

Research Article

SHORT PSYCHODYNAMIC SUPPORTIVE PSYCHOTHERAPY, ANTIDEPRESSANTS, AND THEIR COMBINATION IN THE TREATMENT OF MAJOR DEPRESSION: A MEGA-ANALYSIS BASED ON THREE RANDOMIZED CLINICAL TRIALS

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The efficacy of Short Psychodynamic Supportive Psychotherapy (SPSP) has not yet been compared with pharmacotherapy. A mega-analysis based on three original Randomized Clinical Trials (RCTs) was performed. Patients with (mild to moderate) major depressive disorder were randomized in (24 weeks) SPSP (n = 97), pharmacotherapy (n = 45), or their combination (n = 171). Efficacy was assessed by the Hamilton Depression Rating Scale (HDRS), Clinical Global Impression of Severity and of Improvement (CGI-S), the Symptom Checklist (SCL; depression subscale) and the Quality of Life Depression Scale (QLDS). Pearson χ^2 calculations were used to compare success rates. Analyses of covariance (ANCOVAs) were used to test inter-group differences. Success rates indicated that independent observers (HDRS) found no differences in symptom reduction between SPSP and pharmacotherapy (P = 0.214), but therapists (CGI-S, P = 0.026), and patients (SCL, P = 0.036) favored SPSP. Combined therapy was found superior to pharmacotherapy by all three (patients (P = 0.000), therapists (P = 0.024), independent observers (P = 0.024)). Independent observers (P = 0.062) and therapists (P = 0.430) found no differences between combined therapy and SPSP, but patients (P = 0.016) found combined therapy to be superior. As far as quality of life is concerned, success rates indicated that patients (QLDS) found no differences between SPSP and pharmacotherapy (P = 0.073) or between SPSP and combined therapy (P = 0.217). However, they found combined therapy superior to pharmacotherapy (P = 0.015). The results of the mega-analysis suggest that combined therapy is more efficacious than pharmacotherapy. SPSP and pharmacotherapy seem equally efficacious, except for some indications that patients and therapists favor SPSP for symptom reduction. Combined therapy and SPSP also seem equally efficacious, except that patients think that the first is

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INTRODUCTION

Short-term Psychoanalytic Supportive Psychotherapy (SPSP) is a treatment modality developed, from 1992 on, in the context of the Depression Research Project of the Mentrum Mental Health Care in Amsterdam. SPSP is a face-to-face, individual form of psychotherapy. It is a 6-month cure, consisting of 16 sessions (first eight weekly sessions, then eight biweekly sessions). It is rooted in psychoanalytic theory of normality, pathology, and of technique. In SPSP, the primary goal is to cure depression. The secondary goal is to reduce patient's vulnerability to depression. The SPSP therapist is expected to apply a primarily supportive technique. The SPSP therapist does not shun interpretation, even transference interpretation if it is possible and useful, yet, its technique is largely situated on the supportive side of the interpretive–supportive continuum.

Until now, three Randomised Clinical Trials (RCTs) were conducted to test the relative efficacy of Short Psychodynamic Supportive Psychotherapy (SPSP; De Jonghe [2005]) in the treatment of mild-to-moderate depression in ambulatory psychiatric patients. These trials provided the data for this mega-analysis. Combined therapy (SPSP plus antidepressants) was compared with pharmacotherapy alone [De Jonghe et al., 2001] and with SPSP alone [De Jonghe et al., 2004], and two intensities of combined therapy (medication plus eight or 16 sessions of SPSP) were compared. Combined therapy was clearly found more efficacious than pharmacotherapy alone on all outcome measures. The results of the comparison of combined therapy with SPSP were equivocal: neither therapists nor observers found differences, but patients found combined therapy superior in symptom reduction. Never did SPSP perform better than combined therapy. Finally, there were no significant differences found between the two intensities of combined therapy.

SPSP has not yet been compared with pharmacotherapy alone in a head-to-head comparison. In addition, the effect of SPSP on quality of life has not been investigated or compared with that of the other two treatment modalities.

The aim of this paper is to compare, by pooling the original data of the three trials mentioned above, SPSP with pharmacotherapy alone and with combined therapy. The comparisons cover the effects on both symptom reduction and improvements in quality of life.

The technique used is the mega-analysis of individual patient data. This is distinct from meta-analysis, which

is performed on the outcome of trials (N = the numbers of studies reviewed). Mega-analysis allows for more powerful statistical analyses and the comparison of more interventions. Homogeneity in treatment protocols, patient samples and research methods is particularly important in mega-analysis [Thase et al., 1997]. Since the same research group performed the three trials in question, and used an identical research design for similar study populations, high levels of clinical and methodological homogeneity can be expected. A limitation of mega-analysis is that some of the comparisons do not result from direct randomisation of the subjects.

