Treatment of Post-Myocardial Infarction Depressive Disorder: A Randomized, Placebo-Controlled Trial With Mirtazapine

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Objective: To examine the antidepressant efficacy of a dual-acting antidepressant (mirtazapine) in patients with post-myocardial infarction (MI) depressive disorder. Antidepressants used in post MI trials with a randomized, double-blind, placebo-controlled design have been restricted to selective serotonin reuptake inhibitors (SSRIs). Antidepressant effects have been limited. **Methods:** In a prospective multicenter study, 2177 patients with MI were evaluated for depressive disorder during the first year post MI. Ninety-one patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for major or minor depressive disorder were randomized to a 24-week, double-blind, placebo-controlled trial. Antidepressant efficacy was tested using last-observation-carried-forward procedure and repeated measurements analysis using the SPPS mixed models approach, with as primary outcome reduction in depressive symptomatology on the 17-item Hamilton-Depression Rating Scale (Ham-D), and secondary outcomes the Beck Depression Inventory (BDI) and depression subscale of the Symptom Check List 90 items (dSCL-90) as well as the Clinical Global Impression (CGI) scale. **Results:** Using the "last observation carried forward" (LOCF) method, mirtazapine did not show to be superior to placebo on the Ham-D, but did on the BDI, dSCL-90, and CGI scale over the acute treatment phase of 8 weeks ($n = 91$). Using mixed models analysis over the entire 24 weeks of treatment ($n = 40$), we did find a significant difference favoring mirtazapine to placebo on the Ham-D, BDI, and CGI, but on the dSCL-90, this difference was not significant. **Conclusions:** This trial shows efficacy of mirtazapine on primary and secondary depression measures. Mirtazapine seems to be safe in the treatment of post-MI depression. **Key words:** post myocardial infarction, depressive disorder, antidepressive treatment, mirtazapine.

MI = myocardial infarction; **RCT** = randomized controlled trial; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders; **CAD** = coronary artery disease; **SSRI** = selective serotonin reuptake inhibitors; **TCA** = tricyclic antidepressant; **Ham-D** = Hamilton-Depression Rating Scale; **BDI** = Beck Depression Inventory; **CGI** = Clinical Global Impression; **dSCL-90** = Symptom Check List 90 items, depression subscale; **SES** = standardized effect size.

INTRODUCTION

About 20% of post myocardial infarction (MI) patients experience a major depressive episode and an equal percentage experience a minor depressive episode in the first year post MI (1,2). Recent data suggest that minor depressive disorder is not evanescent, and may occur independent of, or in the course of, a major depressive disorder (3,4). Both major and minor depressive disorders post MI are associated with an increased risk of all-cause mortality, cardiac mortality, and new cardiovascular events (2). Also, post-MI depressive disorder predicts slow recovery and poor quality of life (5–9). Treatment refractoriness of major and minor depressive disorders is associated with increased risk for mortality after the first 6 months post MI (10).

Up to now, the efficacy of psychotherapeutic or antidepressant treatments in published randomized placebo or care as usual controlled trials in post-MI depressive disorder has been limited.

Three randomized controlled trials (RCTs) that did show at least some beneficial and statistically significant change on affective outcome parameters only included patients fulfilling the current Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for major depressive disorder, but the efficacy results are not convincing; one study showed superiority of an antidepressant over placebo on a global assessment scale (11,12) and one on hostility (13).

In a recent study in patients with coronary artery disease (CAD) and major depression, the efficacy of a selective serotonin reuptake inhibitor (SSRI), citalopram, was found to be superior to placebo in reducing 12-week Hamilton-Depression Rating Scale (Ham-D) scores (14). However, the outcome of this study, positive as it is, refers to a different population of patients with moderate-to-severe depression at late stage after hospitalization for cardiac reasons (range = 3 weeks to 31 years; median = 18.9 months).

The choice of antidepressant drug class may well be related to efficacy, as all published placebo-controlled RCTs in post-MI depressive disorder only involved SSRIs. SSRIs are preferred because of the relative cardiotoxicity of tricyclic antidepressants (TCAs). One might postulate that a noncardiotoxic antidepressant with both serotonergic and noradrenergic properties might be more efficacious than an SSRI in depressive disorder in the physically ill. In a comparative study of an SSRI and a TCA in depressed patients with CAD, both were found to be effective (15). However, adverse cardiac events occurred more often in the patients treated with a TCA.

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Using an RCT design, the newer dual-acting antidepressants have not yet been studied in depressed patients with CAD. In an open study, mirtazapine, a nontricyclic antidepressant with presynaptic α_2-antagonist properties, which enhance both noradrenergic and serotonergic neurotransmission, is well tolerated and showed no cardiotoxic effects in cardiovascular compromised patients (16).

