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Combination Treatment for Acute Depression Is Superior Only when Psychotherapy Is Added to Medication

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Key Words
Depression · Psychotherapy · Antidepressive medication · Nefazodone · Interpersonal therapy

Abstract
Background: Although several forms of effective therapy exist for outpatients suffering from major depressive disorder, many patients do not profit from treatment. Combining psychotherapy and medication may be an effective strategy. However, earlier studies have rarely found a clear advantage for the combination. Where an advantage was found, a possible placebo effect of adding 2 types of treatment could not be ruled out as cause for the superior effect of the combination. ***Methods:*** A total of 353 patients were screened, of whom 193 were randomized over 4 conditions: nefazodone plus clinical management, interpersonal psychotherapy (IPT), the combination of the two or the combination of IPT and pill-placebo. All patients suffered from major depressive disorder and had a score of at least 14 on the 17-item Hamilton Rating Scale (HAMD). The patients were treated for 12–16 weeks. At baseline, at 6 weeks and on completion of treatment, ratings were performed by independent raters. The primary outcome measure was the HAMD, and the Montgomery-Asberg Depression Rating Scale (MADRS) the secondary outcome measure. ***Results:*** Of the 193 patients included, 138 completed the trial. All treatments were effective. Using a random regression model, no differences between treatments were found on the HAMD. On the MADRS, however, the combination of medication with psychotherapy was more effective in reducing depressive symptoms compared to medication alone, but not to psychotherapy alone or IPT with pill-placebo. ***Conclusions:*** The results of this study yield support for the use of combining medication with psychotherapy instead of using medication only in the treatment of depressed outpatients. Combination treatment does not have an advantage over psychotherapy alone in the present study.

Introduction

Major depressive disorder (MDD) is a frequently occurring [1] and for many patients chronic and disabling illness [2]. The suffering of participants and their fami-

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lies is impressive and costs for society are large. Treatment of MDD with either medication [3, 4] or psychotherapy [5] is found to be effective. However, many participants will need additional treatment. To further improve the efficacy, combining medication and psychotherapy is preferred by many clinicians. In theory such a combination can have many advantages: better response rates, enhanced compliance and higher participant satisfaction [6]. Most studies, however, have failed to find a clear advantage for the combination [7–11]. In a recent review the combination was found to be slightly more effective than the single conditions, but many methodological shortcomings, foremost lack of statistical power, made a final conclusion difficult [12]. In a second review by Pampallona et al. [13] an advantage for the combination was found, but the studies reviewed included chronic types of depression as well as acute depression, making any conclusions about the value of combined therapy for acute depression equivocal.

As found by Friedman et al. [12], most studies thus far are hampered by including too few participants. The exceptions to this rule are rare: an early study by DiMascio et al. [14] showed a clear advantage for the combination of interpersonal psychotherapy (IPT) and amitriptyline, and more recently in a large study, Keller et al. [15] found the combination of Cognitive Behavior Analysis System of Psychotherapy (CBASP) and nefazodone to be more effective in the treatment of chronic depression than both therapies alone. In a 'mega-analysis' of 6 studies Thase et al. [16] found an advantage of the combination of IPT and medication over psychotherapy (but not over medication alone) in the treatment of severer MDD. In accordance with these findings, the APA guidelines [17] recommend combination treatment for recurrent or severe depression. Since the evidence in favor of combination treatment is rather poor [12], this recommendation may be premature. Furthermore, it is not known whether the combination is simply more effective because more time is spent with the participant (enhancement of the placebo effect [18]) or whether there is indeed an additive effect of the 2 treatments. Because combination therapy is more expensive than either treatment alone, the burden of proof lies with the combination treatment.

The aim of the present study was to compare the efficacy of the combination of psychotherapy and medication with both treatment forms alone in the acute treatment of depressed outpatients. Our main hypothesis was that the combination of both active forms of treatment would be more effective than psychotherapy or medication alone or the combination of psychotherapy with pill-placebo.