On the basis of the results of the original trials, we formulated three hypotheses for this mega-analysis regarding efficacy in mild-to-moderate depressive disorder. As combined therapy clearly outperformed pharmacotherapy in the original trial, the first hypothesis is: Combined therapy is more efficacious than pharmacotherapy. As SPSP never performed better than combined therapy and the latter was superior to SPSP on some measures, the second hypothesis is: Combined therapy is more efficacious than SPSP. As the difference between combined therapy and pharmacotherapy was clearly larger than that between combined therapy and SPSP, the third hypothesis is: SPSP is more efficacious than pharmacotherapy.

METHOD OF THE THREE ORIGINAL TRIALS

The following is a shortened version of the Method section of the original trials. Details about patient selection, measurements, and treatment protocols can be found in the publications relating to the original trials [De Jonghe et al., 2001, 2004].

STUDY SAMPLES

The samples of the three RCTs consisted of consecutively newly registered depressed patients at two outpatient clinics in Amsterdam. General practitioners referred the patients. In addition to written informed consent, inclusion criteria were: age between 18 and 65 years and a DSM-III-R or DSM-IV defined major depression with or without dysthymia. The DSM diagnosis was assessed by means of a semi-structured interview [Huysen et al., 1996]. A further inclusion criterion was a 17-item Hamilton Depression Rating Scale (HDRS; Hamilton [1967]) baseline score of 14 points or more in two trials, and of

12–24 points in the trial comparing psychotherapy to combined therapy. In this last trial, patients with severe depression (HDRS score 25 or more points) were excluded because it was not considered ethical to withhold severe depressed patients medication. The aim was to select for this trial patients presenting mild-to-moderate major depression. We defined mild and moderate depression as specified by a HDRS score between 12 and 18 points, and between 18 and 24 points, respectively. The exclusion criteria were: presenting a psycho-organic disorder, drug abuse, a psychotic disorder, and/or a dissociative disorder, not reliable enough to participate in a clinical trial (e.g., doctor shopping), serious communication problem (e.g., language barrier), physical restrictions (e.g., the patient will soon leave the country), being “too ill” and/or “too suicidal” (e.g., hospitalization is unavoidable), pregnancy or a wish to become pregnant. Non-response to an established psychotherapy was not an exclusion, nor was treatment resistance in prior depressive episodes. Exclusion criteria associated with medication were: a contra-indication for one of the antidepressants prescribed by the pharmacotherapy protocol, a history of adequate treatment with antidepressants during the present depressive episode, and use of psychotropic medication not prescribed by the pharmacotherapy protocol. All patients were allocated (through a randomised and concealed allocation procedure) to one of the treatment conditions.

TREATMENT

All treatments were intended to last for 6 months.

Short psychodynamic supportive psychotherapy.

SPSP is based on the principles described by, among others, de Jonghe et al. [1994]. Approximately half of the therapists were experienced psychotherapists with at least 4 years of experience, half of them were residents with at least 2 years of experience in giving psychotherapy and working with (depressed) psychiatric patients. Residents required weekly group supervision of 90 min by an experienced psychoanalytic therapist (two of the authors, F.D. Jonghe and H. Van), where tape-recorded sessions were discussed. F.D. Jonghe formulated the guidelines of SPSP. The ratio of experienced therapists and residents was comparable in the three trials. We did not explicitly investigate the possible effects of experience on outcome.

The protocol required from the psychotherapists that they would, at each interview, consider alternative treatments if the patients deteriorated or did not benefit from SPSP. In these cases the patient was considered a dropout, and alternative treatment according to best medical practice was to be applied.

Pharmacotherapy. Pharmacotherapy was provided in accordance with an antidepressant medication protocol allowing for changes in medication in response to inefficacy or intolerance. In two trials, first a SSRI (fluoxetine) was given before switching to a

TCA (nortriptyline), and finally an RIMA (moclobemide). In the trial comparing psychotherapy to combined therapy the order was first an SNRI (venlafaxine XR), then an SSRI (fluoxetine or, as a second option, fluvoxamine), then a TCA (nortriptyline), and finally lithium alongside nortriptyline. All patients were treated by a psychiatrist or by an advanced, supervised resident in psychiatry. The 15-min medication consultations took place once every two weeks during the first 2 months of treatment, and once a month thereafter. The intended medication period was 6 months.

Over the course of the 24-week trial, 64% of the completers in the pharmacotherapy condition stayed on the first choice of antidepressant, 31% of them changed from first choice to the second choice of medication and in 5% of the cases there were more than two steps necessary. In the pharmacotherapy conditions of the combined therapies taken together, these percentages were 76, 20, and 4%, respectively. The exact protocol detailing the types of medication and their dosages are mentioned in the publications of the earlier trials.