Accordingly, we conducted a placebo-controlled RCT with mirtazapine in patients with a major and minor depressive disorder post MI. Patients could not be included during the first 3 months post MI to rule out transient adjustment disorder with depressed mood directly related to the MI. Subjects were included between 3 to 12 months post acute MI and were free of other life-threatening medical conditions. The selected patients had to fulfill the criteria for DSM-IV major or minor depressive disorder. In a 24-week trial, the primary objectives were to evaluate the safety and efficacy of mirtazapine treatment of major or major and minor depressive disorder post MI.

METHOD

The intervention study is a multicenter, randomized, placebo-controlled trial, "nested" (nested RCT) in the Myocardial Infarction and Depression-Intervention Trial (MIND-IT) (17). The MIND-IT study is designed to evaluate the effect of psychiatric treatment versus "care as usual" in patients with a post-MI depressive disorder on the combined time-related incidence of cardiac events over an average 27-month follow-up period. More specifically, for this study, only the data on patients in the psychiatric treatment arm were evaluated. Data on "care as usual" patients were not part of this study.

The Institutional Review Board at each clinical center approved the study protocol, and study patients provided written informed consent before enrollment.

Subjects

The MIND-IT study was conducted at the academic hospital of Maastricht, Amsterdam, Groningen, and seven general hospitals. Patients hospitalized with an MI were included in the study. The inclusion criteria were a) age >18 years; b) signed informed consent for study; c) a clinical picture typical for MI; d) an increase of cardiac enzymes: elevation of CK-MB of more than once the upper normal range and CK-MB/CK ratio above the local normal limit, or in case CK-MB not available, elevation of total CK of twice the upper limit range; e) electrocardiographic (ECG) changes: new significant Q waves in at least 2 of 12 leads or new in V1 with R/S ratio >1; and/or g) chest pain for >20 minutes of new or markedly increased chest pain. Exclusion criteria were a) occurrence of MI while hospitalized for another reason, except for unstable angina pectoris; b) lacking capability to participate in study procedures; c) any disease likely to influence short-term survival; d) already receiving psychiatric treatment for depressive disorder; and e) participation in any clinical trial that might intervene with the study.

Patients were screened for depressive symptoms 0, 3, 6, 9, and 12 months after MI using the Beck Depression Inventory (BDI). A trained research assistant evaluated patients scoring above the cut-off on the BDI (≥10 for both men and women), which is found to be optimal in this population (18). In case of a BDI score of ≥10, patients were invited for a standardized psychiatric interview (Composite International Diagnostic Interview, CIDI) (19). Patients diagnosed with a post-MI depressive episode were randomized to the intervention or "care as usual" group. Patients scoring below the BDI cut-off continued to be screened for depressive symptoms.

Patients randomized to intervention could only be included in the pharmacological intervention in case a psychiatrist confirmed the CIDI-research diagnosis. Exclusion criteria involved other psychiatric treatment, including psychotherapy, hypothyroidism, and suicidality. After confirmation by the psychiatrist, the first treatment option offered to patients was the double-blind, placebo-controlled treatment with mirtazapine. The use of an RCT design worked two-fold: a) the safety and effects of mirtazapine in this population could be assessed; and b) the effect of psychiatric intervention on the cardiac prognosis in post-MI depressed patients could be evaluated with both pharmacotherapy and psychological support as separate factors.

TABLE 1. Baseline Characteristics of Included Versus Excluded Patients

Characteristic	Included in Nested Study (n = 84)	Not Included in Nested Study (n = 121)	p^a
Gender			
Male	86.9%	65.5%	
Female	13.1%	33.1%	.001
Age	59.16 ± 11.71	57.30 ± 10.55	.247
ASAT	210.0 ± 186.38	191.53 ± 156.76	.476
CPK	1702.40 ± 1665.36	1622.43 ± 2067.08	.787
Killip			.226
Class 1	84.9%	89.3%	
Class 2	9.2%	9.5%	
Class 3	3.4%	1.2%	
Class 4	2.5%	2.5%	
LVEF			.531
>60%	15.0%	13.5%	
45%–60%	47.5%	40.4%	
30%–45%	25.0%	26.0%	
<30%	12.5%	20.0%	

ASAT = Aspartate Aminotranspherase; CPK = Creative Phosphokinase; LVEF = Left Ventricular Ejection Fraction.
Values for all characteristics except for gender, Killip, and LVEF are mean ± standard deviation.
[a] Baseline differences between both groups where not statistically significant, except for gender.

