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ORIGINAL PAPER

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Should combined pharmaco- and psychotherapy be offered to depressed patients?

A qualitative review of randomized clinical trials from the 1990s

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Abstract Focusing on recent publications from the 1990s, this article qualitatively reviews the comparative efficacy of the combination of pharmaco- and psychotherapy (COMBI) vs either modality alone. There is only a weak empirical basis recommending the routine use of both psychotherapy and pharmacotherapy in acute treatment of Major Depressive Disorders (MDD). Concerning long-term treatment of MDD patients, the methodologically sophisticated study from Frank et al. shows that a COMBI is superior to interpersonal psychotherapy but not superior to medication alone. However, certain subgroups of patients might benefit substantially from COMBI compared to both psychotherapy and pharmacotherapy alone: 1) acute and long-term treatment of more severe forms of chronic depression, and 2) long-term treatment of older MDD patients. Compared to psychotherapy alone, severely depressed MDD patients profit more and faster when treated with combined psycho-pharmacotherapy.

Key words psychotherapy · antidepressants · depression

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Introduction

Treatment of depression with a combination of psychotherapy and pharmacotherapy (COMBI) is frequently recommended, but remains a matter of controversial discussion. The American Psychiatric Association recommends antidepressant medication coupled with psychotherapeutic management or psychotherapy (APA 1993). Contrarily, the Agency for Health Care Policy and Research (AHCPR) Depression in Primary Care guidelines (Depression Guideline Panel 1993) stated that combined psychotherapy and psychopharmacology should not be applied generally because of weak evidence for their superiority over either treatment alone. Referring to these two positions, this article will analyse the usefulness of combined pharmacotherapy and psychotherapy vs pharmacotherapy or psychotherapy alone.

Both qualitative (Hollon et al. 1991) and quantitative reviews (most recently Gaffan et al. 1995) on this subject are available. However, recent publications from the 1990s have not yet been analysed in detail, although Thase (Thase 1999) provided some very valuable aspects. Studies from the 1990s are of special scientific interest because they analyse larger samples. Therefore, they are less likely to suffer from publication bias, although researcher allegiance effects (Gaffan et al. 1995) cannot be excluded in general for any comparative treatment study. But, usually, the younger studies are more likely to meet criteria of evidence-based medicine (Sackett 1998). Therefore, besides a short discussion of the results from former qualitative and quantitative analyses, this article gives an overview of the newer studies. The judgment of study quality follows both the

criteria formulated by the Evidence-Based Medicine Working Group (Oxman et al. 1994) and the Cochrane criteria (Clark, Oxman 2001).

Inclusion criteria for the highlighted studies are: Date of publication ≥1990, original report of a randomised clinical trial, cell-sizes of at least 20, and blindness of raters. According to the Depression Guideline Panel (1993), continuation treatment is defined as the prevention of relapse into the current episode of depression, and lasts 4 to 9 months after return to the clinically well state. Maintenance treatment is defined as the prevention of recurrence of a new episode and goes on for several years. Fig. 1 gives a picture of treatment phases and possible courses of improvement or worsening.

Reporting results from acute and long-term treatment studies separately, this review is subdivided into two parts:

- The first part focuses on general evidence from older studies for additive effects of COMBI compared to single treatment conditions in the treatment of acute episodes of a Major Depressive Disorder (MDD). A short overview is given of results from meta-analyses and results from older qualitative reviews (published before 1990).
- In the second part, more recent studies from the 1990s are discussed:
  1) Studies including mainly patients with pure and uncomplicated forms of MDD
  2) Studies with patient subgroups differing in factors such as depression severity or course of depression.

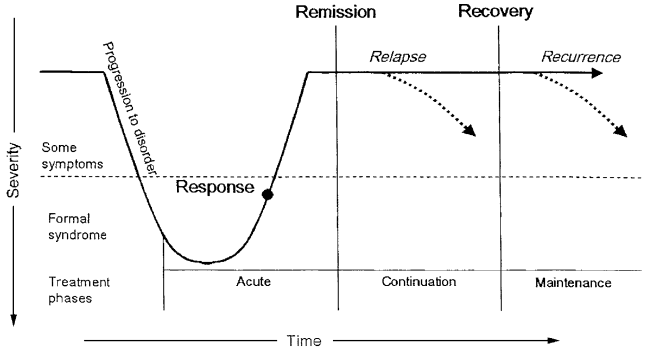

Fig. 1 Five possible change points during treatment: response, remission, relapse, recovery, recurrence (Adapted from "Lessons to be learned from long-term treatment of affective disorders: Potential utility in panic disorder," by D. J. Kupfer: J Clin Psychiatry, 1991, p. 13)

General evidence for additive effects on the basis of meta-analyses and older studies

In their literature review of older studies (published before 1990) Hollon et al. (1991) conclude that in the majority of acute treatment studies there are tendencies or trends indicating that COMBI is superior to either single modality alone. However, there were no significant main results favouring the combined treatment condition.