Combined therapy. Combined therapy consisted of treatment with SPSP and pharmacotherapy simultaneously for a period of 6 months. Different therapists provided the psychotherapy and pharmacotherapy.

FLOW OF PARTICIPANTS AND DESIGN

Table 1 shows the design of the three original trials.

ASSESSMENT OF EFFICACY

The assessment of efficacy in each trial was based on data drawn from three sources: the patients, the treating therapists, and independent observers. The independent observers (main criterion) used the 17-item HDRS [Hamilton, 1967]. This is a scale of 17 items that assesses the severity of depression. It regards questions about symptoms such as sleep, feelings of anxiety, feelings of guilt, eating and weight, hypochondrias, and suicidal ideations. In a recent review of Bagby et al. [2004], the inter-rater reliability (Pearson's r) ranged between 0.82 and 0.98. The independent observers were university students who almost completed their masters degree in Psychology. They were selected in an application procedure by J. Dekker. Before administering the HDRS to patients the observers were trained by F. de Jonghe, who has developed a manual for a semi-structured interview for the HDRS [de Jonghe, 1994]. During the studies, the independent observers discussed their audiotaped assessments monthly with F. de Jonghe. Inter-rater reliability for the independent observers was not statistically assessed.

The therapists used the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) [Guy, 1976]. This assessment instrument uses a 7-step Likert

TABLE 1. Design and flow of participants

| | Combined therapy versus pharmacotherapy [de Jonghe et al., 2001] | Combined therapy versus psychotherapy [de Jonghe et al., 2004] | Short versus very short combined therapy [Dekker et al., 2005] | | | |
|--|--|--|--|---|--|---|
| Assessed for eligibility | 525 | 824 | 463 | | | |
| Excluded | 358 | 616 | 360 | | | |
| Not meeting inclusion criteria | 113 | 158 | 80 | | | |
| Meeting exclusion criteria | 213 | 433 | 251 | | | |
| Refused | 32 | 25 | 29 | | | |
| Randomised | 167 | 208 | 102 | | | |
| Treatment conditions | Pharmaco-therapy | Combined therapy including 16 SPSP sessions | Psychotherapy consisting of 16 SPSP sessions | Combined therapy including 16 SPSP sessions | Combined therapy including eight SPSP sessions | Combined therapy including 16 SPSP sessions |
| Randomized (ITT sample) | 84 | 83 | 107 | 101 | 49 | 54 |
| Started treatment (per protocol sample) | 57 | 72 | 106 | 85 | 45 | 45 |
| Per protocol sample mega-analysis ^a | 45 | 62 | 97 | 73 | Not included | 36 |

^aExcluded HDRS scores <14 and >24.

Scale to assess how depressed a patient is [from normal (1) to extremely ill (7) on the CGI-S] and how much a patient did improve [from very much improved (1) to very much worse on the CGI-I]. The CGI is widely used in clinical research [i.e. Schneider and Olin, 1996; Zaider et al., 2003]. In the combined therapy condition the CGI was provided by the treating psychiatrist.

The patients used the depression subscale of the 90-Symptom Checklist (SCL-90; Arrindell and Ettema [1986]). The SCL-90 is a self-report questionnaire that consists of 90 items measuring a broad range of psychopathological symptoms, clustered in eight subscales. The sub-scales are Agoraphobia (7 items), Anxiety (10 items), Depression (16 items), Somatic complaints (12 items), Insufficiency in thinking and acting (9 items), Hostility (6 items), Suspicion and interpersonal sensitivity (18 items), and Sleep problems (3 items). The remaining nine items are miscellaneous items. Illustrative SCL-90 items are “feeling anxious” and “having a feeling of emptiness”. Items are rated on a 5-point Likert Scale (1 = not at all and 5 = very much). The total score is seen as a general index of self-reported psychopathology. Patients also used the Quality of Life Depression Scale (QLDS; Tuynman-Qua and de Jonghe [1992]). This questionnaire contains 34 items that patients have to answer with “true” or “not true”. Examples of items are: “I just want time to pass”, “I feel hopeful about the future”, “I take good care of myself”, “I can’t be bothered with my friends”, “I enjoy my food”, and “My life has no meaning”. The test-retest correlations of this scale are 0.94 in the United Kingdom and 0.87 in the Netherlands.

Internal consistency α -coefficients are 0.95 and 0.92, respectively. The QLDS was shown to correlate relatively highly with established measures of well-being, and scores obtained with this scale appeared related to severity of depression as assessed by the HDRS. The scale has wide applicability and has been shown to be user-friendly, both for respondents and administrators [Tuynman-Qua and de Jonghe, 1992].