Methods

Participants

The participants were required to be 18 years or older, with nonpsychotic, nonbipolar MDD and a score ≥14 on the Hamilton Depression Rating Scale (HAMD, 17 items) [19]. Three sites participated in the study, all in an urban area. Two of the sites were community mental health clinics, the third an outpatient department of a psychiatric hospital. The participants fulfilled the criteria of MDD as specified in the DSM-IV [20] and were assessed with the Structured Clinical Interview for Axis I DSM-IV Disorders, Dutch translation (SCID) [21]. Laboratory tests were performed at baseline to screen for somatic disorders. Excluded from the study were participants with substance abuse, a serious medical condition, organic psychiatric disorder, severe suicidality, history of psychotic disorder or schizophrenia, bipolar disorder, current use of psychotropic medication and ongoing psychotherapy. Oxazepam at a daily dosage of up to 20 mg was allowed. The study was approved by the boards of the 3 participating centers and an independent ethical commission in concordance with the Helsinki convention. All participants gave written informed consent before entering the study. Participants were not recruited via advertisements, nor were financial incentives given. The treatment costs were covered by mandatory insurance for mental health.

Study Design and Outcome Measures

The study was a randomized, 4-arm, placebo-controlled clinical trial with a parallel group design. The four conditions were: IPT, nefazodone with minimal contact only (NEF) IPT plus nefazodone (NEF/IPT), and IPT plus pill-placebo (IPT/PLA). The primary outcome measure was the 17-item HAMD [19]. The secondary outcome measures were the Montgomery-Asberg Depression Rating Scale (MADRS) [22] and the Clinical Global Impression (CGI) scale [23]. Both the HAMD and MADRS were administered by experienced clinical raters not informed of the treatment condition [24]. The CGI was administered by the treating clinician. The raters were instructed not to inquire about the treatment given. Monthly interrater trainings were held to ensure good interrater reliability. The participants were rated at baseline, after 6 weeks and on completion of the study (12–16 weeks after baseline). In every condition, the CGI was administered at 1, 3, 5, 7, 9 and 12 weeks. In an earlier study, using the same system, interrater reliability ($\kappa = 0.64$) was found to be sufficient [25].

Interpersonal Psychotherapy

IPT has demonstrated efficacy in the treatment of acute depression [26, 27]. A small pilot trial found it feasible and effective for Dutch patients [28]. All therapists were trained in IPT, by the first 2 authors, using the manual of Klerman et al. [29]. In addition, the therapists participated in 3 workshops given by experienced therapists in IPT (Prof. J.C. Markowitz and Prof. S. Stuart) from the USA. All participating therapists had at least 4 years of

experience in treating outpatients. Adherence to the manual was enhanced by supervision every fortnight.

Every session was taped. Sessions of 30 participants were checked at random for adherence to the IPT manual. Of each of these 30 participants, 3 sessions were scored by independent raters and compared to the specific aims of the protocol, using a modified version of the treatment integrity and adherence questionnaire of the National Institute of Mental Health project [30]. All tapes could be qualified as IPT sessions.

To be included in the completer analysis, the participants had to have received all 12 sessions. If sessions were cancelled due to illness, vacation or other reasons, an extra session could be given if the total length of the trial did not exceed 16 weeks.

Medication

Nefazodone is a relatively new antidepressant and has demonstrated efficacy in several clinical trials [31]. All participants were treated by an experienced psychiatrist or resident under direct supervision of a psychiatrist. The physicians were instructed to restrict the time spent with the participants in the study to 30 min at the initial meeting and 15 min at subsequent visits. The physicians used a treatment manual, which was an adaptation of the manual used in the NIMH Treatment of Depression Collaborative Research Program [32]. This was to ensure that no 'psychotherapy' was inadvertently given in the medication condition. Nefazodone was given in neutral, tasteless capsules of 100 mg each. Placebo pills were the same capsules but filled with a neutral substance. Nefazodone was started at 100 mg per day and gradually increased to a minimum of 400 mg. If the physician concluded that there was insufficient improvement after 4 weeks, the dose was increased to a maximum of 600 mg. In case of insufficient response at the end of the trial, the medication was tapered down and stopped. Compliance was measured by pill count and blood level measurement on weeks 6 and 12 of the trial.

Combination Treatment

Both combination treatments were delivered by 2 clinicians, a psychotherapist and a psychiatrist. If the psychotherapist was a psychiatrist, the medication was prescribed by a different psychiatrist. To promote compliance, the physician would 'step in' during psychotherapy sessions to discuss side effects and compliance issues. For both participant and therapists this enhanced the notion that combination treatment was 1 integrated treatment, not 2 separate ones.