In three meta-analyses, which analysed the comparative efficacy of COMBI compared to either modality alone (Gaffan et al. 1995; Conte et al. 1986; Robinson et al. 1990), the trends favouring the COMBI condition did not become significant. In Table 1 characteristics and outcome of the three meta-analyses are listed: The most recent meta-analysis stems from Gaffan, and the most recent study included is from 1987. Mean cell-size of the 5 to 11 studies included is approximately 14. Unfortunately, type and quality of medication is not consequently reported in these meta-analyses.

Both the meta-analyses from Gaffan et al. (1995) and Robinson et al. (1990) found no difference between COMBI and either psychotherapy or pharmacotherapy alone. However, the two investigators analysed only a small subset (5 to 9) of the 28 and 58 studies included in their respective meta-analyses, because their analyses focused mainly on the comparison of psychotherapy vs pharmacotherapy alone. Only Conte et al. (1986), who analysed the largest set of 11 studies, reports a slight superiority of COMBI compared to each monotherapy. However, evidence from the analysis from Conte et al. (1986) is hard to compare, because he used an unusual qualitative-quantitative statistical technique. Furthermore, the Conte analysis included the older studies published between 1974 and 1984. As already mentioned above, these studies with small sample sizes tend to suffer from publication bias, and, compared to the newer studies, Gaffan found them to be more strongly biased with researcher allegiance (Hollon et al. 1991).

Table 1 Meta-analyses of acute treatment studies comparing combined pharmaco-psychotherapy (COMBI) to either treatment alone

Authors (PY)	Publication period	Mean cell-size (range)	Pharm	Outcome criteria	Results	
					Combi > PT	Combi > M
Conte et al. 1986	1974–1984	–	mostly AMI	various	(YES)	(YES)
Gaffan et al. 1995	1976–1987	14.6 (2–39)	–	BDI	NO	–
Robinson et al. 1990	1976–1986	14.3 (4–47)	various	pooled*	NO	NO

NO no superiority; – not analysed; *(YES)* slight superiority (no test of significance); *PY* year of publication; *BDI* Beck Depression Inventory; *AMI* Amitriptylin; – not reported; *Combi* combined psycho-pharmacotherapy; *M* medication; *PT* psychotherapy

* BDI, Zung Self-Rating Depression Scale, Hamilton-Depression-Rating Scale HDRS etc.

Results from studies of the 1990s

Studies from the 1990s have not been reviewed systematically. Studies analysed in former qualitative reviews were published before 1990, and, as listed in Table 1, quantitative analyses cover studies published between 1976 and 1987. In the following section, studies from the 1990s that fulfil the inclusion criteria of this review (see "Introduction") will be discussed. To give a first overview, detailed characteristics and outcome of the studies from the 1990s are displayed in Table 2.

Inspection of Table 2 gives the following picture: 7 studies were conducted in the 1990s, 4 of them on acute treatment and 3 of them on long-term treatment. Most studies have three treatment arms, usually psychotherapy, pharmacotherapy and their combination. Two studies report additional pill-placebo controls (Frank et al. 1990; Hollon et al. 1992), and the study by Frank and colleagues even implemented a control-arm for the combined treatment condition consisting of pill-placebo plus clinical management. Mean sample size is 138 (range = 107–191), and mean cell-size 46 (range = 26–79), if the outlier from the Keller study with a total of 681 patients is not considered. The clear majority of patients are outpatients, medicated with tricyclics, that is, amitriptyline (AMI), nortriptyline (NOR) or imipramine (IMI). Duration of medication and psychotherapy is 8 or 12 weeks in the acute treatment studies. Psychotherapy is usually interpersonal psychotherapy (IPT), or cognitive-behavioural therapy (CBT). Main outcome criterion is the Hamilton Rating Scale for Depression (HDRS), in some studies accompanied by the Beck Depression Inventory (BDI) or the Global As-

Table 2 Treatment studies with combined pharmaco-psychotherapy (COMBI) compared to either modality alone

