Systematic reviews of randomised clinical trials examining the effects of psychotherapeutic interventions versus 'no intervention' for acute major depressive disorder and a randomised trial examining the effects of 'third wave' cognitive therapy versus mentalization-based treatment for acute major depressive disorder

PhD Thesis

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“I know one thing, that I know nothing” (Latin: scio me nihil scire or scio me nescire)

— Derived from Plato’s account of Socrates (424-347 BC)

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Preface and acknowledgements

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Overview of papers

This PhD thesis is based on the following four papers:

Paper 1. Jakobsen JC, Lindschou Hansen J, Simonsen E, Gluud C: The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review with meta-analyses and trial sequential analyses. *Journal of Affective Disorders.* Mar;137(1-3):4-14. Epub 2011 Apr 17 2011

Paper 2. Jakobsen JC, Lindschou Hansen J, Storebø OJ, Simonsen E, Gluud C: The effects of cognitive therapy versus 'no intervention' in patients with major depressive disorder. *PLoS ONE.* 2011;6(12):e28299. Epub 2011 Dec 9

Paper 3. Jakobsen JC, Gluud C, Kongerslev M, Larsen KA, Sørensen P, Winkel P, Lange T, Søgaard U, Simonsen E: 'Third wave' cognitive therapy versus mentalisation-based therapy for major depressive disorder. A protocol for a randomised clinical trial. *BMC Psychiatry 2012; DOI* 10.1186/1471-244X-12-232

Paper 4. Jakobsen JC, Gluud C, Kongerslev M, Larsen KA, Sørensen P, Winkel P, Lange T, Søgaard U, Simonsen E: 'Third wave' cognitive therapy versus mentalization-based treatment for major depressive disorder. A randomized clinical trial. S*ubmitted to Journal of Affective Disorders February 2013*

Abstract

Background

Major depressive disorder afflicts an estimated 17% of individuals during their lifetimes at tremendous suffering and costs. Cognitive therapy and psychodynamic therapy may be effective treatment options for major depressive disorder, but the effects have only had limited assessment in systematic reviews. The two modern forms of psychotherapy, 'third wave' cognitive therapy and mentalization-based treatment, have both gained some ground as treatments of psychiatric disorders. No randomised trial has compared the effects of these two interventions for major depressive disorder.

Methods

We performed two systematic reviews with meta-analyses and trial sequential analyses using The Cochrane Collaboration methodology examining the effects of cognitive therapy and psychodynamic therapy for major depressive disorder. We developed a thorough treatment protocol for a randomised trial with low risks of bias (systematic error) and low risks of random errors ('play of chance') examining the effects of third wave' cognitive therapy versus mentalization-based treatment for major depressive disorder. We conducted a randomised trial according to good clinical practice examining the effects of 'third wave' cognitive therapy versus mentalisation-based treatment for major depressive disorder.

Results

The first systematic review included five randomised trials examining the effects of psychodynamic therapy versus 'no intervention' for major depressive disorder. Altogether the five trials randomised 365 participants who in each trial received similar antidepressants as co-interventions. All trials had high risk of bias. Four trials assessed 'interpersonal psychotherapy' and one trial 'short psychodynamic supportive psychotherapy'. Both of these interventions are different forms of psychodynamic therapy. Meta-analysis showed that psychodynamic therapy significantly reduced depressive symptoms on the Hamilton Depression Rating Scale (HDRS) compared with 'no intervention' (mean difference −3.01 (95% confidence

interval −3.98 to −2.03; P=0.00001), no significant heterogeneity between trials). Trial sequential analysis confirmed this result.

The second systematic review included 12 randomised trials examining the effects of cognitive therapy versus 'no intervention' for major depressive disorder. Altogether a total of 669 participants were randomised. All trials had high risk of bias. Meta-analysis showed that cognitive therapy significantly reduced depressive symptoms on the HDRS compared with 'no intervention' (four trials; mean difference -3.05 (95% confidence interval, -5.23 to -0.87; P=0.006)). Trial sequential analysis could not confirm this result.

The trial protocol showed that it seemed feasible to conduct a randomised trial with low risks of bias and low risks of random errors examining the effects of 'third wave' cognitive therapy versus mentalization-based therapy in a setting in the Danish healthcare system.

It turned out to be much more difficult to recruit participants in the randomised trial than expected. We only included about half of the planned participants. The results from the randomised trial showed that participants randomised to 'third wave' therapy compared with participants randomised to mentalization-based treatment had borderline significantly lower HDRS scores at 18 weeks in an unadjusted analysis (mean difference -4.14 score; 95% CI -8.30 to 0.03; P=0.051). In the adjusted analysis, the difference was significant (P=0.039). Five (22.7%) of the participants randomised to 'third wave' cognitive therapy had remission at 18 weeks versus none of the participants randomised to mentalization-based treatment (P=0.049). Sequential analysis showed that these findings could be due to random errors. No significant differences between the two groups was found regarding Beck's Depression Inventory (BDI II), Symptom Checklist 90 Revised (SCL 90-R), and The World Health Organization-Five Well-being Index 1999 (WHO 5).

Conclusions

Cognitive therapy and psychodynamic therapy might be effective interventions for depression measured on HDRS and BDI, but the review results might be erroneous

due to risks of bias and random errors. Furthermore, the effects seem relatively small.

The trial protocol showed that it was possible to develop a protocol for a randomised trial examining the effects of ‘third wave’ cognitive therapy versus mentalization-based treatment with low risks of bias and low risks of random errors.

Our trial results showed that ‘third wave’ cognitive therapy might be a more effective intervention for depressive symptoms measured on the HDRS compared with mentalization-based treatment. The two interventions did not seem to differ significantly regarding BDI II, SCL 90-R, and WHO 5.

More randomised trials with low risks of bias and low risks of random errors are needed to assess the effects of cognitive therapy, psychodynamic therapy, ‘third wave’ cognitive therapy, and mentalization-based treatment.

Dansk resume

Baggrund

Depression rammer omkring 17% af befolkningen med enorme menneskelige og økonomiske konsekvenser. Kognitiv terapi og psykodynamisk terapi er muligvis effektive behandlingsmuligheder, men disse to psykoterapeutiske behandlinger har ikke tidligere været systematisk undersøgt. De to moderne former af kognitiv terapi og psykodynamisk terapi, henholdsvis 'tredje bølge' kognitiv terapi og mentaliserings-baseret terapi, har ikke tidligere været sammenlignet i randomiserede forsøg.

Metoder

Vi undersøgte effekten af kognitiv terapi og psykodynamisk terapi i to systematiske reviews udført efter Cochrane samarbejdets rekommandationer inklusiv meta-analyse og 'trial sequential analyses'. Vi udarbejdede en udførlig forsøgsprotokol for et randomiseret forsøg med lav risiko for systematiske fejl (hildethed) og lav risiko for tilfældige fejl (tilfældighedernes spil) for at sammenligne effekten af 'tredje bølge' kognitiv terapi og mentaliserings-baseret terapi til behandling af depression. Vi gennemførte et randomiseret forsøg med lav risiko for bias.

Resultater

Vores første systematiske review inkluderede fem randomiserede forsøg som undersøgte effekten af psykodynamisk terapi versus 'ingen behandling' til behandling af depression. Alle fem forsøg brugte hver især sammenlignelig medicinsk antidepressiv behandling i begge behandlingsarme. I alt blev 365 forsøgsdeltagere randomiseret. Alle fem forsøg havde høj risiko for bias. Fire forsøg undersøgte effekten af interpersonal psykoterapi og ét undersøgte effekten af 'short psychodynamic supportive psychotherapy'. Begge disse terapiretninger er forskellige former af psykodynamisk terapi. Meta-analyse af resultaterne fra Hamilton's depressions skala viste at psykodynamisk terapi signifikant reducerede graden af depressive symptomer (gennemsnitlig forskel på Hamilton's depressions skala −3.01

(95% konfidensinterval −3.98 til −2.03; P=0.00001). Sekventiel analyse af forsøgsresultaterne bekræftede meta-analyseresultatet.

Vores andet systematiske review inkluderede 12 randomiserede forsøg som undersøgte effekten af kognitiv terapi versus 'ingen behandling' til behandling af depression. I alt blev 669 forsøgsdeltagere randomiseret. Alle 12 forsøg havde høj risiko for bias. Meta-analyse af resultaterne fra Hamilton's depressions skala viste at kognitiv terapi signifikant reducerede graden af depressive symptomer (gennemsnitlig forskel på Hamilton's depressions skala -3.05 (95% konfidensinterval, -5.23 til -0.87; P=0.006). Sekventiel analyse af forsøgsresultaterne kunne dog ikke bekræfte meta-analyse resultatet.

Vores forsøgsprotokol viste at det var muligt at udarbejde en protokol for et randomiseret forsøg med lav risiko for bias og lav risiko for tilfældige fejl som sammenligner effekten af 'tredje bølge' kognitiv terapi og mentaliserings-baseret terapi til behandling af depression.

Det viste sig at være svært at få rekrutteret nok forsøgsdeltagere til det randomiserede forsøg. Det lykkedes kun at få inkluderet omkring halvdelen af det planlagte antal. Det randomiserede forsøg viste at forsøgsdeltagere randomiseret til 'tredje bølge' kognitiv terapy havde borderline signifikant lavere score (ujusteret analyse) på Hamilton's depressions skala sammenlignet med forsøgsdeltagere randomiseret til mentaliserings-baseert terapi (gennemsnitlig difference -4.14 Hamilton points; 95% CI -8.30 - 0.03; P=0.051). I den justerede analyse var forskellen signifikant (P=0.039). Fem (22,7%) af forsøgsdeltagerne som var randomiseret til 'tredje bølge' kognitiv terapy var i remission ved 18 uger versus ingen af forsøgsdeltagerne som var randomiseret til mentaliserings-baseret terapi (P=0.049). Sekventiel analyser viste at disse resultater kan være fremkommet ved tilfældige fejl. Der var ingen signifikant forskel mellem de to grupper målt på Beck's Depression Inventory (BDI II), Symptom Checklist 90 Revised (SCL 90-R) og The World Health Organization-Five Well-being Index 1999 (WHO 5).