Subjects were recruited from November 1999 to November 2002. A total of 4780 subjects were assessed for eligibility, of which 2177 (46%) patients met the inclusion criteria and agreed to participate. During the screening period of 1 year post hospitalization for the index MI, 375 patients fulfilled the research diagnosis of depressive episode. From these patients, 28 were excluded due to suicide risk and 16 due to end of randomization date. In total, 331 patients were randomized (2:1, to meet the required sample sizes): 209 to the intervention group and 122 to the "care as usual" arm. Of those 209 patients, 37 refused to visit a psychiatrist, nine patients were excluded due to start of antidepressant treatment by general practitioner; in 28 patients, a diagnosis of depressive disorder could not be confirmed by the psychiatrist and 41 patients refused participation. Three patients initially started in the nested study but dropped out after the baseline visit. Of these 108 excluded patients, depressive symptom profile and somatic characteristics did not differ from the 91 patients, who were included in the nested study. Significantly more women were excluded (Table 1). This finding is consistent with other trials (1). Eventually, 91 patients were included in the nested RCT, having a diagnosis of DSM-IV depressive disorder, confirmed by the psychiatrist. Of these, 44 patients (39 major depressive disorder, 5 minor depressive disorder) were randomized to placebo and 47 (41 major depressive disorder, 6 minor depressive disorder) were randomized to mirtazapine (Figure 1).

Intervention

The efficacy of mirtazapine was studied using a double-blind, placebo-controlled design. Patients were randomly assigned to receive either mirtazapine or placebo. The antidepressant was prescribed for a maximum period of 24 weeks, divided in an acute treatment period of 8 weeks and a continuation treatment period of 16 weeks. Pills contained either 15 mg of mirtazapine or matching placebo. Two pills were prescribed on days 1 to 14 in the acute treatment phase. In case of severe side effects, the dose could be lowered to 1 pill, i.e., 15 mg/day. If the clinical response was insufficient (i.e., the reduction of the Ham-D total score less than 50% as compared with baseline),

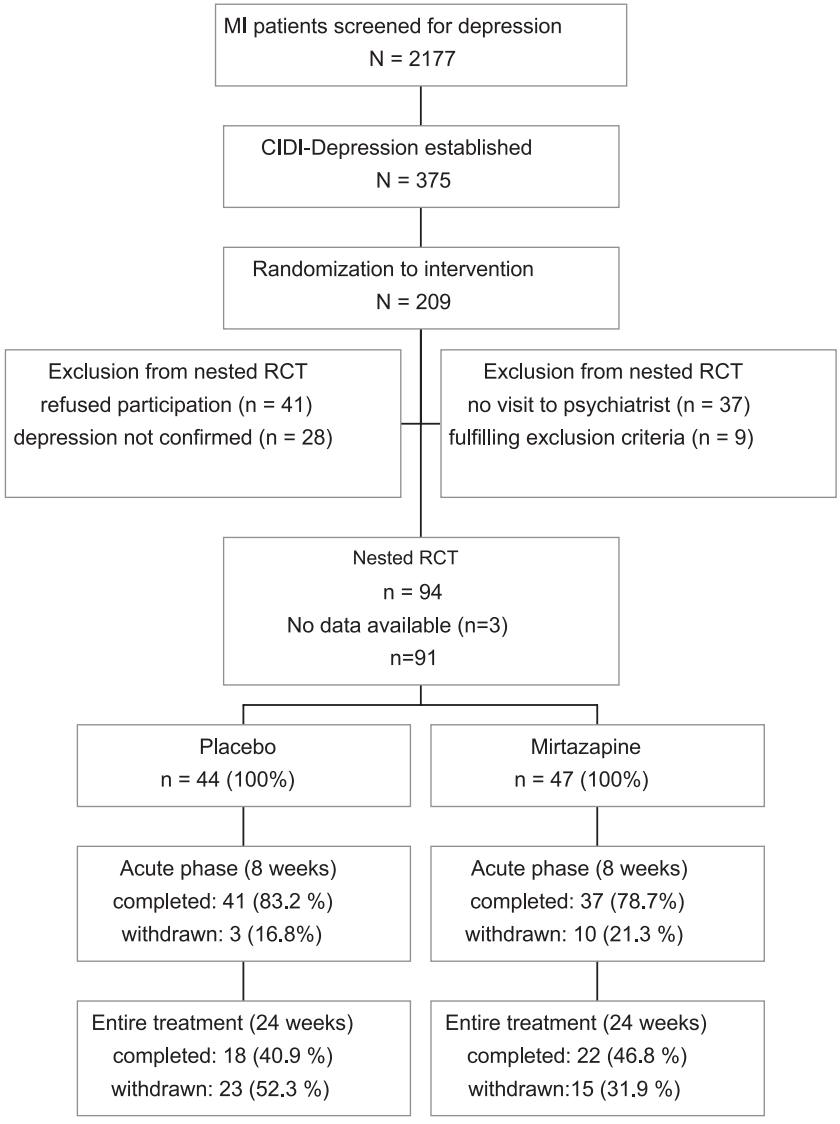

Figure 1. Flow chart of the intervention trial. CIDI = Composite International Diagnostic Overview; MI = myocardial infarction; RCT = randomized, controlled trial.

the investigator could decide to increase the daily dose by one additional tablet, i.e., 45 mg/day. If response was sufficient, the same dosage was given until the end of the study (day 168). Tapering down of study medication followed at the end of the trial.