Authors (PY)	Sample *	Groups	Medication (dosage mg/day)	Duration/n sessions	Main outcome criteria	Results	
						Combi > PT	Combi > M
Acute treatment of major depression (no inclusion criteria concerning severity or pre-treatment course)							
Hollon et al. 1992	107 outp.	1. M 2. CBT 3. M + CBT	IMI (various)	12w/max 20	HDRS-17	NO	NO
Hautzinger et al. 1996	75 inp., 116 outp. non-endogenous dep.	1. M 2. CBT 3. M + CBT	AMI (various)	8w/24	HDRS-17, BDI	NO	NO
Long-Term Treatment of Major Depression							
Frank et al. 1990	128 pat. with recurrent dep.	1. M + CM 2. PL + CM 3. IPT 4. IPT + PL 5. IPT + M	IMI (150–300)	3 y 1 sess./m	HDRS-17	YES	NO
Reynolds et al. 1999	107 pat. with recurrent dep.	1. M + CM 2. CM + PL 3. IPT + M 4. IPT + PL	NOR (80–120 ng/ml)	3 y 1 sess./m	HDRS-17	YES	(YES)
Acute treatment of severe major depression							
de Jong-Meyer et al. 1996	155 inp. + outp.	1. M + ST 2. M + CBT	AMI (various)	8w/24	HDRS, BDI	No	Yes/outp. No/inp.
Acute treatment of chronic depression							
Keller et al. 2000	681 pat. with chronic dep.	1. M 2. PT** 3. M + PT**	NEF (300–600)	12w	HDRS-24	YES	YES
Long-term treatment of chronic depression							
Paykel et al. 1999	158 pat. with residual dep.	1. M + CM 2. 1. + CBT	various (various)	17m/20 + 2	HDRS-17, BDI	–	YES

YES significant superiority; *(YES)* trend for superiority; *NO* no superiority; – not analysed; *PY* year of publication; *pat.* patient; *dep.* depression; *inp.* inpatients; *outp.* outpatients; *CM* Clinical Management; *M* medication; *CBT* cognitive-behavioural therapy; *ST* supportive therapy; *IPT* interpersonal psychotherapy; *PT* psychotherapy; *AMI* amitriptyline; *IMI* imipramine; *NOR* nortriptyline; *NEF* nefazodone; *PL* placebo; *w* week; *m* month; *y* years; *sess.* sessions; *max.* maximum of sessions; *HDRS* Hamilton Rating Scale for Depression; *GAS* Global Assessment Scale; *BDI* Beck Depression Inventory

* if no further specification is given, patients had to meet the diagnostic criteria for an acute episode of MDD

** cognitive-behavioural analysis system; a combination of behavioural, cognitive, and interpersonal techniques used in other forms of psychotherapy

sessment Scale (GAS). Results of comparisons are listed in both directions: COMBI vs psychotherapy and COMBI vs medication.

A comparison of study characteristics and results from Tables 1 and 2 shows that in the older studies cell-sizes indeed are substantially smaller, and, therefore, there is little chance that significant results will be obtained. In the following section, studies from Table 2 are reviewed in detail.

Major depressive disorder

Similar to the older studies, the following studies from the 1990s concentrate on comparative treatment effects on acute MDD episodes, without further specifying the severity or course of depression in their inclusion criteria. There are 3 studies on acute treatment, and 2 studies on maintenance treatment.

Acute treatment

In acute treatment of MDD, there are two more recent replications (Hollon et al. 1992; Hautzinger et al. 1996) of older studies, which indicate that there is no substantial superiority of COMBI compared to either modality alone.

Hollon (Hollon et al. 1992) compared CBT and IMI, each alone and in combination, in the treatment of outpatients suffering from MDD. They tested the hypothesis of a higher response-rate (response criteria HDRS score ≤6) to COMBI compared to both CBT and IMI alone. Besides others, exclusion criteria comprised recent (within the previous 3 months) history of non-response to an adequate trial of IMI (i. e., 150 mg/d for at least 2 weeks).