Konklusioner

Kognitiv terapi og psykodynamisk terapi er muligvis effektive interventioner af depressive symptomer målt på Hamilton's depressions skala. Der er dog risiko for at resultaterne er forkerte grundet risiko for bias og tilfældige fejl. Derudover ser effekterne ud til at være relativt små.

Protokollen viste at det var muligt at udarbejde en protokol for et randomiseret forsøg med lav risiko for bias og lav risiko for tilfældige fejl som sammenligner effekten af 'tredje bølge' kognitiv terapi versus mentaliserings-baseret terapi til behandling af depression.

'Tredje bølge' kognitiv terapi er muligvis en mere effektiv behandling af depressive symptomer målt på Hamilton's depressions skala sammenlignet med mentaliserings-baseret terapi. Effekten af de to interventioner ser ikke ud til at være signifikant forskelig målt på BDI II, SCL 90-R og WHO 5.

Der er brug for flere randomiserede forsøg med lav risiko for bias og lav risiko for tilfældige fejl som undersøger effekten af kognitiv terapi, psykodynamisk terapi, 'tredje bølge' kognitiv terapi og mentaliserings-baseret terapi.

Introduction

Depression

According to the WHO, major depressive disorder is the second largest healthcare problem worldwide in terms of disability caused by illness.[1] It afflicts an estimated 17% of individuals during their lifetimes at tremendous cost to the individual and society.[2,3] Roughly a third of all depressive disorders take a chronic course.[4,5] Approximately 15% of depressive patients will commit suicide over a 10 to 20 year period.[6]

Interventions for depression

Antidepressants

Antidepressant medication remains the mainstay in the treatment of depression.[7] However, meta-analyses have shown that the new antidepressants only obtained beneficial effect in severely depressed patients, and that this effect seems to be clinically small.[8,9] The benefits of antidepressant medication seem to be limited and this raises the question if there are other effective treatments for this serious illness?

Psychodynamic therapy

Psychodynamic therapies origin back to Freud.[10] In some health-care systems it is currently the most commonly used form of psychotherapy.[11] The primary focus of psychodynamic therapy is to reveal the unconscious content of a patient's psyche to alleviate psychic tension.[10] Interpersonal psychotherapy originates from classical psychodynamic therapy,[12] and although interpersonal psychotherapy has integrated elements from other psychotherapies it is generally regarded as a contemporary form of psychodynamic therapy.[12,13] Interpersonal psychotherapy is generally considered as one of the most evidence-based therapies for depression.[11] Our systematic review showed that there were no convincing evidence supporting or refuting the effect of interpersonal psychotherapy or psychodynamic therapy compared with 'treatment as usual' for patients with major depressive disorder.[14] The

potential beneficial effect seemed small and effects on major outcomes were unknown.[14] We concluded that randomised trials examining the effects of interpersonal psychotherapy or psychodynamic therapy were needed.[14] We were not able to identify any former relevant meta-analysis examining the effects of psychodynamic therapies versus 'no intervention' for major depressive disorder.

Cognitive therapy

Behaviour therapy has its roots in the 1950s and has a focus on classical conditioning and operant learning.[15] Behaviour therapy has been called 'first wave' cognitive therapy.[15] 'Second wave' (classical) cognitive therapy is at present the dominant contemporary form of psychotherapy and is focused on information processing.[15] Aaron T. Beck originally developed 'second wave' cognitive therapy for depression.[16] Beck believed that critical life events could accentuate hidden negative beliefs, which could generate negative automatic thoughts. These negative thoughts could lead to symptoms of depression, which then could reinforce more negative automatic thoughts. The main goal of the cognitive model of depression is to correct these negative beliefs and thoughts, in order to treat the depressive symptoms.[16] A recently published systematic review showed that cognitive therapy might not be an effective treatment for major depressive disorder compared with 'treatment as usual' (different forms of non-specific supportive interventions).[17] Another systematic review showed that cognitive therapy had a preventive effect against recurrent depression, and that this effect surpassed the preventive effects of antidepressant medication.[18] Cognitive therapy versus 'no intervention' appears to be an effective treatment for major depressive disorder.[19] We have been unable to find any relevant systematic reviews using Cochrane methodology examining the effects of cognitive therapy versus 'no intervention' for major depressive disorder.

Modern forms of psychotherapy

'Third wave' cognitive therapy

It has been questioned whether the described focus of the original cognitive model of depression to correct negative beliefs and thoughts, is an effective treatment

element.[20,21] Modern forms of cognitive therapy have therefore been developed. These techniques are often classified as 'third wave' cognitive therapies, including dialectical behaviour therapy (DBT), acceptance and commitment therapy (ACT), schema therapy, mindfulness-based cognitive therapy (MBCT), and meta-cognitive therapy (MCT).[22] These therapies have drawn great attention throughout the world, and especially mindfulness has been implemented in numerous different contexts in recent years.[23-25] One systematic review has found that 'third wave' cognitive therapy might prevent relapse of depression,[26] and small trials indicate that 'third wave' cognitive therapy versus 'no intervention' or 'treatment as usual' is effective for acutely depressed patients.[27,28] 'Third wave' cognitive therapy might also be an effective intervention for other psychiatric disorders such as, e.g., borderline personality disorder and psychological distress.[24,29,30] 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.[31] Even though evidence is lacking, it seems theoretically possible that the treatment elements of 'third wave' cognitive therapy might be more effective than classic cognitive therapy for major depressive disorder.[32] We have chosen 'third wave' cognitive therapy as our experimental intervention in the randomised trial because it seemed practically feasible for us to conduct a trial with this intervention.

Mentalization-based therapy

Mentalization-based therapy is a psychodynamic treatment rooted in attachment and personality theory.[33] It aims to strengthen the patients' capacity to understand their own and others' mental states in attachment contexts in order to address their difficulties with affect, impulse regulation, and interpersonal functioning.[33,34] Mentalization-based therapy was originally developed to treat borderline personality disorder[35] but is now used to treat a variety of different psychiatric disorders such as other types of personality disorders, depression, eating disorders, and substance abuse.[33,34] Mentalization-based treatment is based on the principles from mentalization-based therapy but is less strictly defined.

The effects of mentalization-based therapy versus 'treatment as usual' or 'no intervention' for major depressive disorder have not been examined in randomised trials.[14,36] We have chosen mentalization-based treatment as our control intervention in the randomised trial because it seemed practically feasible for us to conduct a trial with this intervention.

'Third wave' cognitive therapy versus mentalization-based treatment

No former randomised clinical trials or systematic reviews have been conducted examining the effects of 'third wave' cognitive therapy versus mentalization-based treatment or therapy.[37]

Objectives of this thesis

- The first objective (**Paper 1 and 2**)[36,38-40] was to conduct two systematic reviews assessing the effects of psychodynamic therapy and cognitive therapy for major depressive disorder.
- The second objective (**Paper 3**)[41] was to develop a thorough protocol for a randomised trial with low risks of systematic errors ('bias') and low risks of random errors ('play of chance') examining the effects of 'third wave' cognitive therapy versus mentalisation-based treatment for major depressive disorder.
- The third objective (**Paper 4**)[42] was to conduct a randomised trial examining the effects of 'third wave' cognitive therapy versus mentalisation-based treatment for major depressive disorder.

Paper 1

The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of randomized clinical trials with meta-analyses and trial sequential analyses

We conducted a systematic review of randomised clinical trials involving meta-analysis[43] and trial sequential analysis[44,45] to answer the question: what are the beneficial and harmful effects of psychodynamic therapy versus 'no intervention' in the treatment of major depressive disorder (**Paper 1**)?[36,40]

Methods

For details regarding the methodology please consult the review protocol published on www.ctu.dk before we began the systematic literature search, and the full publication included at the end of this thesis (**Paper 1**).[36,46] In short, we included all randomised clinical trials comparing the effect of psychodynamic therapy versus 'no intervention' with or without co-interventions.

To be included participants had to be older than 17 years, and the primary diagnosis had to be major depressive disorder.

Results

Our primary literature search identified 3212 publications. Altogether we identified and included 12 publications[47-58] on five trials.[47,48,50,51,58]

The five trials included a total of 365 participants. The experimental interventions were termed 'interpersonal psychotherapy' in four trials[47,48,51,58] and 'short psychodynamic supportive psychotherapy' in one trial.[50]

Only one of the trials used an experimental intervention that we classified as 'adequately defined'.[48] We classified the therapists' level of experience and education in three of the trials as 'intermediate'[47,48,50] and in the remaining two as 'unclear'.[51,58] Four trials used individual therapy,[47,48,50,51] and one trial used group therapy.[58]

The duration of the experimental intervention varied in the five trials from 12 weeks[48,58] to 24 weeks[47] of treatment.

All five trials used the experimental intervention psychodynamic therapy as add on therapy to antidepressants, and all trials used antidepressants in both the experimental and the control groups. The antidepressant medication was not adequately described in one trial.[58] The antidepressant medicine was described and delivered similarly to the compared intervention groups in four of the trials.[47,48,50,51] The antidepressants were: flouxetine (SSRI);[47] nefazodone hydrochloride (5H2 receptor antagonist);[48] amitriptyline (TCA);[51] and fluoxetine, amitriptyline (TCA), and moclobemide (monoamine-oxydase inhibitor).[50] No other co-interventions were documented.

Bias risk

We assessed all five trials as having 'high risk of bias' due to unclear or inadequate bias risk components. The bias risk assessment was conducted according to the instructions in The Cochrane Handbook for Systematic Reviews of Interventions.[43]

Effects of psychodynamic therapy

Primary outcome measures

Four trials[47,48,50,58] assessed the 17-item HDRS as a continuous outcome measure at the end of treatment. One trial[48] also assessed MADRS.