MEGA-ANALYSIS METHOD

STUDY SAMPLE

Some patients were excluded from the mega-analysis. Firstly, the condition consisting of combined therapy with eight sessions of SPSP, from the study examining a dose-response relationship, was excluded because we considered it too different from the other combined therapy conditions (16 SPSP sessions). Even though in the original trial no efficacy differences were found between the eight and 16-session condition, we excluded the first condition to enhance the clinical homogeneity of the mega-analysis sample. Secondly, the trials differed with respect to the required 17-item HDRS baseline score: 14 points or more in two trials, and 12–24 points in the trial comparing psychotherapy and combined therapy. To enhance homogeneity, only patients with HDRS baseline scores of 14–24 were included in the mega-analysis; patients with HDRS scores <14 and >24 were excluded. This led to the exclusion of 12 cases in the pharmacotherapy condition, nine in the SPSP condition and 36 in the combined therapy conditions.

We realised that this is a considerable loss of patients, especially in the pharmacotherapy condition. To evaluate the influence of this loss on our results, we repeated all analyses including also these patients from the three original trials.

The mega-analysis sample therefore consisted of 313 patients: 45 in pharmacotherapy, 97 in SPSP, and 171 in combined therapy (see Table 1).

OUTCOME MEASURES

Relative efficacy is expressed in this study in two different ways: inter-group differences in remission rates or response rates, and in mean scores. Assessments reflect the points of view of the independent observers (HDRS, main criterion), therapists (CGI-S and CGI-I), and of the patients (SCL-D and QLDS). Remission is defined (as in the original trials) as a final HDRS score of 7 points or less, as a CGI-S or CGI-I score of 2 points or less, and as an improvement of at least 1 standard deviation from base rate on the SCL-D depression subscale and the QLDS. Response is defined as a 50% reduction in the HDRS baseline score. Differences in dropout rates were calculated.

STATISTICAL ANALYSES

Pearson χ^2 calculations (two sided, level of significance .05) were used to compare base rates and dropout rates. Pearson χ^2 calculations (one sided, level of significance .05) were used to compare response rates and remission rates [Altman, 1991; Bland and Bland, 1994]. Analyses of covariances (including baseline scores for outcome measures as covariates) were used to test inter-group differences. Our results are calculated in all patients who started with the treatment they were allotted to (a Per-Protocol or modified Intention-to-treat sample). The Last Observation Carried Forward approach was used.

RESULTS OF THE MEGA-ANALYSIS

STUDY SAMPLE

A total of 313 patients were included in our mega-analysis (45 in pharmacotherapy, 97 in SPSP, and 171 in combined therapy). Table 2 presents the characteristics of the study sample.

There were four significant differences between the treatment conditions. The mean CGI-severity baseline score in the pharmacotherapy condition was somewhat higher than in the SPSP and combined condition ($P=0.01$ and 0.04 , respectively). Furthermore, the SCL-D score in pharmacotherapy group was somewhat lower than in the SPSP group ($P=0.03$) and the QLDS score on the combined group was higher than in the SPSP group ($P=0.019$). The three samples did not differ statistically significant with regard to the presence of dysthymia. Although the absolute differences were

probably clinically insignificant, the baseline scores for the outcome measure were included as covariates in the Analyses of covariance of that outcome. Mean HDRS score in first trial was 20.43, in the second trial 19.90, and in the third trial 18.07. The mean HDRS for the total sample of the mega-analysis was 18.7.

DROPOUT

Table 3 presents numbers and rates for dropout.

As can be seen in Table 3, the dropout in pharmacotherapy was 38%, in combined therapy it was 28%, and in SPSP it was 25%. The dropout rates for the three conditions did not differ significantly. Dropout of both SPSP and pharmacotherapy was lower in the combined therapy condition than in mono-therapy conditions (10% versus 25% for SPSP and 25% versus 38% for pharmacotherapy). The difference regarding SPSP was significant ($P=0.001$).

For reasons explained above (Method section), we repeated the analyses including patients with HDRS scores <14 and >24 from the three trials. With regard to dropout rates we found the results to be comparable, except for one finding: A formerly not found significant difference between SPSP and pharmacotherapy was detected (in the new analysis, respectively, 25.5 and 40.4%, $P=0.049$).

REMISSION RATES AND RESPONSE RATES

The remission rates and response rates are shown in Table 4.