In this study 37 % of patients had a history of three or more episodes, 24 % of the sample met criteria for "double depression", and 64 % met criteria of RDC endogenicity. 28 % had a history of antidepressant medication, 64 % a history of psychotherapy. A total of 107 patients were randomly assigned to 12 weeks of treatment, and 64 patients completed the full treatment course: 1) IMI, 2) CBT, or 3) COMBI. Mean initial HDRS scores of the three groups ranged from 23.5 (SD = 4.5) to 24.8 (SD = 3.9). IMI dose was increased from 75 mg/d at study intake to 200 to 300 mg/d in week 3, depending on the individual plasma levels. Main results from all three treatment conditions showed marked symptom reduction from pre-treatment to post-treatment, but combining cognitive therapy and pharmacotherapy did not substantially improve response compared to that observed for either modality alone. Secondary analyses revealed no outcome contrasts between the more and the less severely depressed patients, regardless of whether severely depressed patients were defined as those with initial HDRS ≥ 25 or initial HDRS ≥ 20 (according to the NIMH-TDCRP study). All results were equal in both completer- and noncompleter analyses, but no intention-to-treat analyses were conducted. The overall attrition rate was 40 %, but there were no between-group differences.

Another large study (Hautzinger et al. 1996) investigated the efficacy of 8-week treatments with AMI plus clinical management, CBT alone, or COMBI in 191 depressed inpatients and outpatients.

Former MDD episodes had been experienced by 60% of patients; the majority of these patients had experienced 2 or more episodes in the past, and 40 % of patients reported previous admission to a psychiatric hospital. Mean HDRS scores of the three groups ranged between 22.9 (SD = 3.7) and 25.5 (SD = 6.0). AMI dosages or plasma levels were not controlled or reported. No superiority of either treatment condition was detected. There was only a trend for patients who had received COMBI to show higher response rates (response criteria: both HDRS and BDI ≤9). The hypothesis that both AMI and COMBI are superior to CBT in the inpatient setting, was not confirmed. All analyses were carried out as intent-to-treat analyses.

Attrition rates The overall attrition rate was 30 %. Drop-outs were significantly more frequent in the medication treatment arm (41 %), compared to COMBI (27 %) and cognitive behavioural therapy (23 %). Patients in the psychotherapy only condition dropped out significantly later (M = 74.3 days; SD = 2.3 days), most of them in the follow-up period, compared to the other two conditions. It is not reported how many of the patients dropped out after randomisation, but before start of treatment.

Long-term treatment

Two studies concentrate on the prevention of recurrence of future MDD episodes (Frank et al. 1990; Reynolds et al. 1999). These studies must be highlighted because of their sophisticated methodology, i. e. they are the only ones consistently controlled with medication-placebo.

In an outstanding 5-armed design, Frank (Frank et al. 1990) compared the percentage of recurrence of major depressive episodes over 3 years in patients who had a suffering from MDD, and high probability of recurrence. At least 3 episodes in the past were required for inclusion; the mean number of previous episodes was 6.6 (SD = 5.3). After a 2-week drug-free washout period, patients received the same short-term treatment regimen consisting of a combination of IMI (150 to 300 mg/d) and IPT. Short-term treatment continued until a patient maintained an HDRS of 7 or less. Patients then continued to receive combined treatment for an additional 17 weeks, during which HDRS scores and imipramine dosages were required to remain stable. All patients initially had 12 weekly sessions followed by four biweekly sessions and monthly sessions. The number of monthly sessions varied depending on how long a patient required to reach initial stabilization. After stabilization with continuation treatment, 127 patients were randomly assigned to one of the following treatments: 1)

medication clinical visits with IMI, 2) medication clinic with placebo, 3) IPT alone, 4) IPT and placebo, or 5) COMBI.

For 3 years, IMI was maintained at the dosage used to treat the acute episode and IPT was maintained monthly. *Results* In delaying recurrence, COMBI was superior to IPT alone, but not superior to IMI alone. Recurrence was defined as both HDRS elevation equal or above 15 and the judgment of a blind independent senior psychiatrist indicating the presence of a new episode of MDD. *Attrition rates* Only 22 (17 %) of the patients assigned to the maintenance phase failed to complete the 3-year protocol. There was a trend for greater attrition from the active imipramine cells (24.5 %) and less attrition from the inactive or no-pill cells (12 %), but only 4 patients left the study due to imipramine side effects. However, 32 % of the 230 patients in the acute treatment did not enter continuation treatment, and, another 18 % of the remaining 157 patients from the continuation treatment did not reach maintenance treatment. All together 60 % of patients who entered the study did not reach maintenance treatment, the largest proportion of them (about 30 %) because they failed to respond fully to acute treatment, or because of relapse in the continuation treatment phase.