Meta-analysis with fixed-effect model on the HDRS data from the four trials[47,48,50,58] showed that psychodynamic therapy plus antidepressants significantly reduced depressive symptoms at the end of treatment compared with antidepressants alone. We found a mean difference on -3.01 HDRS (95% CI -3.98 to -2.03; P<0.00001, I^2 =

0) (**Figure 1** in **Paper 1**).[36] Meta-analysis with random-effects model showed an identical result. None of the four trials included data after cessation of treatment.

We performed a 'test of interaction'[59] to analyse if the effect of psychodynamic therapy differed between the three trials using 'interpersonal psychotherapy'[47,48,58] and the one trial using the term 'short psychodynamic supportive psychotherapy'.[50] 'Test of interaction'[59] showed no significant difference (P=0.65) indicating that the effects of these two types of psychodynamic therapy do not seem to differ.

Trial sequential analysis also showed a significant beneficial effect of psychodynamic therapy plus antidepressants compared with antidepressants alone (**Figure 2** in **Paper 1**).[36]

One trial[51,60] included records on hospitalisations. One participant in the experimental group and two in the control group were hospitalised. None of the remaining trials reported on adverse events.

One trial[50] assessed Quality of Life Depression Scale (QLDS)[61] and found that the participants receiving psychodynamic therapy had significantly better scores than the control group. Another trial[47] assessed Satisfaction Profile (SAT-P) for quality of life.[62] The results showed a significant change on two (psychological functioning and social functioning) of the five factors in favour of psychodynamic therapy.

Secondary outcome measures

Three trials[47,48,50] reported the proportion of participants without remission as a dichotomous outcome measure. We had planned to define remission as a HDRS of less than 8, BDI less than 10, or MADRS less than 10. However, this was only possible for De Jonghe et al. 2001[50] (HDRS < 8), so we adopted post hoc slightly different definitions:

- Bellino et al. 2006:[47] a decreased HDRS score of 40% or more, final HDRS score < 9, and a score of 1 or 2 on the improvement item of the Clinical Global Impression Scale.[63]
- Blom et al. 2007:[48] a final HDRS score < 9.

Meta-analysis on the data from the three trials[47,48,50] shows that psychodynamic therapy significantly decreases the odds ratio of 'no remission' to 0.41 (95% CI 0.24 to 0.73; P=0.002, no heterogeneity).

Only one trial[51,60] included records of suicides and suicide attempts. There were no suicides or suicide attempts. None of the remaining included trials reported the number of patients with suicide inclination, suicide attempts, or suicides.

Subgroup analyses

In subgroup analyses of therapists' level of education and experience (intermediate compared to unclear) and of type of therapy (group compared to individual), we found no significant difference on 'test of interaction'[59] and we found no heterogeneity in our results. This indicates that these factors do not seem to influence the effect of psychodynamic therapy.

In our protocol we had planned further subgroup-analyses according to risk of bias and antidepressant medication.[46] However, as all trials were classified as 'high risk of bias' and all trials used antidepressants as co-intervention it was not possible to conduct these subgroup analyses.

Paper 2

The effects of cognitive therapy versus 'no intervention' for major depressive disorder

We conducted a systematic review of randomised clinical trials involving meta-analysis[43] and trial sequential analysis[44,45] to answer the question: what are the beneficial and harmful effects of cognitive therapy versus 'no intervention' in the treatment of major depressive disorder?[38,39]

Methods

We conducted our systematic review of randomised clinical trials involving meta-analysis and trial sequential analysis[44,45,64,65] to answer the question: what are the beneficial and harmful effects of cognitive therapy versus 'no intervention' in the treatment of major depressive disorder?

For details regarding the methodology please consult our protocol published on www.ctu.dk before we began the systematic literature search, and the full publication included at the end of this thesis (**Paper 2**).[39]

In short, we included all randomised clinical trials comparing the effects of cognitive therapy alone versus 'no intervention' alone or cognitive therapy in combination with any co-intervention versus 'no intervention' in combination with a similar co-intervention. These co-interventions had to be administered equally in both intervention groups. We did this because we wanted to quantify the effect of cognitive therapy versus 'no intervention'.

To be included, participants had to be older than 17 years with a primary diagnosis of major depressive disorder.

Results

Search results

Our primary literature search identified 4536 publications. According to our protocol[39] we excluded 4137 publications on the basis of the title or abstract, and further 339 citable units were excluded on the basis of the full publication. These exclusions were done either because the publications did not relate to cognitive therapy and depression, or because they were not randomised trials comparing cognitive therapy versus 'no intervention'. Further 41 publications were excluded because the trial participants or the interventions did not meet our inclusion criteria.

Included trials

We identified and included 19 publications[66-84] on 12 trials[66-69,72-77,79,81] randomising a total of 669 participants.

Only six of the trials[66-69,73,76] used an intervention that we classified as 'adequately defined' (see above). We classified the therapists' level of experience and/or education in two trials as 'high',[75,81] in two trials as 'intermediate',[72,76] in one trials as 'low' [66], and in the last seven as 'unclear'.[67-69,73,74,77,79] Three trials used cognitive group therapy,[66,68,77] one trial used a combination of group and individual therapy,[79] the remaining eight trials used only individual therapy.[67,69,72-76,81]

The duration and the extent of the therapy varied in the different trials from six weekly 30 minute sessions of treatment[73] to 24 weeks of treatment (five times a week during the inpatient stay and weekly during the outpatient phase).[81]

Eight trials used the experimental intervention cognitive therapy as add on therapy to antidepressant medicine.[72-77,79,81] All of the eight trials used different antidepressants. The antidepressant medicine was delivered similarly in the experimental and control groups in all of the trials.

Bias risk

We assessed all of the 12 included trials[66-69,72-77,79,81] as having 'high risk of bias'.[43]

Primary outcome measures

Depressive symptoms

Four trials assessed and reported the 17-item HDRS as a continuous outcome measure at the end of treatment.[72,73,75,76] Eight trials assessed and reported BDI.[66,72-76,79,81]

Meta-analysis with the fixed-effect model on the HDRS data from the four trials,[72,73,75,76] shows that cognitive therapy at the end of therapy significantly reduced depressive symptoms compared with 'no intervention'. We found a mean difference on -3.05 HDRS (95% CI -5.23 to -0.87; P<0.006, I^2=0) (**Figure 1** in **Paper 2**).[38] Meta-analysis with the random-effects model gave identical results.

Meta-analysis with the fixed-effect model on the BDI data from the eight trials [66,72-76,79,81] was in agreement with the results from HDRS (mean difference on -4.86 BDI (95% CI -6.44 to -3.28; P=0.00001, I^2=0)). Meta-analysis with the random-effects gave identical results.

Trial sequential analysis on the HDRS data showed that 'insufficient data' have been obtained to decide if cognitive therapy is superior compared with 'no intervention' (**Figure 3** in **Paper 2**).[38] Trial sequential analysis on the BDI data showed a significant beneficial effect of cognitive therapy compared with 'no intervention' (**Figure 4** in **Paper 2**).[38]

Only two of the trials included assessment data after the cessation of treatment on the HRDS.[72,73] Murphy et al. (1984) assessed the participants at one month after cessation of treatment and Scott et al. (1997) at one year after cessation of treatment.[72,73] Meta-analysis with fixed-effect model on these data showed a mean difference on -0.32 HDRS points (95% CI -0.85 to -0.22; P=0.25, I^2=57%) and -3.68 BDI points (95% CI -8.11 to -0.75; P=0.10, I^2=0) in favour of cognitive therapy. Meta-analysis with random-effects gave an identical result.

Adverse events

Two trials reported adverse events.[66,76] Hollon et al. (1992) reported five serious adverse events in the control group (two participants hospitalised due to symptomatic worsening and three experiencing severe adverse reactions to

concomitant medications).[76] Wong et al. (2008) reported one hospitalisation in the control group.[66] None of the remaining trials reported on adverse events.

Quality of life

None of the included trials assessed the quality of life of the participants.

Secondary outcome measures

Participants without remission

Three trials reported the proportion of participants without remission as a dichotomous outcome measure.[72,76,81] We had planned to define remission as a Hamilton score of less than 8, BDI less than 10, or MADRS less than 10. However, this was not possible, so we post hoc adopted the slightly different definitions of the individual trials. All three trials defined remission as HRDS less than 7,[72,76,81] while one trial also defined remission as a Hamilton score of less than 8.[72] All three trials also defined remission as BDI less than 10.[72,76,81]

Meta-analysis on the HDRS data from the three trials[72,76,81] showed that cognitive therapy compared with 'no intervention' significantly decreases the risk of 'no remission' with an odds ratio of 0.42 (95% CI, 0.21 to 0.85; P=0.02, I^2=0). Trial sequential analysis on these data shows that we cannot exclude risk of random errors due to sparse data and repetitive testing as the cause for the meta-analysis result.

The meta-analysis on the BDI-data from the three trials[72,76,81] showed that cognitive therapy compared with 'no intervention' did not significantly decrease the risk of 'no remission' with an odds ratio of 0.54 (95% CI, 0.27 to 1.09; P=0.08, I^2=0).

Participants with suicidal inclination

Teasdale et al. (1984) reported numbers of patients that deliberate self-poisoned.[67] No patient in the cognitive therapy group self-poisoned. Two of the patients in the control group were treated for deliberate self-poisoning.

Miller et al. (1989) trial used the Modified Scale for Suicidal Ideation.[81] They found no significant difference in suicidal ideation between the different intervention groups, and recorded no suicide attempts or suicides during the trial period.

Hollon et al. (1992) reported three suicide attempts,[76] one participant randomised to cognitive therapy and two participants randomised to the control intervention. One from each group died from their attempt.

Wong et al. (2008) reported no suicide attempts in the cognitive therapy group and two suicide attempts in the control group during the intervention period.[66] Neither of these participants died from their attempt.

None of the remaining trials included records of suicide inclination, suicide attempts, or suicides.