Statistical Analysis

A multilevel regression model for longitudinal data (also called a random regression model) was used to analyze differences between the treatment conditions in the development of scores on the dependent variables from baseline to 6 weeks to 12 weeks. A multilevel regression model is recommended for the analysis of psychiatric data for a number of reasons, the foremost is that the model provides a solution to the problem of missing data [33]. Estimated individual time curves are based on available data from each individual, augmented by information from data for all other individuals. In the present study, because of dropouts, missing data were not completely at random. We added those variables that explained part of the differences between dropouts and nondropouts as covariates into the multilevel model. In this way we increased the likelihood that the data were missing at random.

At the first level of the multilevel model, we had the time variable, with the 3 time points coded as 0, 1 and 2, for the HAMD and MADRS. Because the CGI was administered at 6 time points, the time variable for the CGI was coded as 0, 1, 2, 3, 4 and 5. At the second level, the effects of a priori defined treatment contrasts were estimated, together with the effects of covariates. Two sets of treatment contrasts were analyzed separately. The first set tested the null hypotheses of (1) no difference between the 2 single treatments (NEF vs. IPT); (2) no difference between the combined treatment of NEF/IPT and single treatment with IPT (NEF/IPT vs. IPT), and (3) no difference between the combined treatment of IPT/PLA and IPT (IPT/PLA vs. IPT). In the second set of contrasts the following additional hypotheses were tested: (4) no difference between the combined treatment of NEF/IPT and single treatment with NEF (NEF/IPT vs. NEF) and (5) no difference between IPT/PLA and NEF (IPT/PLA vs. NEF). The multilevel analyses were performed for the primary outcome measure (HAMD) as well as for the secondary outcome measures (MADRS and CGI). All participants for whom data were available, whether or not they completed the treatment, were included in the analyses. Before we started the analyses, we examined the distribution of the outcome variables. These could all be considered normal. The general model included both a random slope and a random intercept. This model allows for variation between the persons in intercept (baseline score) and slope (improvement rate). We tested if the development over time was linear or quadratic. For the HAMD and MADRS the development over time was linear. For the CGI, however, the trend was quadratic. To achieve a linear development over time for the CGI, we performed a logarithmic transformation on time [log(time + 1)].

In addition, an analysis was executed comparing remitted and nonremitted participants at endpoint. The participants were defined as remitted when their HAMD score at 12 weeks was ≤ 8. Logistic regression analyses were performed in order to analyze the association of remittance rate with treatment condition correcting for the effect of severity of the depression at baseline (baseline HAMD). The same treatment contrasts were tested as in the multilevel analyses. The logistic regression analyses were performed for the completer sample and the intent to treat sample. All analyses were performed in SPSS, version 13.0. Significance was determined at a 2-tailed p value ≤ 0.05.

Results

Patient Characteristics

Of the 355 eligible participants, 211 were randomized and 193 entered the study (fig. 1). At baseline there were no significant differences among the 4 treatment conditions on any of the sociodemographic or psychiatric variables (table 1).

The participants were defined as dropouts if they discontinued treatment after randomization. The overall dropout rate was 28.5%. There was no difference in