A similar study from the same working group (Reynolds et al. 1999), conducted in elderly patients with recurrent major depression, investigated the efficacy of maintenance treatment with nortriptylin NOR and Interpersonal Psychotherapy (IPT) in preventing recurrence of major depressive episodes. Patients were required to be 59 years or older, to be at least in their second lifetime episode, with an interepisode wellness interval no longer than 3 years, and not to be suffering from dementia (MMSE $\geq$27). The mean number of previous episodes was 5.3 (SD = 5.8). Patients received open acute treatment with NOR (with plasma steady-state levels of 80–120 ng/ml) and IPT. About 50 % of patients received adjunctive pharmacotherapy during acute treatment. Following successful acute treatment (i. e. HDRS $\leq$10), patients entered a 16-week period of continuation therapy to ensure stability of remission and full recovery. Of 187 patients, 107 were fully recovered after acute and continuation treatment, that is, their remissions were stable for 16 weeks. These patients were randomly assigned to 1 of 4 maintenance therapy conditions: 1) Monthly medication clinic with full dosage NOR (plasma levels of 80–120 ng/ml), 2) clinical management with placebo, 3) monthly maintenance IPT with pill-placebo, 4) and monthly maintenance IPT with NOR. *Results* Concerning the prevention of recurrence, combined treatment with NOR plus IPT was significantly superior to IPT and pill-placebo and showed a trend to superior efficacy over NOR monotherapy ($p = 0.06$). Recurrence of a major depressive episode, as defined by RDC, was determined by structured psychiatric interview. The attrition rate of 10 % was remarkably low in this study, and for this parameter, there were no substantial between-group differences. Of the original 180 patients, 31 % did not enter the maintenance treatment condition, about half of them because of drop out, and half of them because they were nonresponsive or showing relapse.

The following sections address the question whether or not COMBI should be especially recommended for certain subgroups of depressed patients.

More severe major depressive disorder

There are only two studies on acute treatment which exclude mild episodes of MDD (de Jong-Meyer et al. 1996; Thase et al. 1997) and none on controlled long-term treatment of severe forms of MDD. Both acute treatment studies defined severely depressed patients – following the well-known study from Elkin and colleagues (Elkin et al. 1989) – as those with pre-treatment HDRS scores $>$ 20, and more mild depressive patients as those with pre-treatment HDRS scores $\leq$ 19. This definition of severe depression is not very strict. A more usual cut-off point for severe depression is an HDRS score of at least 24.

In a German three-site study (de Jong-Meyer et al. 1996), 155 patients from both inpatient and outpatient settings suffering from endogenous depression were randomly assigned to either the combination of CBT and AMI or to AMI plus supportive treatment. The main hypothesis was that adding CBT to AMI should be superior to AMI plus supportive treatment. Patients were "severely" depressed with long depression and previous treatment histories. Mean initial HDRS ranged from 29.6 (SD = 7.6; AMI) to 27.6 (SD = 5.5; AMI + CBT), with a mean of 9.5 previous episodes. The majority of patients had received antidepressants in the past, and only a small proportion of patients had been treated with psychotherapy, but not with behavioural therapies. Inclusion criteria required a diagnosis of "endogenous depression" according to ICD-9 and DSM-III-R, and both HDRS and BDI scores above 20. After a 7-day washout period patients were randomised to the two treatment arms. AMI started with 100 mg/d, thereafter the dosage was enhanced to a standard of 150 mg/d within the next 4 days. *Results* All patients showed very significant reductions in depressive symptoms on both HDRS and BDI. Inpatients improved significantly more than outpatients, but the expected differences between COMBI and AMI alone were not detected. In secondary analyses improvements and responder rates of the inpatients were comparable between treatments, but outpatient results significantly favoured the COMBI treatment. All analyses were calculated as intent-to-treat analyses. The overall attrition rate was 27.1 %, with no substantial between-group differences.

In their mega-analysis (i. e. meta-analysis with original raw-data) of 6 major RCTs, Thase et al. (1997) found that, for the more severely depressed group of MDD patients, a combination of tricyclic anti-depressants with cognitive-behavioural therapy was significantly more

effective than psychotherapy alone in enhancing post-treatment recovery rates. The mega-analysis comprised data from the Frank and Reynolds studies (see above), from the Elkin study (Elkin et al. 1989), and from three other studies coordinated by the Mental Health Clinical Research Centre, Pittsburgh University. All patients had been treated for 16 weeks with either CBT or IPT alone (n = 243), or IPT plus antidepressant medication (n = 352). Recovery was defined as a 4-week period with HDRS scores of less than 7, maintained until week 16 (post-treatment). Additionally, patients in the more severe group had significantly faster recoveries if treated with COMBI than if treated with psychotherapy alone, but this was not the case in the less severely depressed group.