Subgroup analyses

According to our protocol[39] we had planned a number of subgroup analyses, but we mostly found no heterogeneity in our results. Therefore, we did not conduct subgroup analyses of therapists' level of education and experience (high versus intermediate versus low versus unclear), type of therapy (group versus individual), and use of antidepressants as co-intervention (antidepressant co-intervention versus no antidepressant co-intervention). Our findings indicate that these factors do not seem to influence the effect of cognitive therapy.

We had also planned a subgroup-analysis according to risk of bias.[39] However, as all trials were classified as 'high risk of bias' it was not possible to conduct this analysis.

Paper 3 & 4

'Third wave' cognitive therapy versus mentalization-based therapy for acute major depressive disorder. A protocol for a randomised clinical trial

&

'Third wave' cognitive therapy versus mentalization-based treatment for acute major depressive disorder. A randomised clinical trial

We developed a protocol for a randomised trial with low risks of bias and low risks of random errors,[41] and we conducted a randomised trial examining the effects of 'third wave' cognitive therapy versus mentalization-based treatment for major depressive disorder.[42] After the trial was finished it became clear that the term mentalization-based *treatment* compared to mentalization-based *therapy* more accurately described the mentalization-based intervention, which was assessed in the trial. The term mentalization-based *treatment* is therefore used throughout this thesis.

Methods

For details regarding the methodology please consult our protocol[41] and the full publication included at the end of this thesis.[42]

In short, the trial was conducted at a public psychiatric outpatient clinic only treating patients on sick leave due to psychiatric illnesses.

Inclusion criteria

1. Age from 18 to 65 years.
2. Major depressive disorder (DSM-IV).[85]

3. Score on Beck's depression inventory (BDI II) > 13.[86]
4. Written informed consent.

Exclusion criteria

1. Current psychosis, schizophrenia (DSM IV-TR),[87] or schizotypal personality disorder (DSM IV-TR).[87]
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.

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.

'Third wave' cognitive therapy

The 'third wave' cognitive therapy treatment consisted of a weekly individual psychotherapy session (45-50 minutes) and a 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).

Mentalization-based treatment

The mentalization-based treatment consisted of a weekly individual psychotherapy session (45-50 minutes) and a weekly 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). The temporal extent of the

mentalization-based treatment matched the temporal extent of the 'third wave' cognitive therapy.

Outcomes

Primary outcome

- Score on the Hamilton Depression Rating Scale (HDRS)[88] after end of treatment at week 18.

Secondary outcomes

- The proportion of participants in remission after cessation of treatment at week 18. We chose to define remission as HDRS below 8.[89]
- Global Severity Index score (GSI-score)[90] on the Symptom Checklist 90 Revised (SCL-90-R)[90] after cessation of treatment at week 18.
- Score on the World Health Organisation-Five Well-being Index 1999 (WHO 5)[91] after cessation of treatment at week 18.
- Score on the Beck's Depression Inventory (BDI II)[86] after cessation of treatment at week 18.

A priori sample size estimate

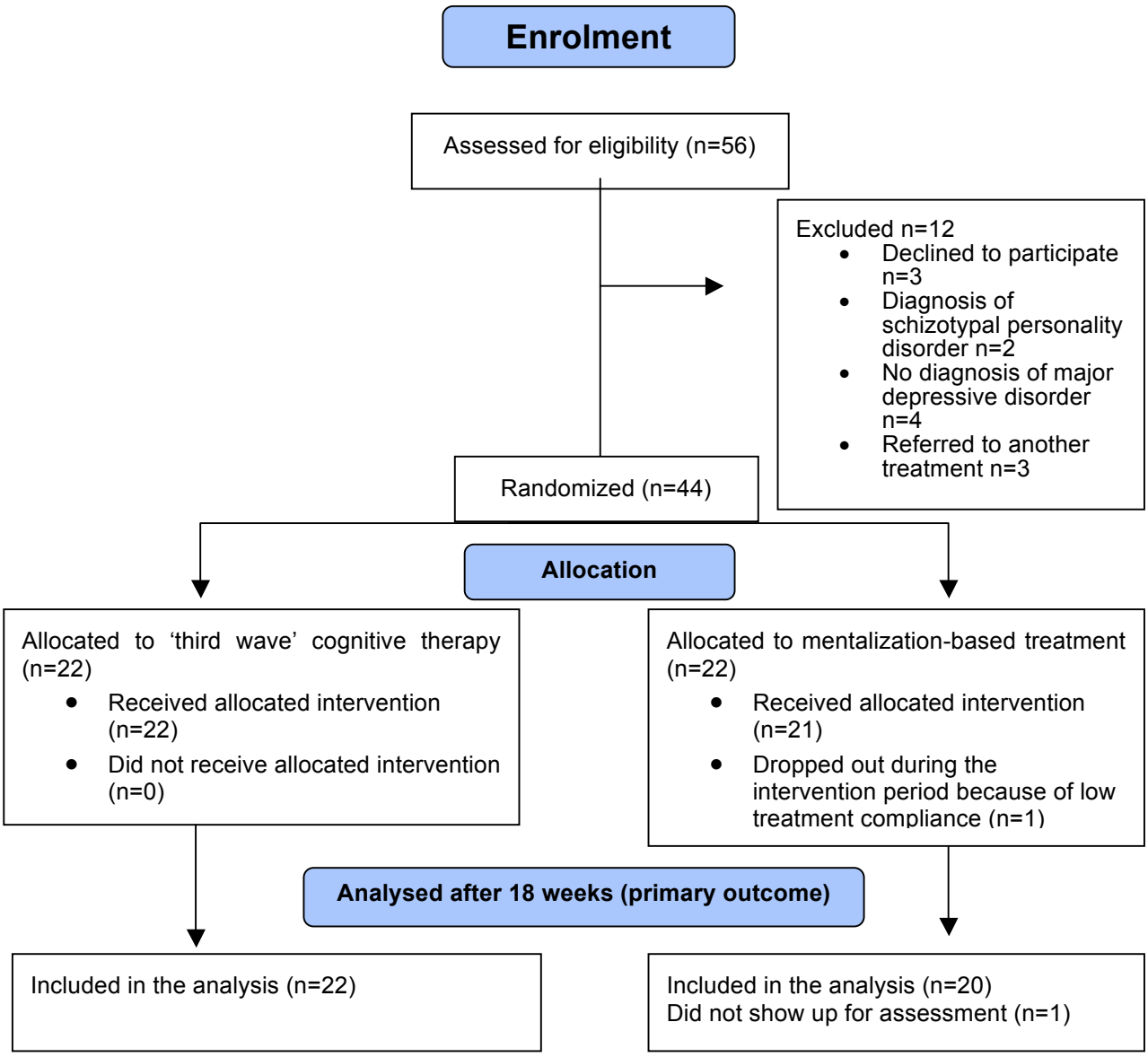
With a 'minimal relevant mean difference' (MIREDIF) between the two interventions of 5 HDRS points, an alpha of 0.05 (type I error), a power of 0.90 (type II error of 10%), and a standard deviation (SD) of 7, the sample size calculation showed that a total of 84 participants would be necessary. We estimated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

Results

Participants

Altogether 22 participants were randomised to 'third wave' cognitive therapy and 22 participants were randomised to mentalization-based treatment.

Details about the participant progress through the phases of the trial (CONSORT 2012 Flow Diagram)



Baseline characteristics of the participants

The baseline characteristics regarding age, number of children, score on HDRS, comorbid depression personality disorder, and psychopharmacological treatment were overall assessed as comparable between the two groups. As it is shown in the following table most of the included participants had comorbid depression and ‘cluster C’ personality disorder.

Baseline characteristics

		Participants randomised to 'third wave' cognitive therapy (n=22)	Participants randomised to mentalization-based therapy (n=22)
Age	mean (SD)	38.5 (8.9)	40.3 (6.8)
Sex	female n (%)	18 (82)	20 (91)
Number of children	mean (SD)	1.4 (1.2)	1.7 (1.1)
Marital status	n (%)		
Single		3 (14)	7 (32)
In a relationship		6 (27)	5 (23)
Married		12 (55)	8 (36)
Separated/divorced		1 (5)	2 (9)
Level of education	n (%)		
Only high school diploma		7 (32)	3 (14)
Medium long education		14 (64)	19 (86)
Long education		1 (5)	0 (0)
Baseline HDRS scores**			
	mean (SD)	22.1 (5.9)	22.5 (4.9)
	median	22.5	23.6
	range	7-30	11-29
Baseline BDI* scores**			
	mean (SD)	36.76 (9.4)	36.32 (9.6)
	median	34	36
	range	20-53	18-56
Mild depression	n (%)	0 (0)	1 (5)
Moderate depression	n (%)	3 (14)	4 (18)
Severe depression	n (%)	18 (86)	17 (77)
Baseline GSI scores (SCL 90-R)***			
	mean (SD)	1.80 (0.59)	1.84 (0.41)
	median	1.72	1.74
	range	0.68-2.79	0.99-2.54
Personality disorders	n (%)		
No personality disorder		5 (23)	6 (27)
One personality disorder		11 (5)	12 (55)
Two personality disorders		4 (18)	3 (14)
Three or more personality disorders		2 (9)	1 (5)
Personality disorders diagnoses	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; *17-item Hamilton Depression rating Scale; ***Beck's Depression Inventory ; ****mild depression: BDI=14-19, moderate depression: BDI=20-28, severe depression: BDI=29-63; *****Global Severity Index score on the Symptom Checklist 90 Revised

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 were lost to follow-up and one was excluded as she did not attend 70% of the sessions

Intervention effects

Primary outcome

Mean score on the HDRS after end of treatment

Participants randomised to 'third wave' therapy compared with participants randomised to mentalization-based treatment had lower HDRS scores after cessation of treatment at week 18 in the unadjusted analysis ('third wave' cognitive therapy: mean 12.9 HDRS points, 95% CI 9.81 to 15.9; mentalization-based treatment: mean 17.0 HDRS points, 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) in favour of 'third wave cognitive therapy but the difference was not significant (P=0.051). The difference was significant according to our prospectively planned significance level[41] in the HDRS baseline adjusted analysis (P=0.039).