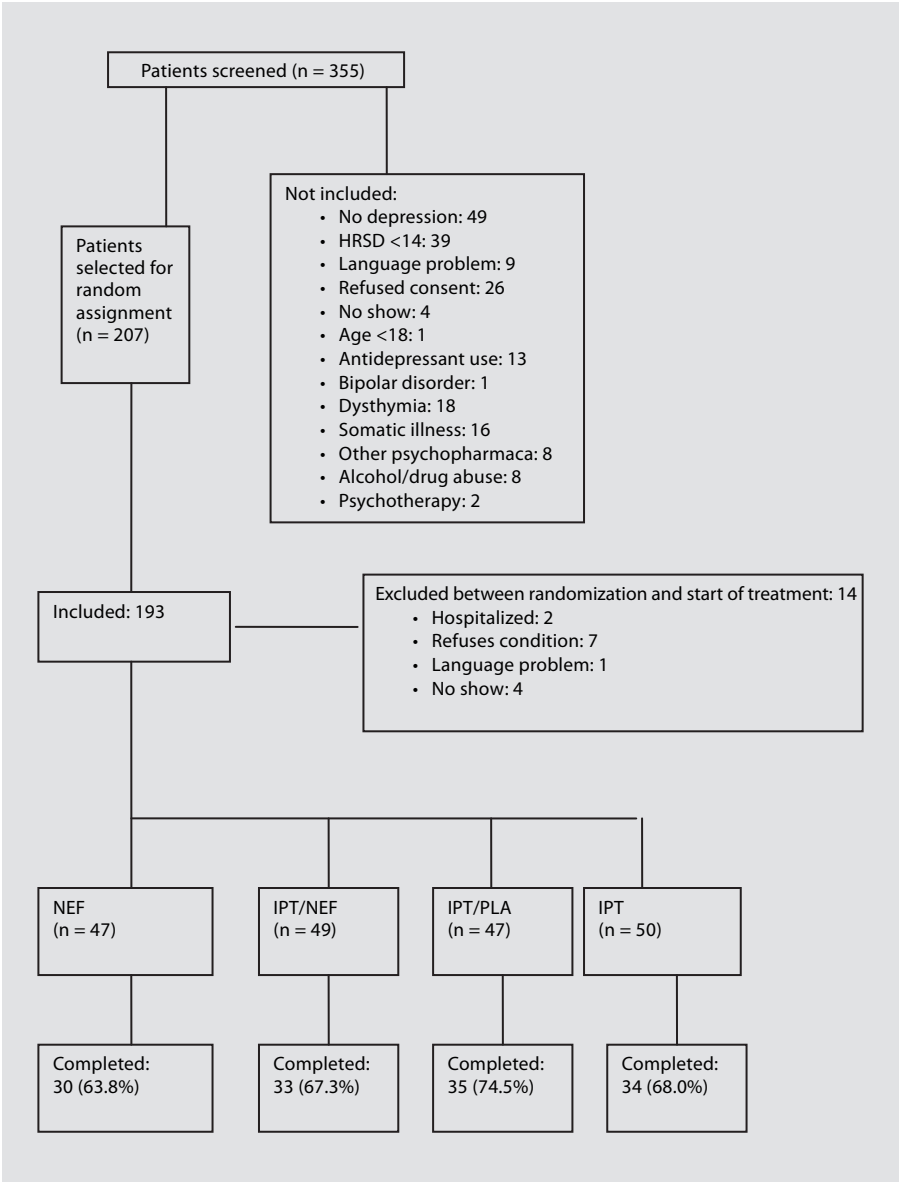

Fig. 1. Randomization and disposition.

dropout among the 4 treatment groups [$\chi^2(3) = 0.810$; $p = 0.847$]. The participants who dropped out did not differ significantly from the completer sample on any of the baseline variables. However, they tended to be more often single [$\chi^2(1) = 3.107$; $p = 0.086$] and from a non-European background [$\chi^2(1) = 4.187$; $p = 0.055$]. Illness-related factors, such as duration and severity of the index episode and number of previous episodes, did not differ between dropouts and completers [$F(1, 178) = 0.003$; $p = 0.956$; $F(1, 190) = 1.069$; $p = 0.302$, respectively $\chi^2(1) = 0.769$; $p = 0.380$). There were no differences between the participants who dropped out after 6 weeks and those who dropped out earlier. Two thirds of the dropouts occurred before 6 weeks of treatment.

Treatment Adherence

The blood levels of the nefazodone group were measured in week 6 and at termination of treatment. Since there is no known dose-response relationship for nefazodone, this measurement was used as an extra check (besides pill count) for compliance. Four participants had a blood level of 0 at week 6, and it must be assumed that these participants did not take the medication. The mean

Table 1. Baseline demographic and clinical characteristics of screened outpatients with MDD (n = 193)