No significant differences in HDRS remission and response, CGI-I and QLDS, were found between SPSP and pharmacotherapy. CGI-S and SCL-D indicated a significant difference in favour of SPSP. All outcomes (except for HDRS-response) indicated significantly higher remission rates in combined therapy than in pharmacotherapy. No differences were found between combined therapy and SPSP, except for the SCL-D favouring combined therapy over SPSP. For reasons explained above (Method section), we repeated the analyses including patients with HDRS scores <14 and >24 from the three trials. With regard to remission and response rates we found the results to be comparable, except for two findings: (1) A formerly found trend in the QLDS success rates comparing SPSP and pharmacotherapy became a significant difference favouring SPSP (in the new analysis, respectively, 53.3% versus 37.5%, one sided $P=0.027$). (2) A formerly found trend in the HDRS response rates became a statistically significant difference favouring Combined therapy above pharmacotherapy (in the new analysis, respectively, 33.3% versus 47%, one sided $P=0.033$).

DIFFERENCES IN MEAN SCORES

Table 5 presents the mean scores for depression on the HDRS, CGI-Severity, CGI-Improvement, SCL-D, and QLDS.

TABLE 2. Characteristics of the per protocol sample

| | Pharmaco- therapy (<i>n</i> = 45) | Psychotherapy (<i>n</i> = 97) | Combined therapy (<i>n</i> = 171) | 1 versus 2 | 1 versus 3 | 2 versus 3 |
|--|---------------------------------------|-----------------------------------|---------------------------------------|-------------|-------------|-------------|
| Sex | | | | | | |
| Male | 35.6 | 33.0 | 32.2 | | | |
| Female | 64.4 | 67.0 | 67.8 | | | |
| Age | | | | | | |
| 19–29 years | 40.0 | 33.0 | 35.7 | | | |
| 30–39 years | 33.3 | 34.0 | 35.7 | | | |
| > 40 years | 26.7 | 33.0 | 28.7 | | | |
| Educational level | | | | | | |
| Low | 13.3 | 15.1 | 15.4 | | | |
| Middle | 35.6 | 34.4 | 37.3 | | | |
| High | 51.1 | 50.5 | 47.3 | | | |
| Living situation | | | | | | |
| Alone | 46.7 | 45.7 | 41.8 | | | |
| Living with at least one person | 53.3 | 54.3 | 58.2 | | | |
| Marital status | | | | | | |
| Married | 20.0 | 20.2 | 20.6 | | | |
| Divorced/widowed | 13.3 | 7.4 | 11.2 | | | |
| Not married | 66.7 | 72.3 | 68.2 | | | |
| Job status | | | | | | |
| Sick/social benefit/other | 53.3 | 53.8 | 55.3 | | | |
| Job | 46.7 | 46.2 | 44.7 | | | |
| Duration present episode | | | | | | |
| < 1 year | 65.9 | 74.2 | 70.8 | | | |
| 1–2 years | 13.6 | 12.4 | 16.1 | | | |
| > 2 years | 20.5 | 13.5 | 13.0 | | | |
| Medication 3 months before study | | | | | | |
| Yes | 13.3 | 27.8 | 22.8 | | | |
| No | 86.7 | 72.2 | 77.2 | | | |
| Depressed episodes within previous 5 years | | | | | | |
| 0 | 47.7 | 69.0 | 61.7 | | | |
| 1 | 25.0 | 17.2 | 22.8 | | | |
| ≥ 2 | 27.3 | 13.8 | 15.4 | | | |
| Psychiatric treatment during present episode | | | | | | |
| Yes | 43.2 | 30.3 | 38.3 | | | |
| No | 56.8 | 69.7 | 61.7 | | | |
| HDRS | | | | | | |
| Mean | 19.0 | 18.7 | 18.7 | | | |
| SD | 2.8 | 3.0 | 3.0 | | | |
| CGI-severity | | | | | | |
| Mean | 4.8 | 4.4 | 4.5 | .011 | .041 | |
| SD | 0.6 | 0.7 | 0.7 | | | |
| SCL-90 depression subscale | | | | | | |
| Mean | 46.4 | 50.3 | 48.5 | .030 | | |
| SD | 11.2 | 8.8 | 9.4 | | | |
| SD | 8.8 | 7.7 | 7.5 | | | |
| QLDS | | | | | | |
| Mean | 16.6 | 15.8 | 17.8 | | | .019 |
| SD | 7.4 | 6.3 | 6.8 | | | |
| Personality disorder | | | | | | |
| No | 33.3 | 30.8 | 34.6 | | | |
| Yes | 66.7 | 69.2 | 65.4 | | | |

HDRS, Hamilton Depression Rating Scale; CGI, Clinical Global Impression; SCL-90, 90-Symptom Checklist; QLDS, Quality of Life Depression Scale.

Bold figures indicate statistical significance.