None of the 22 participants randomised to 'third wave' cognitive therapy were 'lost to follow-up'. Two out of the 22 participants randomised to mentalisation-based treatment were lost to follow-up.

Following imputation of the two missing values in the group randomised to mentalization-based treatment (see 'statistical methods' above) the P-values were 0.064 (unadjusted analysis) and 0.041 (adjusted analysis). 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.

Influence of comorbid personality disorder on primary outcome

Eighteen (81%) of the 22 participants randomised to 'third wave' therapy and 16 (73%) of the participants randomised to mentalization-based treatment had comorbid major depressive disorder and personality disorder (SCID II).[92] There was no significant interaction between the indicator of co-morbid personality disorder type and the intervention indicator. This was also not the case when the indicator of co-morbid personality disorder type was redefined as a dichotomous outcome defined by personality disorder = 'borderline personality disorder' (yes/no) or as a dichotomous outcome defined by personality disorder = 'no personality disorder' (yes/no).

Secondary outcomes

Participants in remission after end of the interventions

In the group of participants randomised to 'third wave' cognitive therapy 22.7% (n=5) were in remission after cessation of treatment (defined as having HDRS < 8) while 0% of the participants randomised to mentalization-based treatment were in remission after cessation of treatment. This difference was significant (P of Fisher's exact test = 0.049).

BDI II,[86] SCL-90-R,[90] and WHO 5[91] 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

Overview of the effects of 'third wave' cognitive therapy versus mentalization-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		
HDRS						
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		
Remission (HDRS<8)						
N/ total	0/22	5/22	0/21	0/20	0.049	Not possible to calculate
BDI II						
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		
SCL 90-R (GSI score)						
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		
WHO 5						
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.

Other outcomes

Admissions and suicidality

One participant 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.

Psychopharmacological medicine at cessation of treatment

The psychopharmacological medication varied greatly between all of the trial participants. However, we have assessed the psychopharmacological medication at cessation of treatment as being comparable in the two intervention groups (**Table 2** in the full publication).[42]

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 principle investigator (PI) and one of these 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 only -0.13 HDRS points (SD 1.25), and the Spearman correlation was 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 only -0.14 HDRS points (SD 2.22), and the Spearman correlation was 0.94. All these 29 interviews were conducted while both interviewers were in the same room as the patient, but only one of the interviewers asked the questions. The interviewers were not allowed to discuss the results before each interviewer had registered the HDRS result.

Reliability of the Structured Clinical Interviews for DSM-IV Personality disorders (SCID II)[92]

Two experienced interviewers performed the baseline SCID II interviews during the trial period. Before randomisation began both interviewers rated the same five patients (interviews recorded on video). In all of the five interviews the interviewers had the same result from the SCID II interview. If one of the interviewers were in doubt about a SCID interview during the trial period, this interview was discussed prior to registration of the results and randomisation of the patient in question.

Therapist adherence to treatment manual

All individual sessions were recorded on an audio recorder and all group sessions were recorded on video. During the trial an independent experienced psychologist rated 4 x 5 of randomly selected recordings (5 sessions each of: 'third wave' cognitive therapy individual therapy, mentalization-based individual treatment, 'third wave' cognitive therapy group therapy, and mentalization-based group treatment). This was done to assess the level of adherence to the treatment manuals. The psychologist 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 results showed high adherence to the treatment manuals for both interventions. The means of the ratings were: five sessions of 'third wave' cognitive therapy (individual): mean 4.6; five sessions of 'third wave' cognitive therapy (group): mean 4.2; five sessions of mentalization-based treatment (individual): mean 4.2; five sessions of mentalization-based treatment (group): mean 3.8.

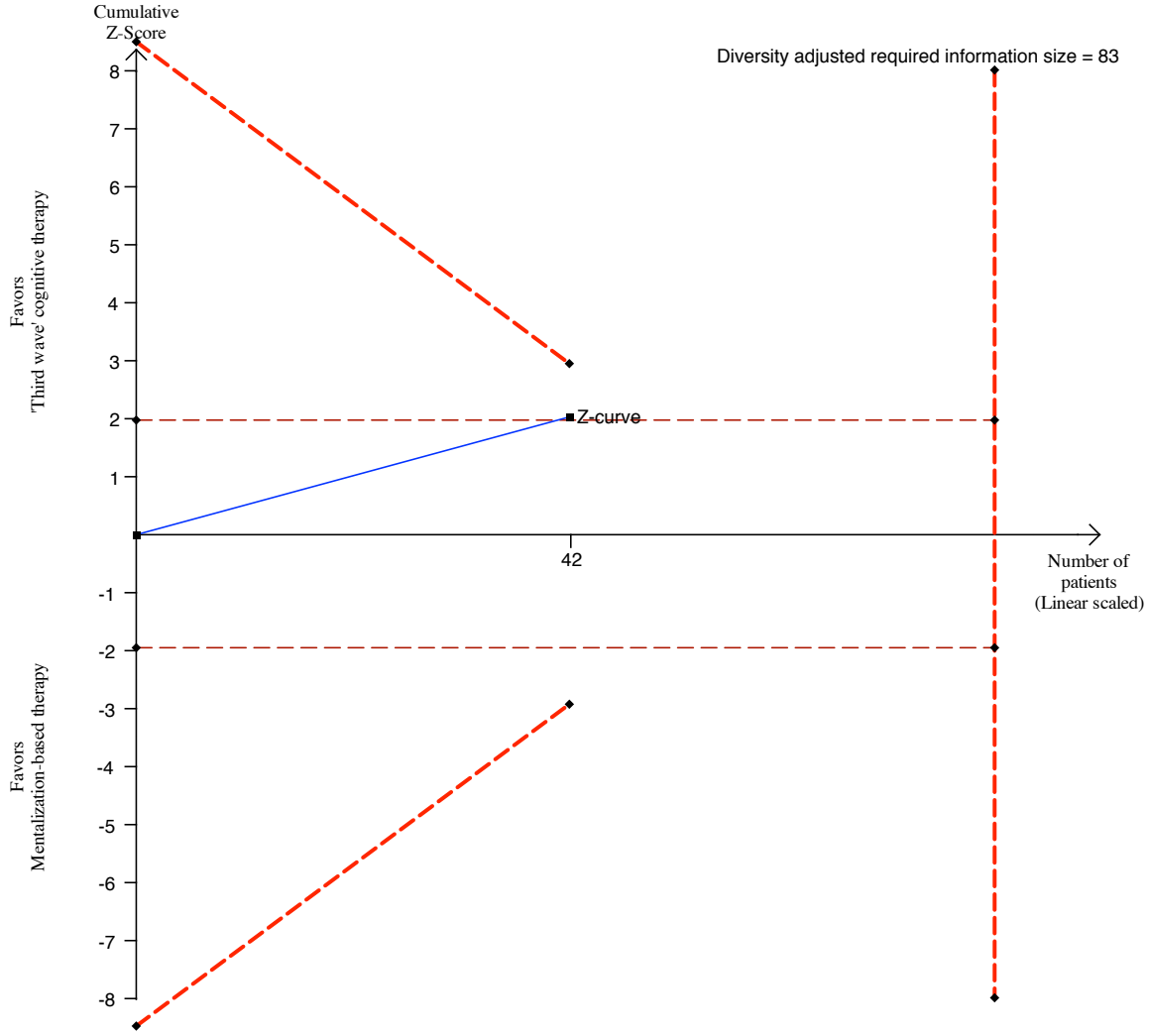
Discussion

The results of the two systematic reviews with meta-analyses and trial sequential analyses suggest that cognitive therapy and psychodynamic therapy may significantly reduce depressive symptoms on the HDRS, corresponding to a mean reduction of a few HDRS points for participants treated with the two psychotherapies. Cognitive therapy and psychodynamic therapy may also increase the probability of remission compared with 'no intervention'. The National Institute for Clinical Excellence (NICE) has suggested a mean difference of three points on the HDRS as a criterion for clinical significant difference between two interventions (drug-placebo).[93] Based on these recommendations as well as clinical experience, the HDRS effects sizes found in our two reviews seem relatively small. Could modern forms of psychotherapy have larger and clearer effects?