	NEF (n = 47)	NEF/ IPT (n = 49)	IPT/PLA (n = 47)	IPT (n = 50)	χ^2	F	p value
Mean age ± SD, years	40.0 ± 11.4	41.0 ± 10.5	37.7 ± 10.5	41.0 ± 12.2		0.899 (3)	0.443
Female, %	68.1	57.4	55.3	74.0	4.915 (3)		0.178
Mean age at first diagnosis ± SD, years	35.7 ± 12.4	34.7 ± 11.1	34.3 ± 12.3	35.0 ± 12.2		0.116 (3)	0.951
Mean length of index episode ± SD, months	14.4 ± 17.4	10.6 ± 11.3	9.4 ± 8.5	10.3 ± 9.2		1.471 (3)	0.224
First episode, %	71.7	75.0	74.5	75.0	0.177 (3)		0.981
Marital status, % single	46.8	36.2	48.9	44.0	1.785 (3)		0.618
Cultural background, % non-European	23.4	24.5	19.1	10.0	4.152 (3)		0.246
Melancholic features, %	56.5	53.3	56.5	58.7	3.628 (6)		0.727
Mean baseline HRSD ± SD	20.5 ± 4.8	21.9 ± 4.3	21.4 ± 5.3	21.6 ± 4.1		0.838 (3)	0.475
Mean baseline MADRS ± SD	28.3 ± 6.7	31.0 ± 5.5	29.8 ± 6.3	29.5 ± 5.3		1.679 (3)	0.173
Mean CGI at first visit ± SD	4.4 ± 0.8	4.7 ± 0.7	4.7 ± 0.8	4.8 ± 0.9		1.675 (3)	0.174

Figures in parentheses are degrees of freedom.

Table 2. Means, standard deviations (in parentheses) and available number of subjects per condition at 6 and 12 weeks for HAMD and MADRS

	HRSD at 6 weeks	n	HRSD at 12 weeks	n	MADRS at 6 weeks	n	MADRS at 12 weeks	n
NEF	15.6 (6.2)	33	15.1 (7.5)	30	22.8 (8.8)	33	21.9 (9.8)	30
NEF/IPT	17.3 (6.0)	37	13.8 (7.7)	33	22.8 (8.9)	37	18.2 (10.9)	32
IPT/PLA	17.3 (7.0)	42	13.7 (9.1)	35	23.9 (8.9)	42	18.7 (12.3)	34
IPT	18.2 (6.1)	36	14.7 (8.1)	34	25.9 (8.6)	36	19.6 (11.3)	34

prescribed dose in the NEF condition at week 9 was 490.6 mg/day (SD = 76.0), in the NEF/IPT condition the mean prescribed dose was 445.1 mg/day (SD = 81.0). Both dosages are well above the minimal recommended dose of 400 mg. The dosage in both combination conditions was significantly lower compared to the nefazodone only condition in week 9 [F(2) = 4.364; p = 0.015] but not at end of the trial [F(2) = 2.416; p = 0.095]. The mean blood level was 0.84 ng/l (SD = 1.03). We found no relationship between blood level of nefazodone and outcome.

Course over Time and Differences between Treatments

Table 2 shows the raw means and the number of available participants at each time point for the HAMD and MADRS. The results of multilevel regression analyses of the course over time are presented for all available participants (as described in the statistics section). The marital status variable (single vs. nonsingle) and nationality variable (European vs. non-European) were added as covariates in the analyses (because the dropouts tended to differ significantly from the nondropouts on these variables). The main effect of time was highly significant ($p < 0.001$) for the HAMD, MADRS and CGI. This indicated that the overall mean level of depression decreased significantly over time. Both the random intercept and random slope were significant in all multilevel models. This means that there was individual variation in the baseline level of depression and the rate of improvement over time. As table 3 shows, none of the interaction effects of the treatment contrasts with time were significant for the primary outcome measure HAMD. As can be seen in figure 2, only small differences between the treatment conditions in the decrease of depressive symptoms over time were found on HAMD.

For the MADRS a difference between the treatments in improvement over time was found. The participants in

