in recent years.<sup>3-5</sup> One meta-analysis showed that third wave cognitive therapy might prevent relapse of depression,<sup>6</sup> and small trials show that third wave cognitive therapy versus no intervention or treatment as usual is effective for acutely depressed patients.<sup>7, 8</sup> One trial has shown comparable effects between cognitive therapy and third wave cognitive therapy in non-melancholic depression, but the trial only included 45 participants.<sup>9</sup>

### Mentalization-based treatment

Mentalizing entails attending to mental states – holding ‘mind in mind’.<sup>10</sup> It is the process by which an individual explicitly and implicitly interpret the action of himself or herself and others on the basis on intentional mental states such as wishes, needs, goals, and reason.<sup>10</sup>

Mentalization-based treatment is rooted in attachment theory and developmental psychopathology and it includes essentials from psychodynamic psychotherapy in a concurrent individual and group

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format.<sup>10</sup> Prior to this trial we carried out a systematic review of randomised clinical trials examining the effects of psychodynamic therapy for major depressive disorder.<sup>11</sup> We found that psychodynamic therapy versus no intervention seems to have a small statistically significant effect on depressive symptoms (mean difference about three HDRS points).<sup>11</sup> However, we identified a limited number of trials, the trials were small, and all the trials had a high risk of bias so our results might be questioned.

Mentalization-based therapy was originally developed to treat borderline personality disorder but is now also used to treat various other psychiatric disorders such as depression, eating disorders, substance abuse, and personality disorders other than borderline.<sup>10, 12</sup> Mentalization-based treatment is based on the concept of mentalization as described by Fonagy and Bateman,<sup>13, 14</sup> and is different from the more strictly defined mentalization-based therapy as manualized by Karterud and Bateman.<sup>13-16</sup> In comparison with mentalization-based therapy, mentalization-based treatment used in this trial has a more open therapeutic stance – letting the patient decide the theme in an associative way. The therapist is less active in directing the theme in the dialog and uses interpretations. Mentalizing deficits can be assumed to underlie depressive symptoms,<sup>17, 18</sup> and many depressed patients have a comorbid personality disorder.<sup>19</sup> We did not identify any trial assessing the effects of mentalization-based treatment or therapy versus no intervention for major depressive disorder.<sup>11</sup>

### **Third wave cognitive therapy versus mentalization-based treatment**

No randomised clinical trials or systematic reviews seem to have examined the effects of third wave cognitive therapy versus mentalization-based treatment or therapy for major depression.<sup>20</sup>

## **Methods**

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9 In the following, we briefly describe the methodology of this trial. For details please consult our  
10 registered (clinicaltrials.gov: NCT01070134) and published protocol.<sup>21</sup>  
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### 13 14 **Objective**

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16 Our objective was to compare the effect of third wave cognitive therapy versus mentalization-  
17 based therapy in a small sample of participants with major depressive disorder.  
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### 20 21 22 **Inclusion of participants**

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24 The trial was conducted at a public psychiatric outpatient clinic only treating patients on sick leave  
25 due to a psychiatric disorder. Patients were referred from general practitioners, psychiatrists in  
26 private practice, and medical and psychiatric departments. No special announcement of the trial  
27 was made to the referrers. All patients referred to the psychiatric clinic had a full psychiatric  
28 examination by a physician who made the preliminary psychiatric diagnoses (DSM-IV-TR).<sup>22</sup>  
29 Eligible patients were then interviewed by the principal investigator (JCJ) who used the depression  
30 part of the structured clinical interview for DSM-IV axis I disorders (SCID I) interview<sup>23</sup> to assess  
31 whether the patient fulfilled the criteria for a major depressive disorder (DSM-IV-TR).<sup>22</sup> Before  
32 randomisation baseline assessments were carried out for all outcome measures and all eligible  
33 patients were assessed with the structured clinical Interview for DSM-IV axis II disorders (SCID  
34 II).<sup>24</sup> We chose to perform the SCID II assessments because we wanted to compare personality  
35 disorders at baseline in the two intervention groups and to exclude patients with schizotypal  
36 personality disorder.  
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50 The participant had to meet all of the inclusion criteria and none of the exclusion criteria.  
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### Inclusion criteria

1. Age from 18 to 65 years.
2. Major depressive disorder, whether first episode or recurrent (DSM-IV-TR).<sup>23</sup>
3. Beck's Depression Inventory (BDI II) score >13 points.<sup>25</sup>
4. Written informed consent.

### Exclusion criteria

1. Current psychosis, schizophrenia, or schizotypal personality disorder (DSM-IV-TR).<sup>22</sup>
2. A significant alcohol or substance abuse (assessed during the preliminary consultations).
3. Initiated or changed medical anti-depressive treatment less than six weeks before randomisation.
4. Pregnancy.
5. No written informed consent.

### Randomisation

Eligible patients with major depressive disorder were randomised 1:1 to third wave cognitive therapy versus mentalization-based treatment. The Copenhagen Trial Unit performed the randomisation centrally, using a computer generated block randomisation sequence that was unknown to the investigators. Participant inclusion began in February 2010 and the last patient was randomised in July 2011. Because of an unequal allocation of the trial participants to one of the two groups in the beginning of the trial (there were only a few participants in one of the groups), the block size was reduced from 12 to 4 and a stratification variable (HDRS score  $\geq 22$  points) was removed. The block sizes were at all times unknown to the trial investigators, and the

Copenhagen Trial Unit performed these changes without informing the investigators of the changes. Otherwise, the methodology was not changed after trial commencement.

## Interventions

Each participant received treatment for 18 weeks. The two intervention groups were 'slow-open' (new patients entered the group continually) with a maximum of seven patients per group.

The time of each of the elements in the comprehensive treatment package (see below) was planned to be similar in the compared intervention groups.

### Shared elements for both intervention groups

All participants were, as part of the outpatient clinic's usual care, offered a communal breakfast twice a week and participated in group psycho-education for one hour a week. During the course of treatment, all participants with children were offered participation in a parent support group (four weekly one-hour sessions). A psychiatric consultant (KAL), who was not otherwise involved in the interventions, assessed each participant and prescribed psychopharmacological treatment when needed. The psychiatric consultant prescribed medication according to the official recommendations.<sup>26</sup> After the first consultation, medical consultations were offered by demand of the participant or the therapists.