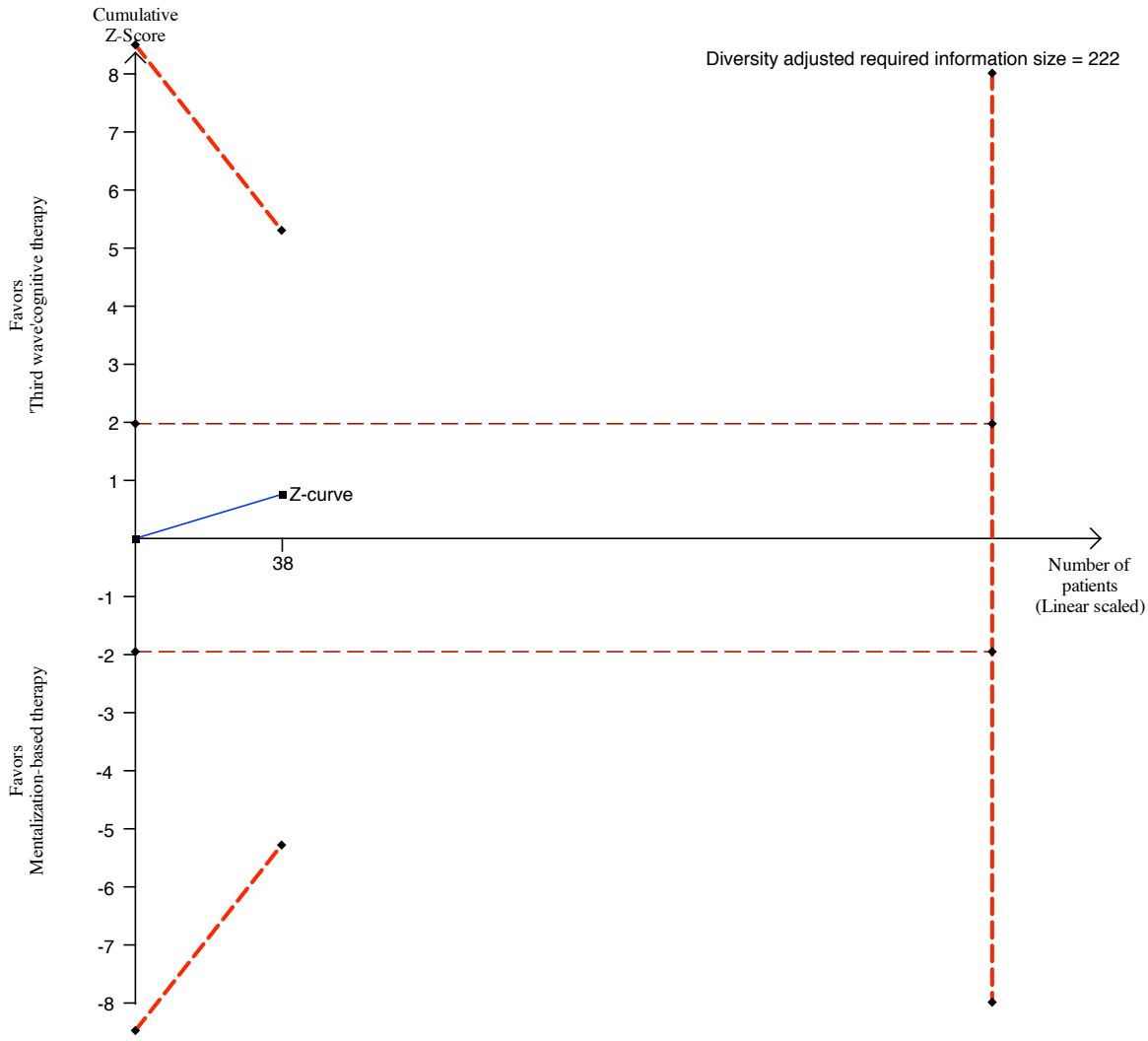
The trial protocol showed that it seemed feasible to conduct a randomised trial with low risks of bias and low risks of random errors examining the effects of the 'third wave' cognitive therapy versus mentalization-based therapy for acute major depressive disorder.

The results from the randomised trial showed that 'third wave' cognitive therapy compared with mentalization-based treatment might be a more effective intervention for lowering depressive symptoms measured on the HDRS and might increase the probability of remission (HDRS<8). If it is assumed that mentalization-based treatment does not have harmful effects, 'third wave' cognitive therapy might have beneficial effects that exceed the recommendations from NICE[93] with effect sizes of over four points on the HDRS.[42] However, these effects should be viewed with great care as we only managed to randomise 44 out of the planned 84 participants. When a trial is stopped before the pre-planned sample size is reached it is necessary to evaluate the calculated P-values more conservatively.[94] Sequential analysis is a useful way to illustrate this:

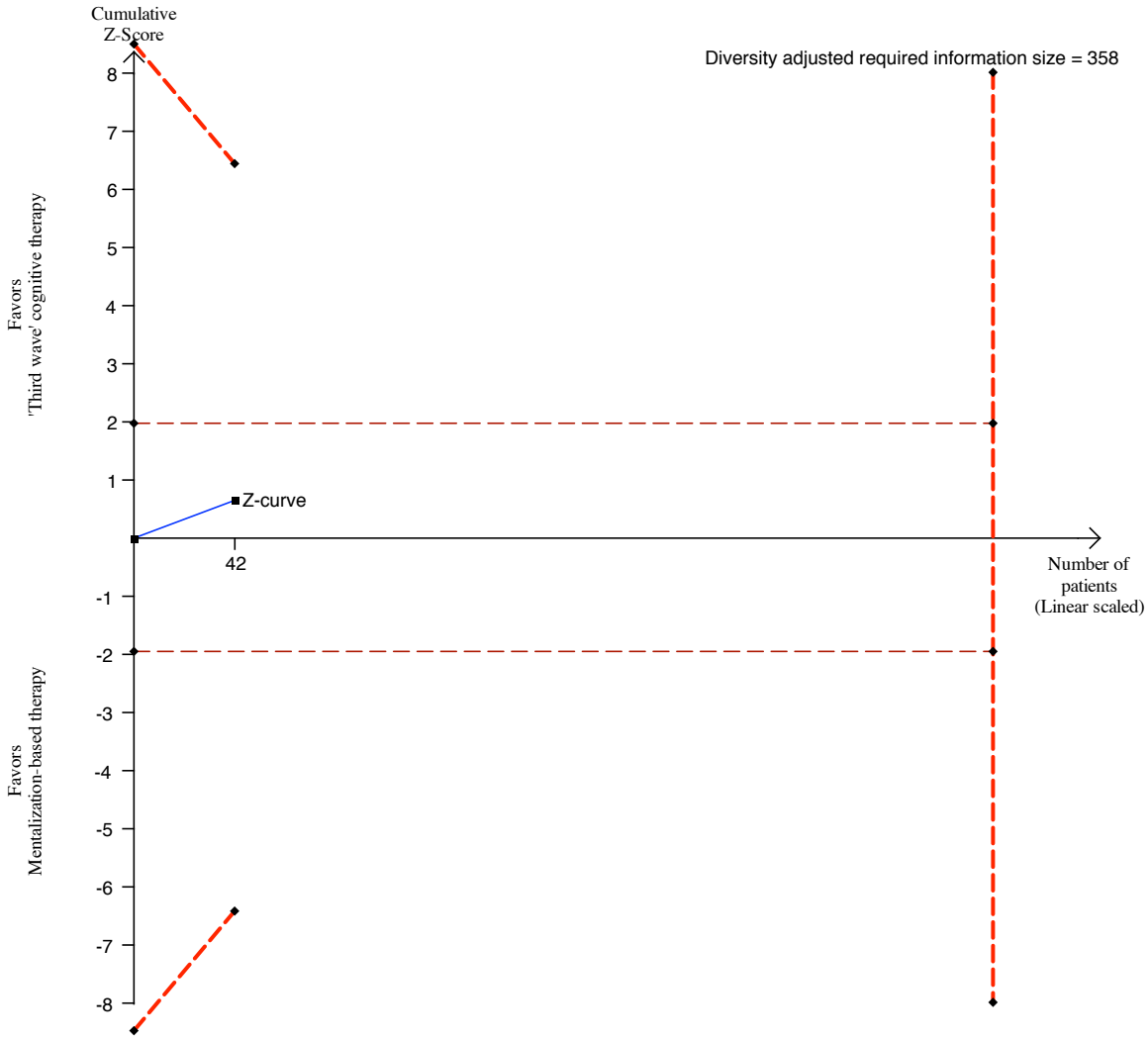
Post-hoc sequential analysis of the HDRS trial results after 18 weeks.[42] It is shown that 42 participants out of the 44 participants were assessed with HDRS after end of treatment (see **CONSORT flow chart in Paper 4**). The required information size of 83 is calculated based on minimal relevant mean difference of 5 HDRS points, a type I error of 5%, a beta of 10% (power of 90%), and a variance of 49. These assumptions are similar to the assumptions used in prospectively planned sample size calculation. The cumulated Z-curve (blue curve) do not cross the trial sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error (either due to sparse data or repetitive testing) in the estimate of a beneficial effect of 'third wave' cognitive therapy compared with mentalization-based therapy.



Post-hoc sequential analysis of the BDI trial results after 18 weeks.[42] It is shown that 38 out of the 44 participants were assessed with BDI after end of treatment. The required information size of 222 is calculated based on minimal relevant mean difference of 5 BDI points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 11.5 BDI points. The cumulated Z-curve (blue curve) do not cross the trial sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error (either due to sparse data or repetitive testing) in the estimate of a beneficial effect of 'third wave' cognitive therapy compared with mentalization-based therapy.



Post-hoc sequential analysis of the SCL-90-R (GSI) trial results after 18 weeks.[42] It is shown that 42 out of the 44 participants were assessed with SCL-90-R after end of treatment. The required information size of 673 is calculated based on minimal relevant mean difference of 0.2 GSI points, a type I error of 5%, a beta of 10% (power of 90%), and a standard deviation of 0.58 GSI points. The cumulated Z-curve (blue curve) do not cross the trial sequential monitoring boundaries (red inner sloping lines) implying that there is a risk of random error (either due to sparse data or repetitive testing) in the estimate of a beneficial effect of 'third wave' cognitive therapy compared with mentalization-based therapy.



A more detailed description of trial sequential analysis is included in the paragraph below.

The two interventions do not seem to have significant differential effects on BDI, SCL 90-R (psychological distress), and WHO 5 (well-being).

Strengths and limitations of the two systematic reviews (Paper 1 and 2)

The two systematic reviews have a number of strengths. The protocols[39,46] were published before we began systematic literature searches in all relevant databases, data extraction, and data analysis. Data was extracted by two independent authors minimising the risk of inaccurate data-extraction, and bias risk in all of the trials was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions.[64] All data were meta-analysed with both a fixed-effect model and random-effects models and all analyses were in agreement in all of our results. Furthermore, trial sequential analyses were performed to assess the risks of random errors.[44,45,64,65] With a relatively limited number of trials and trial participants and with an increasing number of repetitive tests, the risk of falsely rejecting the null hypothesis (type I error) is substantial. Trial sequential analysis is a statistical analysis that enables one to assess the risks of random errors that may occur due to sparse data and multiple testing on accumulating data. Trial sequential analysis is therefore a more robust analysis than the traditional cumulative meta-analysis.[44,45,64,65] There was no significant heterogeneity in our analyses or differences with tests of interaction analyses. This indicates that there may be a comparable treatment effect between the different forms of the two interventions and among the different populations. This may make the results more generally applicable.