All together, patients suffering from more severe acute episodes of major depression profit more from COMBI than from psychotherapy alone. There is evidence that severely depressed patients respond much faster if treated with COMBI than if treated with psychotherapy alone. Unfortunately, the mega-analysis by Thase et al. (1997) does not report results on the comparison of COMBI with medication alone.

More severe chronic depression

Comparatively strong evidence for the superiority of COMBI compared to single medication or psychotherapy comes from trials focusing on patients suffering from more severe forms of chronic depression. There is one study on acute treatment (Keller et al. 2000) and one on long-term treatment (Paykel et al. 1999) of chronic depression. Here, more severe chronic depressions are defined as those with more severe persistent depressive symptoms, such as chronic major depressive disorder (at least 2 years duration), recurrent major depressive disorder with incomplete inter-episode recovery (e. g. developing into minor depression), and double depression (dysthymia combined with major depressive disorder).

Acute treatment

In a 12-center trial with chronic depressive patients (Keller et al. 2000), the combination of nefazodone and psychotherapy was significantly more efficacious than either treatment alone. A total of 618 outpatients were randomly assigned to 12 weeks of outpatient treatment with nefazodone (NEF), psychotherapy (16 to 20 sessions), or both. According to DSM-IV criteria, patients had to be suffering from chronic MDD, i. e. an episode of MDD of at least 2 years duration, double depression (dysthymic disorder with a concurrent diagnosis of major depression), or recurrent MDD with incomplete remission between episodes (at least 2 years duration of illness) and a current MDD episode. Patients had to show an initial HDRS-24 score of ≥ 20, mean HDRS-24 scores varied between 26.4 (SD = 0.33) and 27.4 (SD = 0.32). About 60 % had a history of antidepressant treatment, and 65 % a history of treatment with psychotherapy. A combination of cognitive-behavioural and interpersonal methods was used for psychotherapy. The initial nefazodone dose was 200 mg/d and was increased at weekly intervals in steps of 100 mg/d up to a maximum of 600 mg/d. At least 300 mg/d were required to remain in the study. Patients were required to discontinue taking MAO inhibitors and fluoxetine at least 4 weeks before study entry, and other psychotropic medications at least 2 weeks before entry. *Results* The overall rate of response (both remission and satisfactory response) was 48 % in both the NEF group and in the psychotherapy group, as compared with 73 % in the COMBI group. Remission was defined as an HDRS score of 8 or less at weeks 10 and 12. For patients who did not reach remission, a satisfactory response was defined as a reduction in the score by at least 50 % from baseline and a score of 15 or less. The main efficacy analysis was a piecewise mixed effects linear model. This approach included all patients who attended at least one treatment visit. Attrition rates varied slightly from 21 % to 26 % between the different treatment conditions. In the NEF group, most dropouts were due to adverse events, whereas in the psychotherapy group most dropouts were due to rejection of psychotherapy.

Long-term treatment

Addressing the prevention of relapse in partially remitted MDD patients, Paykel (Paykel et al. 1999) conducted a trial of 1) CBT plus medication and 2) medication plus clinical management alone. Included were 158 patients with recent MDD, but residual symptoms (HDRS ≥ 8 and BDI ≥ 9) of 2 to 18 months' duration. About 35 % of patients had suffered from only one previous episode, 28 % from 2 episodes, and 37 % from 3 or more previous episodes. Among other reasons, patients were excluded if they had previously received CBT for more than 5 sessions. During the acute treatment phase, CBT consisted of 16 sessions during 20 weeks, with 2 subsequent booster sessions. SSRI (nearly 60 %), tricyclics, atypical depressants, or MAO inhibitors were used as antidepressants. The mean daily dose was equivalent to 187 mg/d AMI, or 33 mg/d fluoxetine. Subjects were assessed regularly throughout the 20 weeks' treatment (every 4 weeks) and then for a further year (every 8 weeks). Remission was defined as HDRS < 8 and BDI < 9 at two successive ratings 4 weeks apart, and relapse was defined as both meeting DSM-III-R criteria for MDD and HDRS ≥ 17 over a period of at least 4 weeks. Relapse criteria were more stringent during follow-up: residual symptoms and an HDRS ≥ 13 had to persist over 2 months. *Results* Additional CBT reduced relapse rates over 17 months for acute major depression and persistent severe residual symptoms from 47 % (continued treatment with antidepressants) to 29 %. In addition CBT also increased full remission rates at 20 weeks (24 vs. 11 %), but this effect was relatively small and not as-

sociated with a significant improvement in depression symptom ratings. Both intent-to-treat and completer analyses were conducted, with comparable results. The overall attrition rate was 19.6 %, and no significant between-group differences were reported.