### Third wave cognitive therapy

The third wave cognitive therapy consisted of one weekly third wave cognitive individual psychotherapy session (45 minutes) and one weekly mindfulness-skills training group (1.5 hours). Altogether the third wave cognitive therapy consisted of 18 individual psychotherapy sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.

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9 The weekly individual psychotherapy session included:

- 10 • Introduction of the cognitive model and mindfulness.
- 11 • Exploration of thoughts, feelings, behaviour, and physical sensations.
- 12 • Work on acceptance of difficult feelings and difficult life circumstances.
- 13 • Work on assumptions challenged by behavioural experiments.
- 14 • Self esteem training.
- 15 • Tools to prevent relapse.

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23 The weekly mindfulness-skills training group included:

24 Education in the practical use of six basic mindfulness skills: focusing, acceptance, labeling  
25 feelings, body awareness, self-esteem skills, and mindful communication. The group participants  
26 were encouraged to practice the six mindfulness skills between sessions. The participants went  
27 through the complete skills training group's program three times during the course of the 18 weeks  
28 of treatment.  
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36 The manual for the third wave cognitive therapy was developed specifically for the trial and had  
37 not been used before in a trial setting. Details about the third wave cognitive therapy program is  
38 available elsewhere (<http://ctu.dk/publications/supplementary-material.aspx>).<sup>27</sup>  
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#### 43 **Mentalization-based treatment**

44 The mentalization-based treatment consisted of a weekly mentalization-based individual  
45 psychotherapy session (45 minutes) and a weekly mentalization-based group therapy session (1.5  
46 hours). Altogether the mentalization-based treatment consisted of 18 individual psychotherapy  
47 sessions (45 minutes) and 18 group sessions (1.5 hours), a maximal total of 40.5 hours.  
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Mentalization-based treatment imposes explicit attention to mentalizing in the therapeutic process.

This is established by a therapeutic stance where the therapist aims at demonstrating a 'mentalizing attitude', i.e., validating, 'not-knowing', and curiously questioning the patient about feelings and thoughts.<sup>10, 16, 28</sup> The therapist tries to identify and intervene when the patient is not mentalizing and assists the patient in regulating the level of the emotions so the patient is able to mentalize and to get different perspectives on life events, conflicts, etc.<sup>10, 16, 28</sup>

At the time this project was planned there was no manual available for the mentalization-based treatment. Therefore, we developed our own treatment manual based on mentalization principles.<sup>29</sup> Further details about the mentalization-based treatment is available elsewhere (<http://ctu.dk/publications/supplementary-material.aspx>).<sup>29</sup>

### **Therapists and adherence to the intervention manuals**

Each intervention group had two therapists. The two third wave cognitive therapists (one of these therapists was the principal investigator) and the two mentalization-based therapists had comparable psychotherapeutic education and experience.

All individual sessions were recorded on an audio recorder and all group sessions were recorded on video. An experienced external psychologist not otherwise involved in the trial assessed the degree of adherence to the manuals 0-5 (0: no adherence; 1: adherence about 20% of the time; 2: adherence about 40% of the time; 3: adherence about 60% of the time; 4: adherence about 80% of the time; 5: adherence about 100% of the time). The psychologist randomly selected 4 x 5 sessions using a computer program. The results showed high adherence to the treatment manuals for both interventions. The means of the ratings were: 4.6 in five sessions of individual third wave

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cognitive therapy; 4.2 in five sessions of third wave cognitive group therapy; 4.2 in five sessions of individual mentalization-based treatment; and 3.8 in five sessions of mentalization-based group treatment.

## Outcomes

### Primary outcome

- Score on the Hamilton Depression Rating Scale (HDRS)<sup>30</sup> after end of treatment at week 18.

### Secondary outcomes

- The proportion of participants in remission after cessation of treatment at week 18. We defined remission as HDRS below 8.<sup>31</sup>
- Global Severity Index score (GSI-score)<sup>32</sup> on the Symptom Checklist 90 Revised (SCL-90-R)<sup>32</sup> after cessation of treatment at week 18.
- Score on the World Health Organisation-Five Well-being Index 1999 (WHO 5)<sup>33</sup> after cessation of treatment at week 18.
- Score on the Beck's Depression Inventory (BDI II)<sup>25</sup> after cessation of treatment at week 18.

### Reliability of the Hamilton Depression Rating Scale (HDRS) interviews

Two experienced psychologists performed the Hamilton interviews during the trial period. Prior to the trial, the principal investigator and one of the psychologists both Hamilton interviewed eight patients at the same time point. The mean difference between these two HDRS ratings performed on the same patient at the same time point was -0.13 points (SD 1.25) (intra-class correlation coefficient 0.98; Spearman correlation 0.92). During the trial both psychologists Hamilton



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interviewed 21 patients at the same time point. The mean difference between these two HDRS ratings performed on the same patient at the same time point was 0.29 points (SD 2.21) (intra-class correlation coefficient 0.96; Spearman correlation 0.94). All these 29 interviews were performed with both HDRS-raters present simultaneously. One rater interviewed and rated the interviewee and the other rater only rated the interviewee. The interviewers were not allowed to discuss the results before each interviewer had registered the HDRS result.

### Data-management

All data were handled by research assistants not otherwise involved in the trial and was stored in the principal investigator's office and later at the Copenhagen Trial Unit. Privacy of trial participants was protected in accordance with the Act on Processing of Personal Data and the Health Act. The project was notified to the Danish Data Protection Agency (no.: 2008-58-0020).

### Blinding

The Hamilton interviewers were blinded to treatment allocation and were instructed by the principal investigator to avoid questions beside the Hamilton interview. All interviewees were prior to each interview instructed by the principal investigator not to mention which treatment they were allocated to. It was not possible to blind neither the therapists nor the participants to treatment allocation.

The chief consultant performing the medical consultations was, due to practical circumstances, not blinded to treatment allocation.

A statistician at The Copenhagen Trial Unit performed the statistical analyses blinded with the two intervention groups coded as 'A' and 'B'.

### A priori sample size estimate

With a 'minimal relevant mean difference' (MIREDIF) between the two interventions of 5 HDRS points, an alpha of 0.05 (type I error), a power of 0.90 (type II error of 10%), and a standard deviation (SD) of 7 HDRS points, the sample size calculation showed that a total of 84 participants would be necessary. We estimated that we would need an inclusion period of about two years to recruit 84 participants.