The systematic reviews have a number of limitations. The results are based on a limited number of randomised trials (total of 17) with a limited number of participants, and the characteristics of the included participants as well as the severity of the depressive symptoms differed between the included trials. For these reasons our

results may be questionable. Moreover, all of the trials had high risk of bias. The bias risk assessment is summarized in **Table 2** in the full version of **Paper 1**[36] (page 5) and in **Table 2** in the full version of **Paper 2**[38] (page 10). As it is shown, the majority of the trials did not allow intention-to-treat analysis which is known to increase the risk of biased results mainly because of the characteristics of the participants 'lost to follow-up' might systematically differ from the remaining participants included in the per protocol analysis.[95] The total number of randomised participants is shown in **Table 1** (page 9) in the full publication of **Paper 1** and **Table 1** in the full publication of **Paper 2;** and the number of participants included in each meta-analyses is shown in the figures in the full versions of **Paper 1**[36] and **Paper 2**[38]. The included trials had generally high risk of bias in the majority of the other essential bias risk components we assessed.[36,38] Evidence has shown that all of the bias risk components we have assessed potentially increase the risk of biased results.[95-99] The high risk of bias in the trials included in the **Paper 1**[36] and **Paper 2**[38] question the validity of our results and might explain why some of the analyses showed that psychodynamic therapy and cognitive therapy had statistically significant effects.

Trial sequential analysis of the HDRS data from the review examining the effects of cognitive therapy showed that we could not exclude the risk of random errors.[44,45,64,65] Due to the limited number of included trials in the two reviews, funnel plot or other analysis to explore the risk of publication bias were not performed.[64] Other meta-analyses have shown that publication bias significantly has influenced the results from former publications.[8] It is a further limitation that it was not possible to assess the risk of publication bias.

Altogether, only 7 out of the 17 included trials used an experimental intervention that was classified as 'adequately defined', i.e., using and documenting the use of a therapeutic manual. It was not possible to assess psychotherapeutic treatment fidelity in the included trials because the treatment fidelity was not reported sufficiently. No heterogeneity was shown in the results and this may indicate that the use of treatment manuals, tests of adherence to treatment manuals, as well as the possible differences in psychotherapeutic treatment fidelity do not seem to influence the effects of neither psychodynamic therapy nor cognitive therapy. It is imperative in

clinical trials that the interventions are adequately defined and described and treatment fidelity should be assessed.[100] Factors like personal style, communication skills, and personality of the therapist evidently may influence the way psychotherapy is delivered,[101] and it is difficult to describe and control for these subjective factors. It is therefore important to relate psychotherapeutic interventions to a treatment manual. Otherwise it is unclear what kind of intervention the trial participants were receiving, it is difficult to apply any trial result in clinical practice, and it is impossible to replicate the trial results in other trials.

Only a few of the included trials in the two reviews reported numbers of adverse events, numbers of suicide attempts, numbers of suicides, assessments of quality of life, or included long-term follow-up assessments. Typically adverse events and suicidality are not reported as thoroughly as beneficial outcome measures.[102] Some psychological interventions might have harmful effects. Psychological debriefing for preventing post-traumatic stress disorder has, for example, in some clinical trials showed harmful effects.[103] Possible harmful effects of cognitive therapy and psychodynamic therapy are not thoroughly examined. Outcome measures of quality of life are generally not standardised and thoroughly individually validated.[104] The use of standardised outcome measures for quality of life in research has been limited by difficulties in administering and scoring quality of life, but quality of life can and should be used as a valid outcome measure.[104,105] From a patient perspective, quality of life might be the most important outcome measure. The lack of long-term follow-up assessments show that it is unclear whether cognitive therapy or psychodynamic therapy has any effect on depressive symptoms in the longer term.

The majority of the all of the included trials used antidepressant medication as co-intervention described as being delivered similarly to both the experimental group and the control intervention group.[36,38] Details about the antidepressant medication, including choice of drug, doses, and compliance with the medication were generally poorly reported in the included trials.[36,38] This is a further limitation of the two systematic reviews. If it is assumed that antidepressant medication does have a clinical significant effect, this effect can theoretically interact with the possible effects of the psychotherapeutic interventions. The antidepressant medication can therefore

theoretically either mask or intensify the effects the psychotherapeutic interventions questioning whether the results from the systematic reviews actually demonstrate the effects of psychodynamic therapy and cognitive therapy versus 'no intervention' (see 'Control interventions in randomised trials assessing the effects of psychotherapy for acute major depressive disorder' in the paragraphs below). Furthermore, because compliance with the medication generally was not adequately reported[36,38] any difference in effect between the intervention groups in the included trials might be due differences in medication.

As it is described in the **Paper 1** and **Paper 2**,[36,38] we chose to include all randomised clinical trials examining the effects of cognitive therapy and psychodynamic therapy in adult participants with acute major depressive disorder. This means that we included trials using any kind of outcome (e.g., risk of relapse or preventive effects) but only if the participants were acutely depressed at the time of inclusion. Randomised clinical trials examining preventive effects or effects on risk of relapse randomising non-acutely depressed participants were therefore not included in our two systematic reviews,[36,38] and our review results do therefore not demonstrate the effects of cognitive therapy and psychodynamic therapy on prevention of new depressive episodes or risk of relapse.

It could be argued that interpersonal psychotherapy is not a psychodynamic intervention **(Paper 1)**.[36] Interpersonal psychotherapy takes structure from and has its theoretical roots in psychodynamic therapy but has also integrated elements from other therapies,[12,13,106,107] although interpersonal psychotherapy is not considered a 'third wave' cognitive therapy.[15] In spite of the integrative content of interpersonal psychotherapy we chose to classify interpersonal psychotherapy as a form of psychodynamic therapy.[12,106] Furthermore, we believed that most forms of contemporary psychodynamic therapies, in practice, are delivered in a way similar to interpersonal psychotherapy. Including both psychodynamic therapy and interpersonal psychotherapy in the same review made it also possible to assess whether the two form of psychotherapy have differential effects.

Strengths and limitations of the trial protocol and the randomised trial (Paper 3+4)

The trial protocol and the randomised clinical trial have a number of strengths. First, the trial protocol was registered before randomisation began (ClinicalTrials.gov; no.: NCT01070134). In this protocol the outcome hierarchy and analyses plans were presented. The trial was altogether conducted according to good clinical research practice and therefore with low risk of bias and a high degree of external validity.[108-112] Secondly, 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. Thirdly, both of the psychotherapeutic interventions were delivered using treatment manuals and adherence to the treatment manuals was assessed as relatively high. This makes it possible to implement the two trial interventions in clinical practice and to replicate our results in future trials. It must, however, be noted that the co-interventions (antidepressant medication and psychoeducation) delivered to both intervention groups were not delivered according to a treatment manual and adherence to the co-interventions were therefore not assessed. Implementing a treatment exactly similar to the interventions assessed in the randomised clinical trial will therefore not be impossible. Fourthly, the most commonly used outcomes in trials assessing the effects of psychotherapeutic interventions for depression were used in our trial (HDRS).[17,36,88,113] This makes it possible to relate the 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 (see paragraph below for details), which may be a further strength of our trial. Fifthly, 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 similar participants in the two intervention groups. Sixthly, few participants (4.5%) were 'lost to follow-up' which decreases the risk of biased results.[114]

The trial protocol and trial have a number of limitations. The primary limitation is that only 44 participants were included. The plan was to include 84 participants based on the sample size calculation. The trial inclusion lasted for about two years as planned but the sample size was not reached because there were problems with recruiting

enough participants during the trial period. Not enough eligible patients were referred to the clinic during the trial period. The low number of randomised participants lead to a high risk of type I error and type II error.[43] Furthermore, no long-term follow-up was conducted so the trial results do not show anything about any long-term effects of the two interventions. The antidepressant medication was not delivered according to a treatment manual, it was not recorded how often the trial participants had a consultation about the psychopharmacological medication, and adherence to the antidepressant medication was not assessed. This makes it difficult to assess whether the participants received similar psychopharmacological treatment in the two intervention groups, although the status of the psychopharmacological medication for each participant was assessed at end of treatment.

Prior depressive episodes, duration of the present depressive episode, prior psychiatric admissions, and prior psychotic episodes were not assessed systematically in the randomised participants. The participant characteristics are therefore unclear which makes it difficult to relate the trial results to specific patients in a given clinical setting. All the trial participants were on sick leave due to psychological problems and a high proportion had comorbid personality disorder and depression. The trial results can only be related to this rather vaguely defined group of patients.

The evidence behind the effects of both ‘third wave’ therapy versus ‘no intervention’ and mentalization-based treatment versus ‘no intervention’ is, as mentioned in the introduction, sparse. When two ‘active’ interventions are compared the balance between any beneficial and harmful effects may be unclear. All interventions should ideally at some point be assessed versus ‘no intervention’. Due to practical and ethical circumstances it was not considered possible to conduct a trial with ‘no intervention’ as control intervention.

Mentalization-based treatment is a relatively new intervention and we did not identify any relevant treatment manual we could use. Therefore, the mentalization-based therapists created a new treatment manual. Due to limited resources the mentalization-based manual became relatively short. The specific content of the

control intervention was therefore less strictly defined and this is a further limitation of this trial.

Mentalization-based therapy was, as mentioned, originally designed to treat borderline personality disorder but is now used in a number of different clinical settings.[33,34] In addition, a high proportion of participants with comorbidity of depression and personality disorder was expected.[115] It was assumed that mentalization-based treatment would be a relevant control intervention but the evidence behind this assumption is sparse.

It has been debated if the diagnosis of a personality disorder is accurate when patents are acutely depressed.[116] The results indicate that comorbid personality disorder and depression do not associate 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.

Implications

The primary implication of the results of this thesis is that further randomised trials examining the effects of psychotherapeutic interventions for depression are needed. Such trials should be conducted with low risk of bias and low risk of random errors. 'Third wave' cognitive therapy showed potentially promising results in our randomised trial but the results needs to be replicated in larger trials. There are many forms of 'third wave' cognitive therapy. It would be rational to assess the effects of the manualized form of 'third wave' cognitive therapy used in this present randomised trial, or to assess the effects of another manualized 'third wave' cognitive trial intervention, which also has shown promising effects.