Italics indicate approaching statistical significance.

TABLE 3. Dropout rates

| | Pharmaco-therapy | | Psychotherapy | | Combined therapy | | 1 versus 2 | | 1 versus 3 | | 2 versus 3 | |
|-------------------------|------------------|------|---------------|------|------------------|------|------------|-------|------------|-------|------------|--------------|
| | N | % | N | % | N | % | Pearson | | Pearson | | Pearson | |
| | | | | | | | χ^2 | P | χ^2 | P | χ^2 | P |
| Pharmacotherapy dropout | 17 | 37.8 | — | — | 43 | 25.1 | | | 2.83 | 0.092 | | |
| Psychotherapy dropout | — | — | 24 | 24.7 | 17 | 9.9 | | | | | 10.46 | 0.001 |
| Total dropout | 17 | 37.8 | 24 | 24.7 | 48 | 28.1 | 2.54 | 0.111 | 1.60 | 0.206 | 0.35 | 0.555 |

Bold figures indicate statistical significance.
Italics indicate approaching statistical significance.

TABLE 4. Remission and response rates at treatment termination (week 24)

| | Pharmaco-therapy | | Psychotherapy | | Combined therapy | | 1 versus 2 | | 1 versus 3 | | 2 versus 3 | |
|-------------------------|------------------|----|---------------|----|------------------|-----|------------|--------------|------------|--------------|------------|--------------|
| | % | N | % | N | % | N | Pearson | | Pearson | | Pearson | |
| | | | | | | | χ^2 | One-sided P | χ^2 | One-sided P | χ^2 | One-sided P |
| HDRS remission | 24.4 | 45 | 30.9 | 97 | 40.4 | 171 | 0.63 | 0.214 | 3.87 | 0.024 | 2.36 | 0.062 |
| HDRS-response | 35.6 | 45 | 40.2 | 97 | 48.0 | 171 | 0.28 | 0.298 | 2.21 | 0.068 | 1.50 | 0.110 |
| CGI-severity success | 48.9 | 45 | 66.0 | 97 | 64.9 | 171 | 3.76 | 0.026 | 3.87 | 0.024 | 0.03 | 0.430 |
| CGI-improvement success | 60.0 | 45 | 71.0 | 93 | 73.2 | 168 | 1.66 | 0.099 | 2.98 | 0.042 | 0.15 | 0.348 |
| SCL-depression success | 44.4 | 45 | 60.6 | 94 | 73.4 | 169 | 3.23 | 0.036 | 13.51 | 0.000 | 4.57 | 0.016 |
| QLDS | 40.0 | 45 | 53.1 | 96 | 58.1 | 167 | 2.11 | 0.073 | 4.67 | 0.015 | 0.61 | 0.217 |

HDRS, Hamilton Depression Rating Scale; CGI, Clinical Global Impression; SCL, Symptom Checklist; QLDS, Quality of Life Depression Scale.
Bold figures indicate statistical significance.
Italics indicate approaching statistical significance.

TABLE 5. Mean scores for the outcome measures at treatment termination (week 24)

| | Pharmaco-therapy | | | Psychotherapy | | | Combined therapy | | | 1 versus 2 | | 1 versus 3 | | 2 versus 3 | |
|-----------------|------------------|-------|----|---------------|-------|----|------------------|-------|-----|------------|--------------|------------|--------------|------------|--------------|
| | Mean | SD | N | Mean | SD | N | Mean | SD | N | One-sided | | One-sided | | One-sided | |
| | | | | | | | | | | F | P | F | P | F | P |
| HDRS | 12.82 | 7.79 | 45 | 11.45 | 7.13 | 97 | 10.28 | 6.86 | 171 | 0.84 | 0.180 | 4.22 | 0.020 | 1.86 | 0.087 |
| CGI-severity | 2.73 | 1.29 | 45 | 2.18 | 1.30 | 97 | 2.19 | 1.31 | 171 | 6.02 | 0.007 | 5.56 | 0.009 | 0.23 | 0.317 |
| CGI-improvement | 2.51 | 1.24 | 45 | 2.09 | 1.27 | 93 | 1.99 | 1.07 | 168 | 3.41 | 0.033 | 7.48 | 0.003 | 0.39 | 0.265 |
| SCL-depression | 35.76 | 13.16 | 45 | 36.95 | 13.91 | 97 | 31.38 | 11.81 | 170 | 0.15 | 0.349 | 7.58 | 0.003 | 9.87 | 0.001 |
| QLDS | 22.8 | 8.79 | 45 | 23.16 | 8.63 | 97 | 25.95 | 7.60 | 170 | 0.84 | 0.180 | 6.33 | 0.006 | 3.48 | 0.031 |

HDRS, Hamilton Depression Rating Scale; CGI, Clinical Global Impression; SCL, Symptom Checklist; QLDS, Quality of Life Depression Scale.
Bold figures indicate statistical significance.
Italics indicate approaching statistical significance.