### Statistical analyses

The primary analyses were intention-to-treat analyses. Significance tests were two-sided at a significance level of 0.05.

Continuous outcomes were compared between the two intervention groups using the univariate general linear model with (ANCOVA) and without HDRS baseline value adjustment (ANOVA). The binary outcome was compared between the groups using Fisher's exact test. Logistic regression could not be used since none of the participants in the mentalization-based group obtained remission implying an infinite odds ratio.

As the trial was stopped before the sample size was reached, we *post hoc* decided to conduct sequential analysis to assess the results of significance testing taking sparse data and repetitive testing into consideration.<sup>34</sup> We used the trial sequential analysis program for that purpose.<sup>35-38</sup>

### Results

## Participants

Only 44 out of the 84 planned participants were included in the trial. Twenty-two participants were randomised to third wave cognitive therapy versus 22 participants to mentalization-based treatment. **Figure 1** details the participant flow through the phases of the trial.

## Baseline characteristics of the participants

The baseline characteristics regarding age, sex, number of children, score on the HDRS, baseline diagnosis of personality disorder, and psychopharmacological treatment were overall assessed as being comparable between the two intervention groups. The baseline participant characteristics are described in detail in **Table 1** and the psychopharmacological treatment in **Supplementary material 1**.

## Treatment compliance

None of the 22 participants randomised to third wave cognitive therapy were lost to follow-up or excluded due to the fact that they participated in less than 70% of the sessions. One participant out of the 22 randomised to mentalization-based treatment was lost to follow-up and one was excluded, as she did not attend the required 70% of the sessions (**Figure 1**). The excluded participant was not assessed on any of the outcomes at end of treatment.

## Intervention effects

### Primary outcome

#### Mean score on the HDRS after end of interventions

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Participants randomised to third wave therapy compared with participants randomised to mentalization-based treatment did not differ significantly regarding the 18-week HDRS scores in the unadjusted analysis (mean 12.9, 95% CI 9.81 to 15.9 versus mean 17.0, 95% CI 14.0 to 20.0;  $P = 0.051$ ). The mean difference between the two groups was -4.14 HDRS points (95% CI -8.30 to 0.03) corresponding to a Cohen's D of -0.62. The difference was, however, significant in the analysis adjusted for baseline HDRS score ( $P = 0.039$ ) (**Table 2**).

Sequential analysis demonstrated that the observed significant findings ought to be interpreted conservatively as random errors due to sparse data cannot be excluded (**Figure 2**).

We did not impute missing values because only 2 out of 44 (4.5%) participants had missing values.

Histograms on the data from both intervention groups showed that the data seem to be normally distributed. Using the non-parametric test the P-value was 0.064.

There was no significant interaction between the indicator of a diagnosis of a personality disorder and the intervention effects. This was also the case when the indicator was redefined as a binary quantity defined as any kind of personality disorder (yes/no) or as a binary quantity defined as personality disorder = borderline personality disorder (yes/no).

## Secondary outcomes

### Participants in remission after cessation of treatment

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7 In the third wave cognitive therapy group 22.7% (n=5) were in remission after cessation of  
8 treatment (defined as having HDRS <8 points) versus 0% in the mentalization-based treatment  
9 group. This difference was significant (P = 0.049) (**Table 2**).

#### 14 **BDI II<sup>25</sup>, SCL-90-R<sup>32</sup>, and WHO 5<sup>33</sup> after end of interventions**

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16 No significant difference was found on BDI II, SCL-90-R (GSI-scores), or WHO 5 between the two  
17 intervention groups after cessation of treatment (**Table 2**). Sequential analysis demonstrated that  
18 the observed insignificant findings ought to be interpreted conservatively as random errors due to  
19 sparse data cannot be excluded (see **Figure 3** regarding BDI II).

#### 25 **Other outcomes**

##### 29 **Admissions, suicide attempts, and suicides**

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31 One of the participants randomised to third wave cognitive therapy and two of the participants  
32 randomised to mentalization-based treatment were for a short period (some days) admitted to a  
33 psychiatric hospital during the intervention period.

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38 We recorded no suicide attempts or suicides during the intervention period in any of the 44  
39 participants.

#### 46 **Discussion**

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Our preliminary results indicate that third wave cognitive therapy compared with mentalization-based treatment may be a more effective intervention for lowering depressive symptoms measured on the HDRS and may increase the probability of remission (HDRS <8 points). Furthermore, our trial demonstrated the feasibility of conducting the trial with low risks of bias. However, when only 44 out of the planned 84 participants (52%) of the projected sample size is obtained in a trial, it is necessary to interpret the results cautiously. Had this been an interim analysis, any independent safety and data monitoring committee would have recommended continued randomisation and completion of the trial (**Figure 2** and **Figure 3**).<sup>34</sup> Furthermore, the two interventions do not seem to have significant differential effects on BDI (subjective depressive symptoms), SCL 90-R (psychological distress), and WHO 5 (well-being).

Compared with the baseline scores, both intervention groups improved during the trial period on all continuous outcomes. We did not include a control group receiving no intervention in this head-to-head trial so it is unclear whether it was trial intervention effects, regression towards the mean, or the natural progression of the disorder in this sample which was responsible for these changes.<sup>39</sup> More randomised clinical trials are needed to assess the effects of third wave cognitive therapy and mentalization-based treatment for major depressive disorder.

## Strengths

First of all, the trial was conducted with an overall high level of methodological quality and we assessed the validity of the trial results according to the procedure proposed by Jakobsen et al., including adjusting the thresholds for significance according to the number of randomised participants and the planned sample size.<sup>34</sup> We also proved the feasibility of our trial design, which can be used for larger trials provided that funding can be raised. Our trial has a number of additional strengths: (1) The trial protocol was registered before randomisation began at