The oral daily dose (30 to 45 mg) of the study drug was prescribed as single night-time dose (i.e., 30–60 minutes before bedtime). The first dose of study medication had to be taken in the evening of day 1 of treatment. At every visit, drug accountability was assessed. In case of noncompliance, patients were withdrawn from the trial.

Efficacy of mirtazapine was measured for the acute phase (8 weeks, $n = 78$) and the entire treatment phase (24 weeks, $n = 40$). Responders were defined as patients with a reduction of at least 50% on the 17-item Ham-D score (20) or a Ham-D score ≤ 9. Remission was defined as Ham-D score ≤ 7.

Data Collection

In the first visit to the psychiatrist (week 1), the in-/exclusion criteria for treatment were evaluated. The assessment included a DSM-IV checklist for depressive disorders, medical history taking on relevant somatic and psychiatric disorders, and pretrial medication. Laboratory screening involved electrolytes, blood cells, and thyroid function. Further vital signs such as blood pressure, heart rate, body weight, and height were measured.

During the trial, seven visits were scheduled at baseline, 1, 2, 4, 8, 16, and 24 weeks after randomization. Depression, adverse events, side effects, concurrent medication, vital signs, and Clinical Global Impression (CGI) scale were assessed every visit. Depression severity was assessed using the Ham-D. All psychiatrists were trained in assessing the Ham-D to enhance rating quality. Secondary outcome was measured with the BDI and the depression scale of the Symptom Check List 90 items (dSCL-90) (21). The CGI was used to evaluate global clinical impression and improvement.

To determine safety of treatment, ECG variables were used. Twelve lead ECG variables were heart rate, PR interval, QRS interval, and QT interval. These measures were assessed at baseline, 8, and 24 weeks.

As an extra compliance monitoring, in the second week of drug treatment, a blood sample was taken for measurement of mirtazapine level. The analyses of these data were not done until all patients had finished the trial, to prevent the risk of deblinding before the trial ended.

Of the 47 patients randomized to mirtazapine, a blood sample was taken on 33 patients. Of 14 patients, the blood sample data were not available due to drop out of treatment before sampling ($n = 9$) or missing ($n = 5$). A plasma level of mirtazapine ≥ 0.5 ng/ml (standard deviation (SD) = 17.98) was detectable in all patients allocated to mirtazapine from whom a blood sample had been obtained.

Statistical Analyses

To estimate the required sample size, the method of Knapp and Miller (22) was used. In the absence of previous outcome data, these guidelines recommend to estimate the SD by dividing the range of values of the response variable by 6. The mean range of the Ham-D 17 item is 26. An effect size of 2.5-point difference between the mirtazapine and placebo group and a statistically significant difference in response rate was expected a priori. When the level of significance α is set at 0.05, the power β at 0.80, and the hypotheses are tested two tailed, the required sample size is 89.

For statistical analyses, SPSS (SPSS Inc, Chicago, IL) for Windows 11.0 software (Microsoft Corp, Redmond, WA) was applied. Efficacy outcome was analyzed on an intention-to-treat basis and so 91 patients who received medication (mirtazapine or placebo) were analyzed. For patients not completing the entire trial, the "last observation carried forward" (LOCF) technique was used. Before carrying out parametric analysis, dependent variables were checked for normality (skewness/kurtosis) and the presence of outlying values, thereby following the lines described by Hair and associates (23).

GLM repeated measures were used to analyze the standardized effect size (SES) of mirtazapine in comparison to placebo.

In addition, we applied a repeated measurements analysis using the SPSS mixed models approach; outcomes were assessed repeatedly during follow-up (1, 2, 4, 8, 16, and 24 weeks post randomization for Ham-D; 8 and 24 weeks post randomization for BDI and dSCL-90). Optimal use is made of the available data at the repeated assessments, which are clustered within subjects. We developed mixed models consisting of treatment allocation as a factor, and the corresponding baseline variable and timing of the assessment as covariates.

RESULTS

There were no statistically significant baseline differences between the mirtazapine and placebo groups in age, gender, size of MI (using maximum ASAT), and cardiac status (using Killip Class) (Table 2). During the first 8-week acute treatment phase, 10 patients from the mirtazapine group and 3 from the placebo group dropped out, which is significant ($\chi^2 = 4.80$; $df = 1$; $p = .03$).