All outcome measures indicated that combined therapy was superior to pharmacotherapy. No significant differences were found between SPSP and pharmacotherapy, except for two (CGI-S and CGI-I) favouring SPSP. All outcomes, except two (SCL-D and QLDS, favouring combined therapy) showed no significant differences between combined therapy and SPSP.

For reasons explained above (Method section), we repeated the analyses including patients with HDRS scores < 14 and > 24 from the three trials. With regard to differences in mean scores we found the results to be comparable, except for one finding: A formerly not found significance on the QLDS was now found to be a significant difference, favouring SPSP over pharma-

cotherapy (in the new analysis, respectively, 23.43 versus 20.89 points, one sided $P = 0.047$).

DISCUSSION

In this mega-analysis we pooled the original data of three RCTs published earlier. This allowed for three head-to-head comparisons: SPSP and pharmacotherapy (a comparison that was not included in the earlier publications), SPSP and combined therapy and pharmacotherapy and combined therapy. In addition, we assessed the effect of the treatment modalities on improvements in quality of life. The same research group conducted the RCTs in similar populations using an identical research design, thereby ensuring clinical and methodological homogeneity.

SPSP AND PHARMACOTHERAPY

Turning to symptom reduction, the main outcome of the mega-analysis (HDRS) suggests that SPSP and pharmacotherapy are equally efficacious in the treatment of mild-to-moderate depression. These findings are in line with the literature about comparisons between cognitive psychotherapy and antidepressants [e.g., Blackburn and Moore, 1997; Jarret et al., 1999; Keller et al., 2000], and between IPT and antidepressants [DiMascio et al., 1979; Elkin et al., 1989]. Similar conclusions were reached in a recent meta-analysis comparing psychotherapy with pharmacotherapy (De Maat et al. [2006], accepted for publication in *Psychotherapy Research*). However, secondary outcome measures show that there are indications that the clinicians (CGI-S) found SPSP superior to pharmacotherapy, as did the patients with regard to symptom reduction (SCL-D). It seems that more research is necessary to reach final conclusions in this area. We found no differences between the two treatment modalities in terms of improvements in quality of life. We did not find any data in the literature for comparison with our findings.

COMBINED THERAPY AND PHARMACOTHERAPY

Patients, therapists, and independent observers alike find combined therapy more efficacious than pharmacotherapy alone, both for symptom reduction and improving quality of life. These results are in line with the results of the original trial. As far as symptom reduction is concerned, our findings concur with the results of Pampallona et al. [2004], who report an odds ratio of 1.86 in favour of combined therapy compared with drug treatment alone in the treatment of depression.

COMBINED THERAPY AND SPSP

With respect to symptom reduction, independent observers and therapists did not discern a difference between combined therapy and SPSP. Patients, on the

contrary, favoured combined therapy over SPSP. These results are again in line with the results of the original trial. Apparently, the patients, or the scale they use, register subtle differences that go unnoticed by therapists and independent observers. In the literature, the relative merits of combined therapy and psychotherapy are still a matter of debate. Some reviewers find no differences [Blom et al., 2000; Conte et al., 1986; Wexler and Cicchetti, 1992] others find combined therapy to be superior [Friedman et al., 2004; Segal et al., 2002]. Our results are mostly in line with the former.

That there were generally no differences found in outcome between these conditions may be due to the fact that our population was mildly to moderately depressed. In the mega-analysis of Thase et al. [1997], the authors did find that combined therapy was superior to psychotherapy in more severe depression (HDRS > 20), but not in less severe cases.

Differences in symptom reduction (according to the patients) had no clear correlation with differences in improvements of quality of life. The difference measured in QLDS remission rates was not, but in QLDS mean end score was significant (favouring combined therapy). Of course, it is the question whether a difference of 3.15 points on the QLDS scale is *clinically* significant according to the patients.

DROPOUT RATES

Dropout rates in SPSP (25%) were similar to psychotherapy dropout rates in other studies, varying from 16 [DeRubeis et al., 2005] to 44% [Hollon et al., 1992]. In pharmacotherapy, at week 24, 38% of the patients had prematurely stopped taking medication. In the original trial [De Jonghe et al., 2001], the pharmacotherapy dropout rate at week 8 was only 5%. The increase in dropout of pharmacotherapy during the treatment period had various reasons, one of them being adverse effects, even up to week 24. Some of the reasons in the later stages of the treatment were also "not feeling better" and, perhaps somewhat surprisingly, "feeling better". A publication regarding the detailed analyses of dropout in the pharmacotherapy conditions and the corresponding reasons is being prepared [Aalst et al., In preparation; De Maat et al., 2006]. Pharmacotherapy compliance in the first 8 weeks of our study can be considered rather fair. Recent reviews [Anderson, 2000; Linden et al., 2000] mention dropout rates of 33–48% in pharmacotherapy conditions within the first 6–8 weeks.