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7 ClinicalTrials.gov. In this protocol the outcome hierarchy and plans for analyses were  
8 presented. Our trial was altogether conducted according to good clinical research practice, with  
9 low risk of bias (adequate allocation sequence generation, adequate allocation concealment,  
10 adequate blinding, no risk of selective outcome reporting, low risk of incomplete outcome data  
11 bias, no risk of 'for profit' bias), and a high degree of external validity.<sup>40-44</sup> (2) Both of the trial  
12 interventions were conducted using manuals (available at [http://ctu.dk/publications/supplementary-](http://ctu.dk/publications/supplementary-material.aspx)  
13 [material.aspx](http://ctu.dk/publications/supplementary-material.aspx)) and adherence to the manuals was assessed as relatively high by an independent  
14 Danish psychologist trained both in mentalization-based therapy and third wave cognitive therapy.  
15 The manualization of the trial interventions makes it possible, to some extent, to implement the  
16 two trial interventions in clinical practice and to replicate or refute our results in future trials, but  
17 both treatment manuals are currently only available in Danish, which limits the possibility for non-  
18 Danish speakers to assess the quality of the treatment manuals. We are in the process of  
19 translating the third wave cognitive manual, which will be published at a later time point. The  
20 mentalization-based treatment is described thoroughly elsewhere.<sup>13-16</sup> Nevertheless, it is a clear  
21 limitation that the manuals are not currently available in English. Both the cognitive therapists and  
22 the mentalization therapists were involved in developing the treatment manuals for the respective  
23 psychotherapeutic treatments, which might make the therapist enthusiasm and thoroughness  
24 similar in the two intervention groups. (3) We have used the most commonly used outcomes in  
25 trials assessing the effects of psychotherapeutic interventions for depression (i.e., HDRS and  
26 BDI).<sup>11, 30, 45, 46</sup> This makes it possible to relate our results to results from other trials examining the  
27 effects of interventions for depression. Moreover, using HDRS as outcome makes it possible to  
28 perform blinded objective outcome assessment, which is a further strength of our trial. (4) The  
29 baseline characteristics of the trial participants as well as the psychopharmacological medication  
30 in the two groups were comparable which indicates that the randomisation succeeded in allocating  
31 comparable participants to the two intervention groups. (5) Only 2 out of the total of 44 participants  
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6 were not assessed after end of treatment, which decreases the risk of biased results.<sup>47</sup> (6) All  
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8 outcomes suggested that the participants randomised to third wave cognitive therapy had  
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10 improved more than the participants randomised to mentalization-based treatment. This supports  
11  
12 the validity of our results, even though most of these differences were non-significant.  
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## 15 16 **Limitations**

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18 Our trial has a number of limitations. This small-scale trial was in essence failed because we only  
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20 included 44 out of the planned 84 participants. The trial inclusion lasted for about two years as  
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22 planned but we had problems with recruiting participants. Basically, not enough eligible depressed  
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24 patients were referred to the clinic within the planned trial period. The great advantage of the  
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26 randomised clinical trial in general is that all known and unknown participant characteristics will be  
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28 similar at baseline in compared intervention groups.<sup>39</sup> However, even though our baseline  
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30 characteristics indicate similarity between the two groups on assessed baseline characteristics, it  
31  
32 is unlikely that all baseline characteristics will be similar when only 44 participants are randomised.  
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34 The low number of randomised participants in this small-scale trial increases the risks of wrong  
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36 results due to type I errors, and type II errors,<sup>48, 49</sup> and our adequate trial methodology cannot  
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38 necessarily compensate for these increased risks. Moreover, our results do not show anything  
39  
40 about long-term effects of the two interventions.  
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42 The chief consultant prescribing the psychopharmacological treatment was not blinded to  
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44 intervention allocation. Although we assessed the psychopharmacological treatment to be  
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46 comparable in the two randomised groups at cessation of the trial interventions (**Supplementary**  
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48 **material 1**), the lack of blinding might have influenced the psychopharmacological treatment. The  
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50 chief consultant is a mentalization-based therapist and was involved in developing the  
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52 mentalization-based treatment manual. The first author and primary investigator conducted the  
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7 third wave cognitive therapy and wrote the manual for the third wave cognitive therapy program,  
8 which may also increase the risks of bias.  
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12 We did not perform power calculations for the secondary outcomes before randomisation began,  
13 which is a further limitation. If an analysis of a secondary outcome has a power of less than 80%,  
14 then either the secondary outcome should be classified as an exploratory outcome or the *P*-value  
15 and the confidence interval thresholds for significance should be adjusted, just as the thresholds  
16 are adjusted if a sample size has not been reached.<sup>34</sup>  
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23 Because of an unequal allocation of the trial participants to one of the two groups in the beginning  
24 of the trial, the block size was reduced from 12 to 4 (see '**Randomisation**'). The block sizes were  
25 at all times unknown to the trial investigators, and the Copenhagen Trial Unit performed these  
26 changes without informing the investigators. However, a block size of four is small making it  
27 possible to foresee which group a given eligible participant will be allocated to before  
28 randomisation. This might question whether the allocation concealment was effective.  
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36 The trial was conducted at an outpatient psychiatric clinic with special interest for treatment of  
37 personality disorders and depressive patients were not routinely referred to the clinic before the  
38 trial began randomisation. Our results showed that a high proportion of the trial participants had  
39 comorbid personality disorder and depression. This might explain why the baseline HDRS scores  
40 indicated that the trial participants were only moderately depressed although all of the trial  
41 participants were on sick leave due to psychological problems. Some of the trial participants might  
42 suffer primarily from psychological problem other than depressive symptoms, i.e., personality  
43 related problems. We did not assess number of prior depressive episodes in the included  
44 participants, which makes it unclear whether our trial results demonstrate intervention effects in  
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7 participants with a first time depression or recurrent depression. Our results can only be related  
8 to patients comparable to our trial participants, i.e., patients diagnosed with major depressive  
9 disorder on sick leave due to psychiatric problems.  
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14 Highly specialised mentalization-based treatment was the primary psychotherapeutic method used  
15 at the outpatient clinic prior to the trial, the co-interventions (communal breakfast and psycho-  
16 education) were also a part of the treatment program prior to the trial, and experienced and  
17 specialised third wave cognitive therapists were members of the staff at the psychiatric clinic  
18 where the trial was conducted. Furthermore, all patients referred to the psychiatric clinic were on  
19 sick leave due to psychiatric problems, and even though the evidence behind the specialised  
20 treatments is lacking we considered that some form of specialised treatment was needed for all  
21 patients at the psychiatric clinic. We did, therefore, not consider it ethically justifiable to use a  
22 control group receiving no intervention, placebo, or only the co-interventions. All these  
23 considerations and practical circumstances led to the choice of the psychotherapeutic  
24 interventions and the design of this head-to-head trial comparing third wave cognitive therapy and  
25 co-interventions versus mentalization-based therapy and co-interventions. The co-interventions  
26 where delivered similarly to both treatment groups and the possible effects of co-interventions will  
27 therefore even out between the compared intervention groups unless there are significant  
28 interactions. Nevertheless, it is a clear limitation that our interventions are not and have not been  
29 compared versus no intervention or a more simple and basic form of psychotherapy plus co-  
30 interventions.<sup>39</sup> If a trial comparing the effects of two active interventions shows no difference in  
31 effect it is not clear whether the two interventions are equally effective or equally ineffective – and  
32 if an experimental intervention seem superior compared with a control intervention then the effect  
33 size of the experimental intervention will be unclear because any beneficial or harmful effects of  
34 the control intervention might influence the trial results.<sup>39</sup> All interventions should be assessed  
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versus no intervention before being introduced into clinical practice.<sup>39</sup> Furthermore, the combination of specialised psychotherapy and co-interventions constitute a relatively comprehensive treatment, which might not always be accessible to psychiatric patients in clinical practice – this might limit the generalizability of our results.