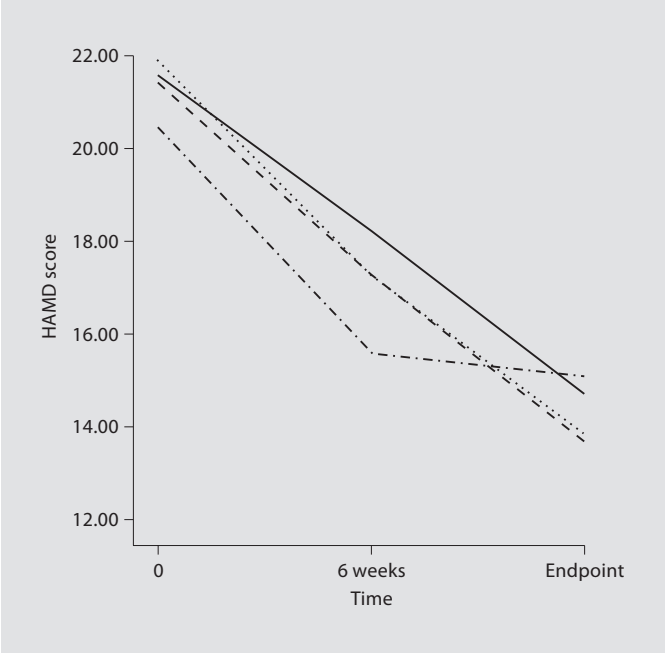

Fig. 2. Scores on the HAMD in time of IPT (———), IPT + NEF (· · · · · ·), IPT + PLA (– – – –) and NEF (– · – · –).

the NEF condition improved much less than the participants in the NEF/IPT condition (table 3 and fig. 3). Figures 2 and 3 show that the course over time for the NEF condition was different from the other conditions from 6 to 12 weeks. While the other conditions continued to improve from 6 to 12 weeks, the NEF condition showed only a very small improvement. For the CGI a significant difference in the development over time was found between the single treatments IPT and NEF in favor of IPT (p = 0.035).

Remittance

Remittance rates (HAMD ≤8 at end of trial) were overall 19.3% in the intent to treat sample and 26.5% in the completer sample. Logistic regression analysis using baseline HAMD and the treatment contrasts as predictors of remittance rate showed that the combination of NEF/IPT was more effective than NEF [for the intent to treat sample: adjusted OR (95% CI) = 3.22 (1.02–10.12), p = 0.045; and for the completer sample: adjusted OR (95% CI) = 3.10 (0.87–11.07), p = .081]. Receiving the NEF/IPT treatment increased the odds of being remitted

Table 3. Results of 2 multilevel regression analyses for the HAMD and the MADRS

Effect	First set of contrasts			Second set of contrasts		
	estimate	SE	p	estimate	SE	p
HAMD						
Overall baseline value (intercept)	18.53	1.63	<0.001	16.62	1.70	<0.001
Overall improvement rate (time)	–3.43	0.63	<0.001	–3.02	0.67	<0.001
Differences in improvement rates						
NEF vs. IPT	0.40	0.92	0.661			
NEF/IPT vs. IPT	–0.50	0.91	0.583			
IPT/PLA vs. IPT	–0.20	0.88	0.824			
IPT vs. NEF				–0.40	0.92	0.661
NEF/IPT vs. NEF				–0.90	0.93	0.333
IPT/PLA vs. NEF				–0.60	0.90	0.506
MADRS						
Overall baseline value (intercept)	26.12	2.16	<0.001	24.12	2.24	<0.001
Overall improvement rate (time)	–4.83	0.85	<0.001	–3.65	0.89	<0.001
Differences in improvement rates						
NEF vs. IPT	1.18	1.23	0.339			
NEF/IPT vs. IPT	–1.67	1.22	0.175			
IPT/PLA vs. IPT	–0.56	1.18	0.639			
IPT vs. NEF				–1.18	1.23	0.339
NEF/IPT vs. NEF				–2.85	1.25	0.024
IPT/PLA vs. NEF				–1.73	1.21	0.154

The parameter estimates are adjusted for the effects of marital status and cultural background. SE = Standard error.

by a factor of 3.22 and 3.10, respectively, compared with receiving the NEF treatment only. There was a trend for IPT/PLA to be more effective than NEF [adjusted OR (95% CI) = 2.64 (.84–8.23), p = 0.096, in the intent to treat sample]. All other treatment contrasts did not differ significantly ($p > 0.10$).

Discussion

This study was designed to detect a possible advantage of the combination of psychotherapy and medication over single treatment in MDD. We did not find any difference between the 4 conditions on the HAMD, our primary outcome measure. However, on the MADRS we found an advantage of the combination of IPT with nefazodone over nefazodone but not over psychotherapy alone. Looking at remittance rate (HAMD ≥8), again NEF/IPT was more effective compared to NEF. After 6 weeks almost no improvement occurred in the NEF condition (fig. 3), whereas all other conditions showed further improvement. Although we defined the HAMD as primary outcome measure, findings with the MADRS deserve consideration, especially since the HAMD has increasingly come under fire [34, 35]. Amongst other criticisms it is claimed that the HAMD is biased in favor of somatic symptoms, making it a less appropriate measure for psychotherapy research. With the CGI we found IPT to be more effective compared to nefazodone alone, but as the CGI may be more vulnerable to bias [18], this finding may be less generalizable.