TABLE 2. Baseline Characteristics of Included Patients

Characteristic	Mirtazapine Group ($n = 47$)	Placebo Group ($n = 44$)	p^a
Gender			
Male	87.2%	81.8%	
Female	12.8%	18.2%	.34
Age	56.6 ± 11.1	57.9 ± 9.7	.54
ASAT	201.8 ± 156.9	198.2 ± 178.2	.92
CPK	1700.2 ± 1530.8	1757.0 ± 1773.8	.88
Ham-D	18.6 ± 5.2	16.8 ± 3.6	.05
Heart rate	63 ± 11.9	62.8 ± 12.9	.94
Killip			
Class 1	91.5%	86.4%	
Class 2	6.4%	11.4%	
Class 3	2.1%	0%	
Class 4	0%	2.3%	.75
LVEF			
>60%	13.0%	15.4%	
45%–60%	41.3%	51.3%	
30%–45%	28.3%	23.1%	
<30%	17.4%	10.3%	.45
PR interval (ms)	162.7 ± 31.2	159.8 ± 43.7	.72
QRS interval	93.2 ± 19.1	93.1 ± 26.8	.97
QT interval	404.9 ± 30.3	386.5 ± 90.7	.23

ASAT = Aspartate Aminotranspherase; CPK = Creative Phosphokinase; Ham-D = Hamilton-Depression Rating Scale; LVEF = Left Ventricular Ejection Fraction.

Values for all characteristics except for gender, Killip, and LVEF are mean ± standard deviation.

[a] Baseline differences between both groups where not statistically significant, except for Ham-D.

Concurrent Medication

Medications used concurrently were acetylsalicylic acid ($n = 76$; 92.7%), acenocoumarol ($n = 5$; 5.4%), nitrate ($n = 34$; 37%), β-blocking agents ($n = 71$; 86.6%), calcium-antagonists ($n = 18$; 22%), digoxin ($n = 1$; 1.2%), diuretics ($n = 11$; 12%), ACE-inhibitors ($n = 26$; 31.7%), AII-antagonists ($n = 5$; 6.1%), and statins ($n = 70$; 76.1%). The median number of cardiovascular drugs taken was 4 (range = 2–7). Overall, there was no difference in specific drugs between groups ($p = .71$). However, in those receiving mirtazapine, ACE-inhibitors were significantly more frequently prescribed ($p = .05$). β blockers were prescribed significantly more frequently ($p = .03$) to patients receiving placebo.

Efficacy During the Acute Phase

The mean Ham-D score in the acute phase (8 weeks) decreased 7.29 points (SES = 1.30) in the mirtazapine group and 5.31 points (SES = 0.96) in the placebo group. At baseline, there was a difference of 1.85 points on the Ham-D scale, the mirtazapine group showing a higher score. After correcting for baseline difference in depression scores, the difference of 1.98 points between both groups was not statistically significant ($F = 2.86$; $df = 1$; $p = .09$). Twenty-seven patients in the mirtazapine group ($n = 47$) and 18 patients in the placebo group ($n = 44$) were responders. This difference was not statistically significant ($\chi^2 = .78$; $df = 1$; $p = .18$). Sixteen patients taking mirtazapine showed remission (Ham-D score ≤ 7) in comparison to seven patients taking placebo. This difference was not significant ($\chi^2 = 3.17$; $df = 1$; $p = .08$) (Table 4).

The mean BDI score during the acute phase decreased 4.6 points (SES = 0.68) for the mirtazapine group and 1.72 points (SES = 0.39) for the placebo group. This difference was statistically significant ($F = 5.51$; $df = 1$; $p = .02$).

The mean dSCL-90 depression score for the mirtazapine group decreased with 6.6 points (SES = 0.67). The depression score for the placebo group decreased 2.23 points (SES = 0.38). The difference between the mirtazapine and placebo group was statistically significant ($F = 6.48$; $df = 1$; $p = .01$).

The CGI severity during the first 8 weeks decreased 1.41 points (SES = 1.69) for the mirtazapine group and 0.72 points (SES = 0.89) for the placebo group. This difference was statistically significant ($F = 6.67$; $df = 1$; $p = .012$) The CGI improvement score decreased for subjects receiving mirtazapine 1.03 points (SES = 1.34) during the acute phase and 0.45 points (SES = 0.51) for subjects receiving placebo. This difference was not significant ($F = 3.65$; $df = 1$; $p = .06$).