Methodological considerations

Before discussing the results presented here, it is important to highlight some major methodological problems namely attrition bias, effect sizes and power, selection bias, and possible explanations for effects resulting from a combination of two active treatment conditions.

Attrition bias

The majority of studies used the intent-to-treat model and/or reported differentiated results for completers and "all assigned". Owing to the low drop-out rates in the studies analysed here, the dropout-problem is not considered to be too severe. Outstanding is the low attrition rate in the Reynolds study (10 %; Reynolds et al. 1999), and also in the Frank study (17 %; Frank et al. 1990) among the patients assigned to the maintenance phase over the long treatment period of 3 years. In the majority of studies there was no differential attrition from treatment conditions that might bias the composition of the final groups. Furthermore, there are no significant group differences concerning the reason for drop-outs.

Effect-sizes and power

In comparative pharmaco-psychotherapy research in the years before 1990, cell-sizes rarely exceed 20 subjects (see again Table 1). With these cell-sizes there was a very small chance to detect even medium (defined as ≥ 0.25 and < 0.40 in the statistic software "Sample Power 2.0") to large effect sizes (defined as ≥ 0.40). Concerning the studies included in our review, Hollon (Hollon et al. 1992) calculated medium to large effect sizes of 0.44 and 0.35 for comparisons between the combined treatment vs pharmacotherapy alone and vs cognitive therapy alone, respectively. But cell-sizes were too small [25], to detect these effect sizes (e. g. m1-m2/SD = 8) with a power of 0.80 ($\alpha = 0.05$) correctly on the HDRS; two-tailed sample size calculations would result in cell-sizes of 45. Therefore, the authors argue that there might be clinical significance, although statistical significance is missing. However (given medium effect sizes of ≤ 0.25), neither Hautzinger et al., nor de Jong-Meyer et al. obtained significant results, despite sufficient power (about 0.80) and sufficient cell-sizes.

Selection bias

Biasing via selection involves instances in which the entire sample selected is likely to be differentially responsive to one or the other modality in a manner that is *non-representative* of the population of interest. It could be guessed that 50 % of the patients included in most of the above acute treatment trials had experienced multiple episodes (e. g. Frank et al. 1990; Hollon et al. 1992). Although not always reported, these patients are likely to have longer histories of treatment with tricyclics. Therefore, a good deal of these patients could be considered as (at least partially) tricyclics-refractory patients.

In most acute treatment trials patients are re-treated with tricyclics, resulting in a reduced probability for response. These trials do not answer their original question of whether or not a COMBI is superior to each modality alone in acute treatment of an MDD episode, but they address possible additive effects of psychotherapy in (partially) tricyclics-refractory patients. This selection bias could reduce the probability for treatment success for both patient groups treated with tricyclics and COMBI relative to patients treated with psychotherapy alone. Last but not least, the identification of psychotherapy non-responders may be more complex, because only a proportion of psychotherapists use CBT or IPT techniques, and even fewer apply psychotherapy in a standardised manner.

Possible effects resulting from the combination of two active treatments

When attempting to explain non-significant trends favouring COMBI vs either modality alone, at least two models should be mentioned (Beitman, Klerman 1991). In the magnitude model, COMBI is seen as enhancing the response for each individual patient above the effect seen for an individual treatment modality. On the contrary, in the frequency model, COMBI is seen as increasing the likelihood that any given patient will receive some type of treatment to which he or she will respond. Either model may produce mean differences favouring the COMBI over either or both single modalities, but the examination of variance in response and scatterplots of individual response may help to distinguish between the two models. In general, a recommendation for the wide application of COMBI could arise mainly from the magnitude model. In case of the frequency model the task would rather be to assign the individual patient to the kind of treatment to which he will respond.

Besides the interaction between pre-existing individual differences in response and the type of treatment, there may also be interaction between the combined treatment modalities. The effects of the two different treatment modalities could be additive or less than additive because of overlay. It can also not be excluded that in daily practice interactions between pharmaco- and psychotherapy occur. When the patient is treated by dif-

ferent persons with different disease concepts, conflicting information may be provided to the same patient with negative consequences e. g. on compliance.