The dropout rates in the combined therapy condition in our study were 28%. Combining SPSP with medication reduced the dropout rates for both treatment components (in SPSP from 25 to 10% and in pharmacotherapy from 38 to 25%).

In our study the overall dropout rates did not differ between the three treatment modalities. This is in accordance with findings in literature. Casacalenda

et al. [2002] report a dropout rate for psychotherapy of 22% and of 37% for medication, the difference not being statistically significant. A review by Friedman et al. [2004] shows no significant differences between dropout rates of combined therapy versus psychotherapy. Finally, Pampallona et al. [2004] conclude that the dropout rates for combined therapy and pharmacotherapy do not differ.

LIMITATIONS

Our study has several limitations. Firstly, the study sample suffers from the selection bias inherent to all RCTs. Most trials exclude patients with, for example, serious comorbidity, suicidal intentions or substance abuse. Patients meeting all inclusion and no exclusion criteria applied in RCTs represent only a small proportion of the depressed target population. (In our studies, 26% of the assessed patients were finally included.) A cautious approach is therefore required to the generalization of conclusions from RCTs. Secondly, there are some differences at baseline between the study samples of the three original trials. Since the baseline scores for outcome measures were included in analyses as covariates, these differences have been accounted for. Thirdly, the pharmacotherapy protocols in the three original trials differed slightly (the SPSP manual, on the other hand, was identical). We did not, however, find significant differences between the mean scores or remission rates of combined therapy in the three samples of the original RCTs. Furthermore, meta-analytic studies have shown that there are no clinically significant differences between antidepressants in terms of treating depressed outpatients [Anderson, 2000]. Fourthly, we are well aware that the comparison of SPSP and pharmacotherapy is not based on the randomization between these two treatments. This may have affected the results. However, we believe both groups are comparable as the studies were performed in the same outpatient facilities with the same study design and within the same population. Furthermore, we tested for pre-treatment differences and performed covariance analyses. Fifthly, in a secondary analysis, we repeated all analyses including patients with HDRS scores of <14 and >24 from the three original trials to evaluate the influence on our results of the loss patients due to restricting our main calculations to patients with HDRS scores 14–24. The findings were in line with those of our original analyses. However, dropout rates and quality of life favoured SPSP above pharmacotherapy. This we consider an indication that in, a broader range of HDRS scores, SPSP, on some points, may outperform pharmacotherapy. Sixthly, as there are many statistical comparisons in this mega-analysis, it could be argued that a Bonferroni correction is needed to prevent type I statistical errors. To this end a significance level of for instance 0.016 (0.5/3 as we had three sources of information) might be taken as

threshold. If this correction is applied, eight of the 17 significant differences disappear, four of them concerning the differences in success rates between combined therapy and pharmacotherapy, three concerning the comparison of SPSP and pharmacotherapy. This means all the more that our results must be interpreted with caution. A final limitation is that, from sheer necessity (we did not have follow-up data at our disposal), we restrict our mega-analysis to the short-term effects of time-limited treatments.

STRENGTHS

Firstly, in our opinion the strong clinical and methodological homogeneity of this mega-analysis adds to its strength. Secondly, our data come from three sources (independent observers, patients, and therapists). There are two reasons why we consider this to be a strength. Evidence-based medicine values the opinions of patients and clinicians highly, alongside those of independent observers. In addition, a recent systematic review by Bagby et al. [2004] shows that the Hamilton depression scale, which is widely used in depression research, has considerable psychometrical and conceptual flaws. A final strength of our mega-analysis is the inclusion of the effect of treatment on quality of life, which is, after all, the ultimate goal of the treatment.

CONCLUSIONS

In the treatment of outpatients with mild-to-moderate major depressive disorder the results of the mega-analysis suggest that independent observers, patients, and therapists alike found SPSP plus pharmacotherapy to be more efficacious than pharmacotherapy alone, for both symptom reduction and improving quality of life. The results also suggest that independent observers found SPSP and pharmacotherapy equally efficacious. There is some indication that patients and therapists favour SPSP over pharmacotherapy in regard to symptom reduction, but, then again, not in improving quality of life. No efficacy difference was found between SPSP and combined therapy, except that patients thought that combined therapy was more efficacious in terms of symptom reduction.

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