Efficacy During the Entire Treatment Phase

From baseline to week 24, the Ham-D score decreased 8.0 points (SES = 1.21) for the mirtazapine group and 5.56 points

TABLE 3. Scores on the Depressive Symptom Rating Scales and Clinical Global Impression Scale During the Entire Trial Using LOCF and Mixed Models

Week	0	1	2	4	8	16	24	mm[a]
Mean Ham-D score								
Mirtazapine	18.66	15.82	13.68	12.23	11.37	11.15	10.66	10.38
Placebo	16.81	14.22	13.35	11.91	11.50	10.99	11.25	11.77
Mean BDI score								
Mirtazapine	14.61				10.01		9.79	9.68
Placebo	13.44				11.72		11.47	12.29
dSCL-90 score (depression scale)								
Mirtazapine	34.32				27.72		27.41	23.70
Placebo	30.29				28.06		28.47	26.00
Mean CGI score								
Mirtazapine	4.0	3.73	3.34	3.07	2.59	2.59	2.50	2.79
Placebo	3.79	3.53	3.44	3.07	3.07	2.95	2.91	3.06

LOCT = "last observation carried forward"; BDI = Beck Depression Inventory; dSCL-90 = Symptom Check List 90 items, depression subscale; CGI = Clinical Global Impression.

[a] Overall follow-up means based on mixed models.

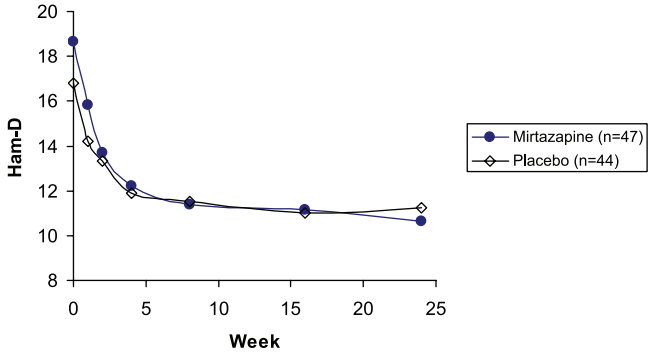

Figure 2. Effects of mirtazapine versus placebo in post-myocardial infarction depressive disorder, measured with Hamilton-Depression Rating Scale (Ham-D 17) (entire treatment phase).

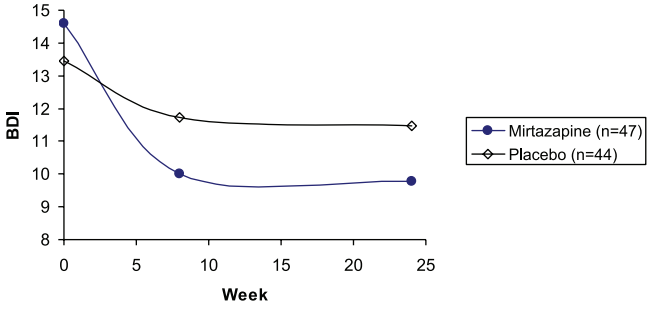

Figure 3. Effects of mirtazapine versus placebo in post-myocardial infarction (MI) depressive disorder, measured with Beck Depression Inventory (BDI) (entire treatment phase).

(SES = 0.78) for the placebo group. This difference of 2.44 points was not significant ($F = 1.11$; $df = 1$; $p = .36$). Over the entire treatment phase, 23 patients receiving mirtazapine and 17 receiving placebo responded. A χ^2 test showed no significant difference ($p = .22$). Twenty patients taking mirtazapine showed remission (Ham-D score of <7), compared with 15 patients taking placebo. This difference was not significant ($p = .27$).

Mean BDI scores showed a trend toward a decrease ($F = 2.73$; $df = 1$; $p = .07$) for the mirtazapine (4.82 points; SES = 0.64) and placebo group (1.97 points; SES = 0.36).

TABLE 4. Difference in SES Using LOCF and Mixed Models Analyses

Scale	Mirtazapine	Placebo	Difference in SES	*p*
Mirtazapine versus placebo (8 weeks) using LOCF				
Ham-D	1.30	0.96	0.34	.09
BDI	0.68	0.39	0.28	.02
dSCL-90	0.67	0.38	0.33	.01
CGI	1.69	0.72	0.97	.01
Mirtazapine versus placebo (24 weeks) using LOCF				
Ham-D	1.21	0.78	0.43	.36
BDI	0.64	0.36	0.28	.07
dSCL-90	0.65	0.32	0.33	.02
CGI	1.80	1.09	0.71	.05
Mirtazapine versus placebo (24 weeks) using mixed models				
Ham-D	1.60	1.40	0.20	.003
BDI	0.73	0.15	0.58	.05
dSCL-90	1.08	0.73	0.35	.11
CGI	1.45	0.90	0.55	.007

SES = standardized effect size; LOCF = "last observation carried forward" method; Ham-D = Hamilton-Depression Rating Scale; BDI = Beck Depression Inventory; dSCL-90 = Symptom Check List 90 items, depression subscale; CGI = Clinical Global Impression.