When comparing our study to that of Keller et al. [15], who used a very similar design (although without inclusion of a pill-placebo + psychotherapy condition) in the treatment of chronic depressed patients, a number of important differences emerge. The outcome was much better altogether in the Keller et al. study, and there was a clear advantage for the combination of psychotherapy and medication over both conditions alone. The reasons for this difference could be several.

First, in all 3 arms of the Keller et al. study, the time spent with the participants was considerably more than in our study: the participants in the psychotherapy conditions were seen twice weekly and in the pharmacotherapy arms once weekly. Since the Keller et al. study did not have a psychotherapy + pill-placebo arm, it cannot be ruled out that the advantage for the combination treatment in the Keller et al. study was due to increased time in therapy, as has been suggested by others [36].

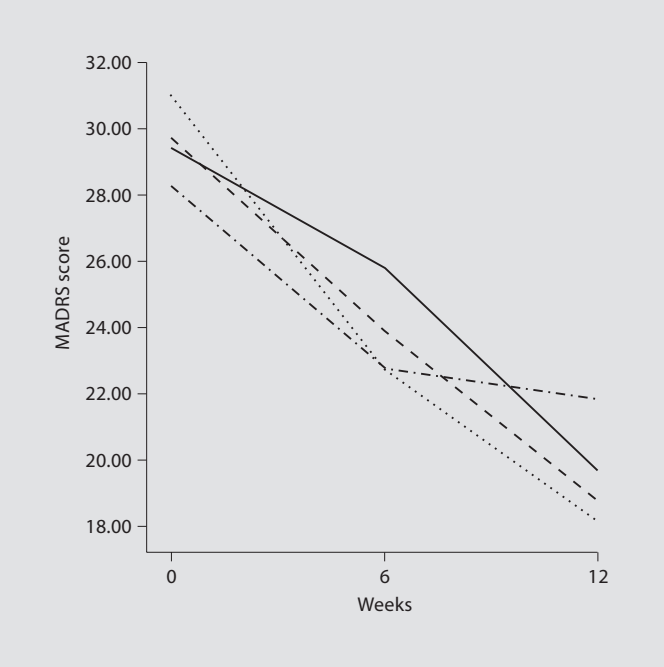

Fig. 3. Scores on the MADRS in time of IPT (———), IPT + NEF (· · · · ·), IPT + PLA (– – – –) and NEF (– · – · –).

Secondly, CBASP, especially 'designed' for the treatment of chronic depression, could of course have greater efficacy than IPT, but in view of the other differences between the study of Keller et al. and ours this may be a premature conclusion.

Finally, in our study the participants were referred for treatment and were more or less 'standard' participants as seen in secondary care centers. The participants in the Keller et al. study were recruited via advertisements. The severity of depressive symptoms could also play a role, but this is difficult to determine, since the Keller et al study uses the 24-item HAMD, whereas in our study the 17-item version was used.

In this study nefazodone was chosen because of its relatively mild side effect profile. At the time of the start of our trial nefazodone was thought of as a safe drug. Since several studies have reported hepatotoxicity of nefazodone [37], it has been withdrawn in several countries including the Netherlands. In the USA the use of nefazodone is restricted. However, because it has been used in other clinical trials on combination treatment [15] the use of nefazodone in this study allows comparison of treatment results across studies.

Major strengths of our study were the inclusion of a psychotherapy-pill-placebo condition, the measurement of blood levels as an extra check for compliance and the fairly large number of participants included. However, there are also several limitations to this study, which have to be acknowledged.

An overall dropout rate of around 30% negatively affects the generalizability of our results. However, this percentage probably reflects the dropout rate found in many outpatient practices and is not very different from similar studies in this field [12].

To conclude, our findings suggest that in clinical practice, combination therapy should only be considered if IPT is added to medication and not the other way round. Combination treatment offers no advantage over psychotherapy alone in the present study.

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