Unspecific components of psychotherapy, like providing information and supportive social contact, are measured with "psychotherapy-placebo", that is, clinical management or unspecific supportive groups, and unspecific medication effects are typically quantified with pill-placebo. However, the studies from the Pittsburgh group (Frank et al. 1990; Reynolds et al. 1999) are the only ones that have a pill-placebo arm, showing that both treatment modalities are effective in that particular study. To date, unfortunately, no conclusion can be drawn concerning the magnitude of specific and especially of unspecific components of the combined treatment versus different monotherapies, because most of the studies described here had none of these placebo conditions. Since placebo psychological treatment is difficult to achieve, the comparison of different forms of psychotherapy – e. g. CBT vs IPT – might be an interesting solution.

Discussion

From former reviews and meta-analyses, there is some agreement that in the treatment of acute major depressive episodes in the outpatient setting there is no significant superiority of a COMBI over psychotherapy alone or over medication alone. This conclusion is supported in the studies reviewed here.

In prevention of recurrence of depressive episodes COMBI is superior to maintenance interpersonal psychotherapy, but not superior to medication. Maintenance interpersonal psychotherapy does not appear to be effective in ultimately preventing a recurrence, though it may delay by months the onset of the next episode (Frank et al. 1990). These results are contrary to the usual argumentation of psychotherapists that psychotherapy is more effective in reducing relapse rates than medication. However, maintenance-IPT was conducted on a low-dose monthly basis, whereas full-dose imipramine was continued throughout.

Although controlled trials with direct comparisons of different psychotherapies are still scarce, it can be discussed, whether or not CBT is more appropriate to prevent relapse in MDD patients compared to IPT. An argument could be that CBT explicitly aims at changing cognitive processes, and that this might lead to an increased long-term efficacy. Contrarily, IPT mainly aims at improving the interpersonal relationships of a patient and to help the patient in managing reactive grief, widowhood or other role changes.

These thematic priorities make IPT possibly most appropriate for older people, where bereavement and grief are common problems. Indeed, the combination of IPT and medication produces remarkable advantages in the long-term treatment of older MDD patients – compared to both psychotherapy and medication monotherapy (Reynolds et al. 1999). This result is contrary to the popular argument that psychotherapy is less indicated in older patients.

The results from Frank and colleagues (Frank et al. 1990) are consistent with other controlled long-term investigations on the efficacy of imipramine (Keller et al. 1995; Mueller et al. 1999), which show that pharmacological maintenance treatment is effective if it consists of the same drug treatment, given at the same doses as that administered for the initial response, and if it lasts 2 episode cycles. SSRI are known to cause fewer adverse events leading to dropouts (Lima, Moncrieff 2000), and, therefore are more likely to show lower dropout rates in maintenance therapy.

In long-term treatment, medication compliance may be a considerable problem, especially when treating an outpatient over the recommended long period of 5 years. A higher dropout rate for pharmacotherapy alone versus COMBI has been reported in former reviews. But, with the exception of the Hautzinger study (Hautzinger et al. 1996), we found no support for this hypothesis. A possible explanation is the high level of drug counselling and social support, especially in the more complex study designs of the studies cited above. For example, in the Frank study, patients in the drug groups received information material and a large amount of clinical management.

The advantage of COMBI seems to be most obvious for patients with more severe forms of chronic depression. COMBI was superior to medication alone in patients with the following diagnoses: 1) dysthymia with additional MDD, or 2) persisting MDD or 3) partially remitted MDD with poor episode recovery (Keller et al. 2000). The results of the Keller study are somewhat unusual for acute treatment studies. It cannot be excluded that the relatively low mean dose of nefazodone, a more mild antidepressant, may be the cause of the low response rate in the "medication alone" group compared to the combination of nefazodone with psychotherapy. However, the results of Paykel (Paykel et al. 1999) favour the hypothesis that patients with partial remission and/or incomplete episode recovery following medication may profit most from COMBI.

On the contrary, in milder and more uncomplicated forms of acute MDD, a COMBI is neither superior to psychotherapy nor to pharmacotherapy. However, the severity of depression is a clear indication for the addition of pharmacotherapy to psychotherapy (Thase et al. 1997). For MDD patients suffering from more severe acute episodes, a COMBI is more effective in reducing depressive symptoms compared to psychotherapy alone. Patients also recover faster in the acute phase when treated with antidepressants and psychotherapy, than if treated with psychotherapy alone.

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