### **Mentalization-based treatment**

We did not find any relevant treatment manual we could use for the mentalization-based treatment, and we therefore created our own manual (<http://ctu.dk/publications/supplementary-material.aspx>).<sup>29</sup> The therapists in the mentalization-based treatment group were educated and experienced in psychodynamic therapy and group therapy and had underwent basic training and education in mentalization-based treatment according to Bateman and Karterud.<sup>13-16</sup> Mentalization-based treatment was originally designed to treat borderline personality.<sup>10, 12</sup> Few participants were diagnosed with borderline personality disorder (**Table 1**), and it can be argued that mentalization-based treatment was not a relevant intervention for the depressed participants of this trial. However, mentalization-based treatment is now used to treat a number of different disorders other than borderline personality disorder, including depression.<sup>10, 12</sup> Furthermore, a study has shown that female inpatients with depression showed a significantly lower capacity for mentalization compared with healthy controls – and deficits in mentalizing capacity were related to illness duration, number of admissions, and cognitive impairment.<sup>17</sup> The authors conclude that the investigation of mentalization may be of particular importance for the development of targeted psychotherapeutic interventions for depression.<sup>17</sup>

### **Comorbid personality disorders**

A large proportion of the included participants were diagnosed with cluster C personality disorders (anxious or fearful personality disorders).<sup>23, 24</sup> It has been debated if a diagnosis of a personality

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disorder is accurate when patients are acutely depressed.<sup>19</sup> Our results indicate that comorbid personality disorder and depression does not lead to a poorer outcome compared to patients with depression alone – but this could be because the diagnoses of the personality disorders in our trial are inaccurate because the depressive symptoms might mimic pathological personality traits. Furthermore, the limited number of included participants significantly reduces the power of this analysis.

### **BDI compared to HDRS as outcome**

It is a common belief among clinicians that BDI is a more 'reactive' outcome than HDRS,<sup>50</sup> and it might be surprising to some why we identified a borderline significant effect on the HDRS results but no significant effect on the BDI. However, two systematic reviews with meta-analysis have included trials that simultaneously used HDRS and BDI to assess the effects of the same interventions.<sup>50, 51</sup> The results showed that BDI under such circumstances shows significantly less effect sizes compared to the HDRS.<sup>50, 51</sup> A greater percentage of participants would be considered improved if ratings of change were based on the HDRS rather than BDI.<sup>50</sup> The results from these two reviews<sup>50, 51</sup> are in agreement with our present results and may explain why we found a borderline significant effect on HDRS and no significant effect on BDI. On the other hand, it is also possible that HDRS compared to BDI overestimates participant improvement.<sup>51</sup>

It was impossible to blind the participants to treatment allocation. To ensure some degree of blinding we chose HDRS over BDI because it was possible to perform objective blinded outcome assessment using the HDRS. BDI is a self-administered questionnaire, which makes blinded objective outcome assessment impossible. We therefore expected the results on HDRS to be a more clinically valid compared to the BDI results – but we cannot exclude that breaking of blinding

and biased assessment of the HDRS may have occurred. In accordance with the CONSORT Statement we did not assess degree of unblinding.<sup>40</sup>

## Implications

First of all, if a larger more definitive trial has to be conducted then a more realistic estimate of the recruitment rate will be needed and more centres should be involved. On average, we recruited approximately one participant every third week and we expected to be able to recruit approximately one participant every week. Basically, not enough eligible participants were referred to the clinic during the inclusion period and we had to terminate the trial due to economical and practical constraints – this was the primary reason why we did not randomise more participants. Before the randomisation began, we did not systematically assess how many participants it was possible to recruit. This should also be done before a larger trial is conducted so the sample size can be reached. Moreover, we did not take any specific actions promoting the trial outside the clinic. If a future trial is to be conducted it should be considered to promote the trial through advertising or use of other measures to motivate potential referrers to refer more eligible participants. Besides the problems with recruiting enough participants, it was otherwise feasible to conduct a randomised clinical trial with low risk of bias assessing the effects of third wave cognitive therapy versus mentalization-based treatment for major depressive disorder.

The apparent difference in intervention effect found on the HDRS might be caused by random error ('play of chance'), unaccounted bias, or a signal of a real effect.<sup>49</sup> The National Institute for Clinical Excellence (NICE) have suggested a mean difference between two compared interventions of three HDRS points as a criterion for 'clinical significance'.<sup>52</sup> Most interventions for depression, both psychopharmacological as well as psychotherapeutic, rarely exceed having a beneficial effect of more than three HDRS points.<sup>1, 11, 53-55</sup> We used an anticipated intervention

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effect of five HDRS points to estimate the necessary sample size and this anticipated intervention effect was optimistic. Calculating Bayes factor based on the anticipated intervention effect, the observed intervention effect, and the standard error of the observed intervention effect shows a Bayes factor of 0.14, which is above the recommended threshold for significance of 0.1.<sup>34</sup> This underlines that our results should be regarded as insignificant and that an anticipated intervention effect lower than five HDRS points ought to be used in sample size calculations in future trials assessing the effects of third wave cognitive therapy and mentalization-based therapy. We found a mean difference of more than four HDRS points which, compared to other interventions, is relatively high. These results might be used to calculate a necessary sample size in a larger more definitive trial. However, HDRS might not at all be a clinically relevant outcome and other more clinically relevant outcomes might be more valid to use in future trials. Severity of depression as measured by the total HDRS score has failed to predict suicide attempts,<sup>56, 57</sup> and some publications have questioned the usefulness of the HDRS and concluded that the scale is psychometrically and conceptually flawed.<sup>57, 58</sup>

## Conclusions

Our preliminary results show that third wave cognitive therapy compared with mentalization-based treatment may be a more effective intervention for depressive symptoms measured on the HDRS. The effects of the two interventions did not seem to differ significantly regarding BDI II, SCL 90-R, and WHO 5. More randomised clinical trials are needed to assess the effects of third wave cognitive therapy and mentalization-based treatment.