The mean dSCL-90 depression scores over 24 weeks decreased 6.91 points (SES = 0.65) for the mirtazapine and 1.82 points (SES = 0.32) for the placebo group. Comparable with the acute phase, this difference was found to be significant ($F = 3.88$; $df = 1$; $p = .02$).

The CGI severity during the entire treatment decreased 1.5 points (SES = 1.80) for the mirtazapine group and 0.88 points (SES = 1.09) for the placebo group. This difference was significant ($F = 3.87$; $df = 1$; $p = .05$) The CGI improvement score decreased for subjects receiving mirtazapine 1.03 (SES = 1.34) points during the entire treatment phase and 0.42 points (SES = 0.47) for subjects receiving placebo. This difference was not statistically significant ($F = 3.27$; $df = 1$; $p = .074$) (Table 3 and Figures 2 and 3).

Mixed models analysis revealed a significant difference of 3.24 points on the Ham-D ($F = 9.039$; $p = .003$) favoring mirtazapine to placebo, controlling for baseline Ham-D and timing of the outcome assessment. The estimated Ham-D follow-up means were 10.38 (standard error 0.33) for patients receiving mirtazapine and 11.77 (standard error 0.33) for patients receiving placebo.

This analysis also showed a significant difference on the BDI ($F = 4.026$; $p = .05$) favoring mirtazapine to placebo, controlling for baseline Ham-D and timing of the outcome assessment. The estimated BDI follow-up means were 9.68 (s.e. 0.89) for patients receiving mirtazapine and 12.29 (s.e. 0.94) for patients receiving placebo.

Using mixed models analysis, however, there was only a nonsignificant difference on the dSCL-90 depression score ($F = 2.6$; $p = .11$) controlling for baseline Ham-D and timing of the outcome assessment. The estimated dSCL-90 depression follow-up means were 23.7 for patients receiving mirtazapine and 26.0 for patients receiving placebo.

Mixed models shows a significant difference on the CGI ($F = 7.4$; $p = .007$). Follow-up means were 2.79 in patients receiving mirtazapine and 3.06 in patients receiving placebo.

In our study, treatment effects did not differ when controlled for history of depression (acute phase: $F = 3.9$; $df = 1$; $p = .052$; entire treatment phase: $F = 2.01$; $df = 1$; $p = .16$).

Adverse Effects and Events During the Entire Treatment

Patients from both the mirtazapine ($n = 47$) and placebo groups ($n = 44$) reported adverse effects. Most reported complaints were fatigue, appetite changes, dizziness, and headache. These adverse events are comparable with adverse events reported for mirtazapine in psychopharmacological manuals. Serious adverse events reported were heart failure ($n = 1$), angina pectoris ($n = 1$), and atrial fibrillation ($n = 1$) in the mirtazapine group and angina pectoris ($n = 1$) in the placebo group. No patients were excluded from the study because of cancer, drug overdose, or death during the study. Reasons for hospitalization were unstable angina pectoris, shortness of breath, palpitations, and revascularization (coronary angioplasty or bypass surgery). Number of hospitalizations was 10 in the placebo group and 8 in the mirtazapine group, which was not statistically significant ($p = .34$) (Table 5).

TABLE 5. Number of Adverse Events and Hospitalization of Mirtazapine Versus Placebo

Adverse Effect	Mirtazapine Group ($n = 47$)	Placebo Group ($n = 44$)	p
Fatigue	21	9	.02
Appetite changes	13	3	.02
Dizziness	5	8	.31
Headache	7	2	.61
Other	69	67	
Hospitalization	8	10	.34

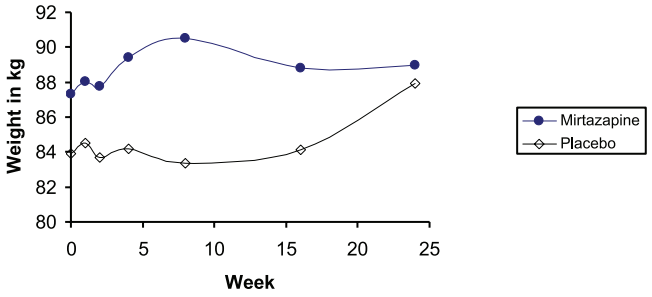

Figure 4. Weight curves mirtazapine versus placebo.

Blood pressure and heart rate did not differ between the two groups. Mirtazapine increased the mean weight by 1.7 kg ($p < .0001$) within the first 8 weeks; in the placebo group, the weight did not change significantly; there was a slight decrease at 16 weeks (Figure 4).

Adverse Cardiovascular Effects

The ECG variables heart rate, PR duration, QRS duration, and QT_c interval did not show any significant changes during the treatment phase.