HDRS as an outcome measure

The systematic reviews and other reviews have showed that most trials examining the effects of interventions for depression primarily use HDRS as outcome measure.[8,14,17,36] HDRS was also chosen as the as our primary outcome measure in the randomised trial. The evidence behind interventions for depression is therefore in

essence based upon the HDRS. As mentioned in the paragraphs above, the clinical relevance of a mean difference on only a few points on the HDRS has been questioned. Not many experienced Hamilton interviewers would, e.g., ascribe any real clinical significance to a mean difference between two compared interventions of one Hamilton point. NICE has suggested a mean difference between two compared interventions (drug-placebo) of three points on the HDRS as a criterion for clinical significance.[93] It is difficult set a specific threshold value but it is essential to discriminate between statistical significance and clinical significance. Based on these considerations the aim was to quantify the effects of cognitive therapy and psychodynamic therapy in the two systematic reviews. To be included any trial co-intervention had to be delivered similarly to the experimental intervention group and the control group. The review results show that the benefit from cognitive therapy and psychodynamic therapy compared with 'no intervention' was only a few points on HDRS and BDI. The results from the two systematic reviews indicate that cognitive therapy and psychodynamic therapy seem to have relatively small HDRS effect sizes (mean differences) compared with 'no intervention', especially when the extent (number of therapy sessions etc.) of the two interventions are considered. The results from the randomised trial indicate that 'third wave' cognitive therapy might have greater HDRS effects, and new randomised trials examining the effects of 'third wave' cognitive therapy are needed. Nevertheless, the HDRS might not at all be a useful instrument to quantify the effects of interventions for depression.[117] Severity of depression as measured by the total HDRS score has failed to predict suicide attempts,[117,118] and some publications have questioned the usefulness of the HDRS and concluded that the scale is psychometrically and conceptually flawed.[117,119] The two other outcome measures often used to assess depressive symptoms, MADRS and BDI, probably correspond to HDRS.[120,121] The HDRS has during 40 years been the gold standard to quantify depressive symptoms in clinical trials.[119] There may be a need for development and use of other assessment methods.[117]

HDRS compared to BDI as outcome measure

It is a common belief among clinicians that BDI is a more 'reactive' assessment measure than HDRS,[122] and it might be surprising why we found a significant

possible beneficial effect on the HDRS results but no significant effect on the BDI results **(Paper 4)**;[42] and cognitive therapy significantly decreased the probability of 'no remission' in **Paper 2**[38] when the HDRS data were analysed but no significant difference was found analysing the BDI data. However, trials simultaneously using HDRS and BDI to assess the effects of the same intervention have been assessed in two systematic reviews with meta-analysis.[122,123] The results from these two reviews show that BDI under such circumstances shows significantly less effect sizes (mean difference divided by standard deviation (SD)) compared to HDRS.[122,123] A greater percentage of participants would be considered improved if ratings of change were based on the HDRS rather than BDI.[122] The results from these two reviews[122,123] are in agreement with the results from our randomised clinical trial and can potentially explain why there was found a significant effect on HDRS and no significant effect on BDI. HDRS might accurately reflect participant improvement and BDI might underestimate it.[123] On the other hand, it is also possible that HDRS compared to BDI overestimates participant improvement, e.g., caused by inadequate blinding of the outcome assessors.[123] HDRS was chosen as the primary outcome over BDI because HDRS makes it possible to blind the outcome assessment in contrast to BDI, which is only a self-reported outcome measure. It is evidently impossible to blind psychotherapeutic trial participants to treatment allocation. Therefore, it was expected that the results on HDRS would be a more valid outcome compared to the BDI results — but, as mentioned, we cannot exclude lack of blinding and biased assessment of the HDRS. In accordance with the CONSORT Statement the degree of unblinding was not assessed.[108]

Control interventions in randomised trials assessing the effects of psychotherapy for acute major depressive disorder

Trials assessing the effects of psychotherapy for depression have primarily used either 'no intervention' or treatment as usual (TAU) as 'non-active' control interventions.[14,17,36,38] The term 'treatment as usual' most often refers to an intervention where participants are treated, as they would have been if they had not been included in a trial. Treatment as usual is a collective term of different non-specific interventions.[17] 'No intervention' is a control 'intervention' without any 'active'

treatment elements, e.g., a waiting list control group. An experimental intervention can also be assessed as an add-on intervention. For example, a randomised trial can assess the effects of adding cognitive therapy to an antidepressant drug delivered similarly to both the experimental and control group. In **Paper 1**[36] and **Paper 2**[38] included in this thesis we have classified such comparisons as experimental interventions assessed versus 'no intervention', because co-interventions had to be delivered similarly to both the experimental and the control group. Any shown difference in effect between the experimental and control group would therefore be caused by the experimental intervention — if we assume that there is no interaction between the trial interventions and the co-interventions (see the paragraph below).

Our group has previously published two systematic reviews[14,17] that can appear similar to **Paper 1**[36] and **Paper 2**[38] included in this present thesis. The reviews assessing cognitive therapy and psychodynamic therapy versus 'no intervention' are included in this thesis, while the two reviews assessing cognitive therapy and interpersonal psychotherapy (including psychodynamic therapy) versus treatment as usual are published elsewhere.[14,17] We chose to assess the effects of the psychotherapies versus 'no intervention' and treatment as usual in separate reviews because we believed that using 'no intervention' or treatment as usual as control interventions results in potentially answering different clinical questions. To clarify the methodological differences between choosing the two different kinds of control interventions, a systematic overview of the methodological strengths and limitations and the corresponding clinical interpretative implications of the two types of control interventions will be presented in the following paragraphs.

Overview of the methodological strengths and limitations using 'no intervention' and treatment as usual as control interventions

'No intervention' as control intervention

Methodological strengths: The strength of using no intervention as control intervention is that the effect size of the experimental intervention can be assessed.

The size of benefit and harm is shown by the results if the control group does not receive any treatment. To be able to assess the balance between benefits and harm it is therefore necessary to compare experimental interventions with 'no intervention'.

Methodological limitations: If the control group receives no treatment it might rightfully be difficult to get a trial approved by an ethics committee. If an evidence-based treatment exists it will be unethical not to treat a group of participants. Moreover, potential participants might be reluctant to participate if one of the trial interventions contains no active treatment elements.

Treatment as usual as control intervention

Methodological strengths: A clinician can relate trial results to what a given average patient gains by an experimental intervention compared with the treatment the patient usually receive. Such knowledge is clinically relevant and provides a perspective on the intervention effects. Moreover, if the control intervention group receive some kind of intervention it will be easier to ethically justify the trial and to obtain informed consent.

Methodological limitations: Treatment as usual most often contains some unspecific treatment elements with unknown effects. If an intervention has not been assessed in former trials using a control intervention without any 'active' treatment elements and the given experimental intervention show no difference in effect compared to another 'active' intervention (e.g., treatment as usual); it can be unclear whether the compared 'active' interventions are equally effective or equally ineffective. If one of the interventions is shown to be more effective than the other, it is not clear if one of the compared interventions really is more effective than the other, or if one of the interventions simply has harmful effects.

Assessment of add-on interventions in randomised clinical trials

If an experimental intervention is assessed as an add-on intervention to an evidence-based co-intervention delivered similarly to both the experimental and control group, it may be easier to conduct the trial ethically and practically. However, even though the effects of the co-intervention theoretically even out between the intervention

groups, there might be an interaction between the co-intervention and the experimental intervention. The effects of the control interventions delivered similarly to all intervention groups might therefore mask or intensify the effects of an add-on experimental intervention. All of the participants in the randomised trial[42] received psychoeducation, were offered breakfast, and were treated with antidepressant medication and the 'third wave' cognitive therapy and the mentalization-based therapy were assessed as add-on interventions in the randomised clinical trial.[42] It is, therefore, possible that the psychoeducation, the breakfast, and the antidepressant medication in some way interacted with the effects of the two psychotherapies either masking or intensifying the effects of the psychotherapy. It is also possible that such interactions between co-interventions and psychotherapy are different depending on the form of psychotherapy, i.e., 'third wave' cognitive therapy or mentalization-based therapy. These possible interactions between the psychotherapies and the co-interventions further limit the interpretability of the results from the randomised clinical trial.[42]

Recommendations for future research

Randomised trials examining the effects of different kinds of psychotherapy versus 'no intervention' for depression are needed. It seems relevant to examine 'third wave' cognitive therapy in larger randomised trials. If the effects of 'third wave' cognitive therapy are as our results suggest it may have an impact on patients as well as health care costs. Future research should also focus on comparing different forms of manualized psychotherapy and comparing psychotherapeutic interventions with other interventions for depression. First and foremost such trials should be conducted with low risks of bias, low risks of random errors, and long-term follow-up.[124] Outcome measures should include 'quality of life', adverse events, suicide inclination, suicide attempts, and numbers of suicides. There may also be a need for a new gold standard assessment method other than HRDS to assess depressive symptoms, and if possible more effective interventions for depression must be developed.

Conclusions

Cognitive therapy and psychodynamic therapy might be effective interventions for depression measured on HDRS and BDI, but the review results might be erroneous due to risks of bias and random errors. Furthermore, the effects seem relatively small.

The trial protocol showed that it was possible to develop a protocol for a randomised trial with low risks of bias and low risks of random errors.

The trial results showed that 'third wave' cognitive therapy may be a more effective intervention for depressive symptoms measured on the HDRS compared with mentalization-based treatment. However, too few participants were included and the sample size was not reached. The two interventions did not seem to differ significantly regarding BDI II, SCL 90-R, and WHO 5.

More randomised trials with low risks of bias and low risks of random errors are needed to assess the effects of cognitive therapy, psychodynamic therapy, 'third wave' cognitive therapy, and mentalization-based treatment. Outcomes should include long-term follow-up assessing both benefits and harms with clinically relevant outcome measures.

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