## Contributors

JCJ and CG wrote the first draft. JCJ, CG, KAL, PS, US, and ES planned and designed the trial. JCJ and MK performed the reliability tests. KAL, PS, US, and ES contributed with psychiatric expertise. PW conducted the statistical analyses. TL contributed with statistical expertise. All authors contributed academically to the manuscript and have accepted the manuscript for publication.

## Competing conflicts of interests

We have received external funding for the trial from the Health Science Fund, Region Zealand, Denmark (governmental funding). The amount of funding was altogether 38,292 EUR (salary for co-workers, tuition fee for the university, costs for interviews, etc.). There were no commercial sponsors. The principal investigator was also a therapist in the third wave cognitive therapy treatment and has developed the treatment manual for the third wave cognitive therapy. The consultant performing the medical consultations during the trial period was not blinded to the treatment allocation of the participants and developed the mentalization-based treatment manual in close cooperation with the two mentalization-based therapists. Other authors have no competing interests.

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## **Data sharing**

No additional data available.

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## **Acknowledgments**

We would like to thank all the participants in the trial for patiently cooperating with the assessments. We would also like to thank Anita Jensen for helping with data management; Lotte Dragsted and Marianne Lyngby for performing the Hamilton interviews; Gitte Nielsen for assistance in developing the treatment manual for the third wave cognitive therapy; and Jane Lindschou for expert assistance with the randomisation. Lastly, we would like to thank all the co-workers at the psychiatric clinic in Roskilde. Without their patience and cooperation the trial would have been impossible to conduct.

## **Conflicts of interest**

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## **Contributors**



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### **Ethical considerations and regulatory approval**

There were no immediate ethical problems regarding this trial. Research has not identified any significant adverse effects or risks from either of the compared interventions. Before randomization began approval was obtained by the Regional Ethics Committee of Zealand (no: SJ-43) and the trial was registered at the Danish Data Protection Agency (no: 2008-58-0020).

All participants were informed of the trial in writing and verbally before randomization. Written informed consent was obtained from every participant before inclusion. All trial participants were, on request, permitted access to further information about the project. No expense allowance was offered to the trial participants

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## Tables

### Table 1. Baseline characteristics

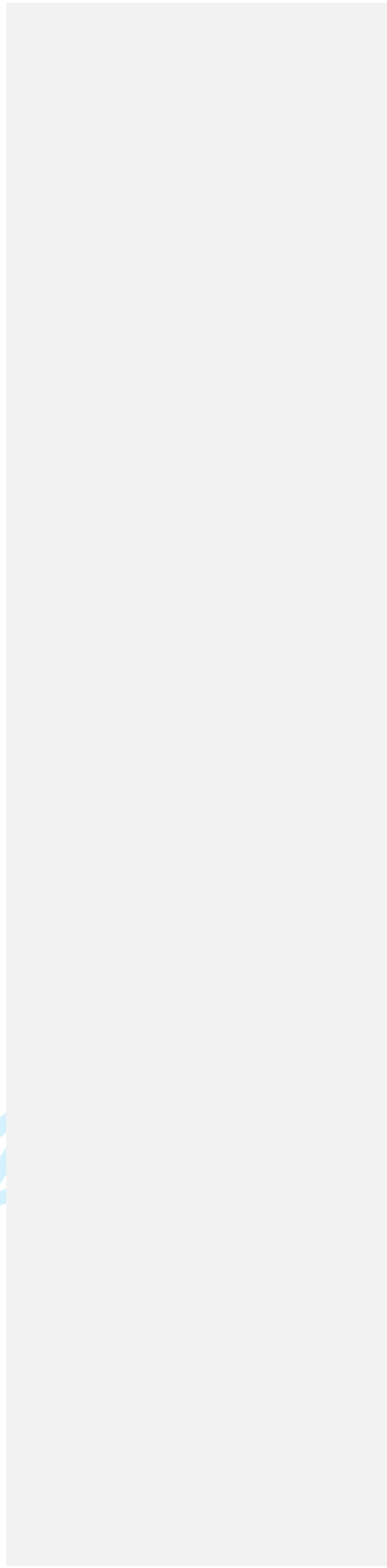
		Participants randomised to third wave cognitive therapy (n=22)	Participants randomised to mentalization-based therapy (n=22)
<b>Age</b>	mean (SD)	38.5 (8.9)	40.3 (6.8)
<b>Sex</b>	female n (%)	18 (82)	20 (91)
<b>Number of children</b>	mean (SD)	1.4 (1.2)	1.7 (1.1)
<b>Marital status</b>	n (%)		
Single		3 (14)	7 (32)
In a relationship		6 (27)	5 (23)
Married		12 (55)	8 (36)
Separated/divorced		1 (5)	2 (9)
<b>Level of education</b>	n (%)		
Only high school diploma		7 (32)	3 (14)
Medium long education		14 (64)	19 (86)
Long education		1 (5)	0 (0)
<b>Baseline HDRS** scores</b>			
mean (SD)		22.1 (5.9)	22.5 (4.9)
median		22.5	23.6
range		7-30	11-29
<b>Baseline GSI scores (SCL 90-R)***</b>			
mean (SD)		1.80 (0.59)	1.84 (0.41)
median		1.72	1.74
range		0.68-2.79	0.99-2.54
<b>Personality disorders</b>	n (%)		
No personality disorder		5 (23)	6 (27)
One personality disorder		11 (50)	12 (55)
Two personality disorders		4 (18)	3 (14)
Three or more personality disorders		2 (9)	1 (5)
<b>Personality disorders diagnoses</b>	n (%)		
Paranoid		1 (5)	0 (0)
Borderline		4 (18)	1 (5)
Avoidant		7 (32)	5 (23)
Obsessive-compulsive		4 (18)	3 (14)
Dependant		1 (5)	0 (0)
Depressive		7 (32)	8 (36)
Personality disorder NOS		1 (5)	4 (18)