DISCUSSION

This trial, embedded in the MIND-IT study, is, to our knowledge, the first randomized, placebo-controlled trial on the efficacy of a novel dual-acting antidepressant (mirtazapine) compared with placebo in patients with post-MI minor and major depressive disorder. Randomization resulted in comparability of both groups as far as demographic data, physical health status, number of major and minor depression diagnoses, severity of MI, and somatic characteristics are concerned. At baseline, there was a difference of 1.85 points on the Ham-D scale, the mirtazapine group showing a higher score.

In this study, the primary measure used to compute effect sizes was Ham-D. Using LOCF statistical procedures after correcting for baseline differences in Ham-D, we did not find statistically significant changes in the Ham-D scores at 8 and 24 weeks of treatment (primary outcome measure). On secondary measures, however, we did find statistically significant improvement on self-report rating scales (BDI 21-item, depression subscale of the dSCL-90, and CGI). Mirtazapine compared with placebo resulted in a significant greater decrease in BDI and dSCL-90 scores over 8 and 24 weeks of treatment and after 8 weeks on the CGI.

To increase statistical power of the study, we also applied mixed models statistical procedure. After correcting for baseline differences in Ham-D, we did find a significant difference favoring mirtazapine to placebo on the Ham-D, BDI, and CGI, but not on the dSCL-90.

The effect size of mirtazapine in this patient population exceeds that in patients with similar mild depression in physically healthy depressed patients (24). Judd et al. described an SES at 12 weeks of 1.19 versus 1.70 at 8 weeks of our study. Our effect size is also comparable with the recently reported effect size in major depressed patients with CAD (14). This

may indicate that a dual-acting antidepressant is at least as effective as an SSRI. Our placebo effect size, however, was much higher than that of Judd's group (1.59 versus 0.61). This high placebo effect is comparable with other studies in post-MI depression (9,12). The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study (10) investigated whether treating post-MI depression and social isolation by means of cognitive behavioral therapy affected cardiac prognosis. Only small effects on depressive symptoms after 6 months (SES = 0.2–0.3) were reported. Moreover, although treated patients had a significant improvement in depressive symptoms at 6 months, usual care patients improved almost as much. Similarly, the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) study (12) reported that sertraline treatment for patients with post-MI depression had no or only small short-term antidepressive effects compared with placebo (SES = 0.1–0.2). Differences in effect sizes, comparing treatment versus placebo, were between 0.3 and 0.5 in the nested RCT of the MIND-IT study.

Our efficacy findings are at least comparable with those of the SADHART and ENRICHD studies.

There are some limitations in this study that might have resulted in the modest efficacy outcome. First, the inclusion of different subtypes of depression (minor depressive disorder and mild major depressive disorder) might have affected the statistical significance of the improvement on the 17-item Ham-D.

Second, despite specific training in the use of the Ham-D to minimize interrater variability, a significant difference in Ham-D responder scores at 24 weeks between sites was found ($\chi^2 = 6.84$; $df = 2$; $p = .03$). Because there is no reason to expect a difference in the severity of depression between the participating centers, we believe that both differences in Ham-D scores and moderate significant effect size may be related to interrater variability.

Third, because of the long duration of our trial (24 weeks), patients in both drug and placebo groups tended to improve with time, which may have obscured differences at the end of 24 weeks. Since the mirtazapine group had a 2 point higher HAMD-score than the placebo-group at baseline, potential regression to the mean might be responsible for the significant effect at 24 weeks favoring mirtazapine. However, correcting for baseline difference in all efficacy analyses, as we have done, may have dealt with this problem appropriately.

Furthermore, although included and excluded patients did not differ on most parameters, they differed in gender. Significantly more women were excluded. This might hamper generalizability of our findings.

Concurrent medication use between groups was not different except that patients in the mirtazapine group were prescribed significantly more ACE-inhibitors compared with the placebo group during the trial. The placebo group used β-blocking agents more often. Based on our data, a clear pharmacological rationale for these differences in use of ACE-inhibition and β blockers prescribed in the course of treatment cannot be given.

Mirtazapine proved to exhibit no significant cardiac changes as far as ECG variables was concerned. Weight increased 1.7 kg in the first 8 weeks of treatment with mirtazapine. Patients from both groups reported adverse effects. The difference in number of hospitalizations was not statistically significant. Mirtazapine is found to be safe in the treatment of this patient population.

Besides SSRIs that have proven efficacy and safety in other trials, mirtazapine should be considered in the treatment of patients with major or minor depression in the first year post MI. These data may help the clinician to safely reduce depression in the post MI period and aim for improvement of cardiac outcome.

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Appendix

A. Honig and A. M. G. Kuyper contributed equally to this work.

*The following investigators in institutions in The Netherlands participated in the MIND-IT study:

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Data Management: Trial Coordination Center (TCC), Groningen, Netherlands

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