\*SD=Standard Deviation; \*\*HDRS=17-item Hamilton Depression rating Scale; \*\*\*SCL-90-R=Global Severity Index score on the Symptom Checklist 90 Revised

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**Table 2. Effects of third wave cognitive therapy versus mentalisation-based treatment**

Outcome measure	Group randomised to third wave cognitive therapy (N=22)		Group randomised to mentalization-based treatment (N=22)		P-value of unadjusted analysis at end of treatment	P-value of adjusted analysis* at end of treatment
	Baseline	End of treatment	Baseline	End of treatment		
<b>HDRS</b>						
N	22	22	21	20	0.051	0.039
Mean	22.1	12.9	22.5	17.0		
95%CI	19.5-24.8	9.81-15.9	20.3-24.8	14.0-20.0		
<b>Remission (HDRS&lt;8)</b>					0.049	Not possible to calculate
N/ total	0/22	5/22	0/21	0/20		
<b>BDI II</b>					0.46	0.46
N	21	21	22	17		
Mean	36.8	17.6	36.3	20.5		
95%CI	32.5-41.1	12.2-23.0	32.1-40.6	14.5-26.4		
<b>SCL 90-R (GSI score)</b>					0.52	0.66
N	22	22	22	20		
Mean	1.80	0.88	1.84	1.00		
95%CI	1.54-2.05	0.62-1.15	1.66-2.02	0.74-1.25		
<b>WHO 5</b>					0.54	0.46
N	22	22	21	20		
Mean	3.55	10.5	4.33	9.45		
95%CI	1.84-5.25	7.66-13.4	3.13-5.53	7.18-11.7		

\*= Adjusted for baseline values of each outcome

Abbreviations: HDRS=Hamilton Depression Rating Scale (17-item); N=Number of participants; CI=Confidence interval; BDI=Beck's Depression Inventory; SCL 90-R=Symptom Checklist 90 Revised; GSI=Global Severity Index score; WHO 5=World Health Organisation-Five Well-being Index 1999, a high score associates to a high level of well-being.



## Figure Legends

### Figure 1 (CONSORT flowchart)

### Figure 2

Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks. 42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.<sup>35-38</sup> These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

### Figure 3

Post-hoc sequential analysis of the results on Beck's depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.<sup>35-38</sup> The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data

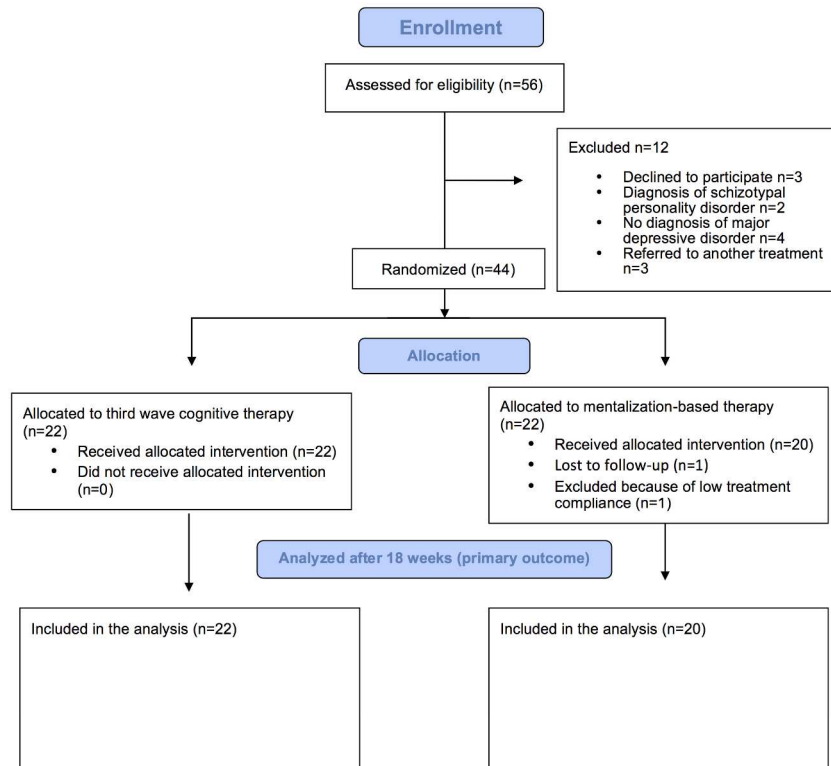
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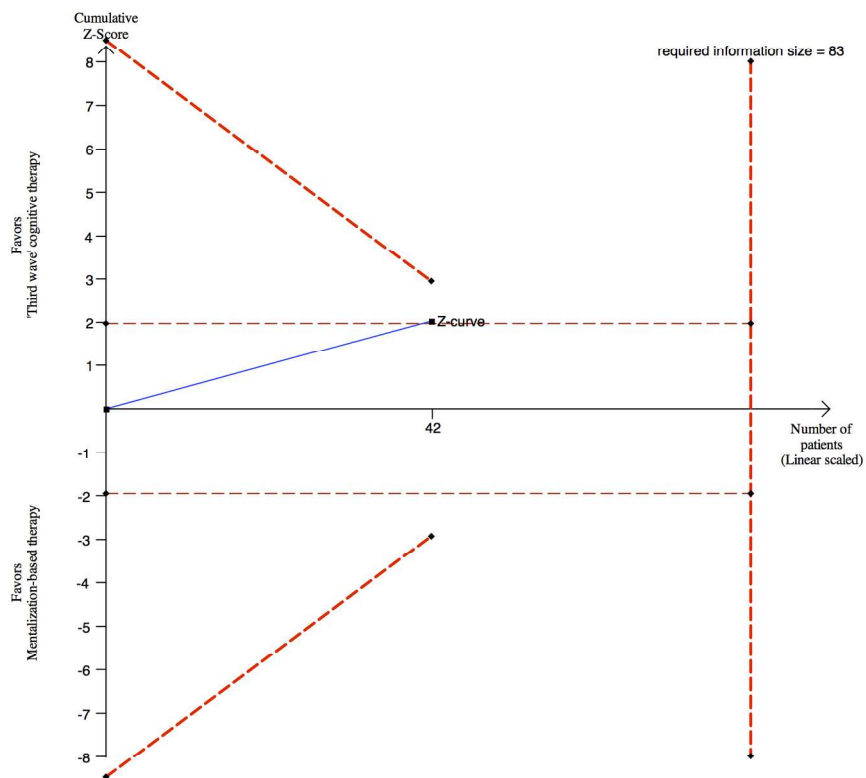
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CONSORT 2010 Flow Diagram



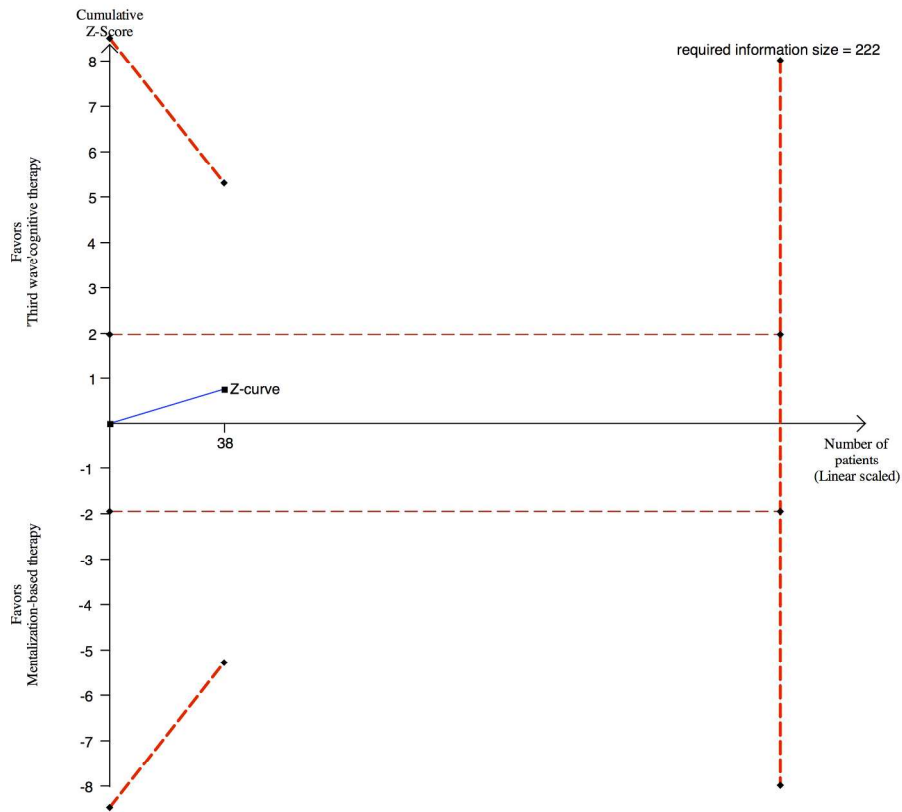
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Post-hoc sequential analysis of the results on the Hamilton depression rating scale (HDRS) after 18 weeks. 42 participants out of the 44 participants were assessed with HDRS after end of treatment. The required information size of 83 participants is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49.40-43. These assumptions are similar to the assumptions used in prospectively planned sample size calculation of 84 participants. The cumulated Z-curve (blue curve) does not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of a beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

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Post-hoc sequential analysis of the results on Beck's depression inventory II (BDI II) after 18 weeks. 38 out of the 44 participants were assessed with BDI II after end of treatment. The required information size of 222 participants is calculated based on minimal relevant mean difference of 5 BDI II points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI II points.<sup>40-43</sup> The cumulated Z-curve (blue curve) do not cross the sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error due to sparse data in the estimate of no beneficial effect of third wave cognitive therapy compared with mentalization-based therapy.

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## Supplementary material 1. Psychopharmacological medication

	Participants randomised to third wave cognitive therapy		Participants randomised to mentalization-based treatment	
	At baseline (N=22)	At end of treatment (N=22)	At baseline (N=22)	At end of treatment (N=20)
No medication	3 (13%)	5 (23%)	2 (9%)	2 (10%)
SSRI*	9 (40%)	9 (41%)	13 (59%)	7 (35%)
Dual-action antidepressants**	11 (50%)	6 (27%)	4 (18%)	6 (30%)
Other antidepressants***	1 (5%)	0 (0%)	2 (9%)	2 (10%)
Pregabalin (150mg/ day)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Mood stabilizers****	2 (9%)	1 (5%)	1 (5%)	1 (5%)
Benzodiazepines*****	3 (14%)	2 (9%)	7 (32%)	5 (25%)
Antipsychotics*****	5 (23%)	4 (18%)	5 (23%)	2 (10%)
Medication for attention-deficit hyperactivity disorder*****	2 (9%)	1 (5%)	0 (0%)	0 (0%)
Disulfiram (200mg/ day)	1 (5%)	0 (0%)	1 (5%)	1 (5%)

\*SSRI (selective serotonin reuptake inhibitors): fluoxetine 20mg - 60mg/ day; sertraline 100mg-200mg/ day; citalopram 20mg-40mg/ day; escitalopram 10mg-20mg.

\*\*duloxetine (60mg-90mg/ day); venlafaxine 75mg-225mg/ day; mirtazapine 15mg-45mg/ day

\*\*\*agomelatine (50mg/ day); amitriptyline (100mg/ day).

\*\*\*\*lamotrigine (25mg-100mg/ day); valproate (600mg/ day).

\*\*\*\*\*oxazepam 15mg-45mg/ day; bromazepam 4.5mg/ day; zolpidem 5mg/ day; oxazepam 15mg/ by demand; alprazolam 0.5mg/ by demand; diazepam 5mg/ by demand; zopiclone 7.5mg/ by demand.

\*\*\*\*\*quetiapine 25-100mg/day; olanzapine 2.5mg-5mg/day; chlordiazepoxid 15-25mg/ by demand.

\*\*\*\*\*methylphenidate 36mg/ day; atomoxetine 80mg/ day.

## CONSORT CHECKLIST

**Table.** CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial<sup>a</sup>

Section and Topic	Item No.	Checklist Item	Reported on Page No.
<b>Title and abstract</b>	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
<b>Introduction</b> Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
<b>Methods</b> Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	7
Participants	4a	Eligibility criteria for participants	6-7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-10
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	10-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomization; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	13
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	13
<b>Results</b> Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	see cor 14
	13b	For each group, losses and exclusions after randomization, together with reasons	14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	17-18
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	see Tab
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Se Tabl
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	See Tal Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	26
<b>Comment</b> Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	17-20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17-20
<b>Other information</b> Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	22

<sup>a</sup>We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see <http://www.consort-statement.org>.