Combining psychotherapy and pharmacotherapy for the treatment of depression: A critical review of outcome studies

ABSTRACT

Background
Treatment of depressed outpatients with a combination of psychotherapy and medication could have important clinical advantages.

Aims
The authors hope to answer the question whether combination therapy is the most effective treatment for outpatients suffering from Major Depressive Disorder.

Method
A search in Medline was performed in combination with extant reviews and cross-references.

Results
We found a total of 24 papers, encompassing 21 studies. Overall we did not find evidence in favor of combination treatment. In the case of specific subgroups of patients, combination treatment may however be more effective than single treatment conditions.

Conclusion
Due to methodological problems found in virtually all of the studies, no definitive conclusions on the value of combination treatment can be made. More research in this area is needed. This is essential because combination treatment could well have advantages in improvement of outcome as in areas such as quality of life and treatment compliance.
Introduction

It is clear that major depressive disorder (MDD) is a serious and debilitating illness. It is also a commonly occurring illness. For instance, in the Netherlands the 12-month prevalence of depression is estimated to be 7.6% (Bijl & Ravelli, 2000). Various treatments for MDD are reported to be successful, but in clinical practice remission rates rarely exceed 30%. Clearly there is room for improvement.

One of the possible strategies is to combine two (or more) effective treatments. While there are other possible combinations (combining medications, combining pharmacotherapy and non-verbal therapy and others), in this chapter we will consider the combination of psychotherapy and pharmacotherapy (hereafter “combination treatment”).

One of the disadvantages of this combination is that it is more expensive to deliver than either therapy alone. For this reason alone the burden of proof is on combination therapy.

We shall give an overview of efficacy studies published in the last 20 years. This review is meant to answer the following questions:

1. Is the combination of psychotherapy and pharmacotherapy more efficacious than either treatment alone?
2. Does this combination offer (perhaps additional) advantages other than efficacy?

This review is largely based on an earlier publication (Blom et al., 2000a). Because a number of studies on combination treatment have been published since then we felt it necessary to update the original article.

Theoretical advantages and disadvantages of combination treatment
The main purpose of combining treatments is of course to enhance efficacy of treatment. Some (Klerman, 1991) speculate that psychotherapy and pharmacotherapy may have a synergistic effect: pharmacotherapy improves the biological symptoms of
depression (sleep, concentration) and psychotherapy the more psychological
symptoms (coping, overall social functioning). Other advantages could be found in the
facilitation of psychotherapy by medication by reducing somatic symptoms with
medication and helping the patient profit more from psychotherapy (Klerman, 1991).
A further theoretical advantage of combination treatment may lie in the enhancement
of compliance (Paykel, 1995).
It has certainly been found that combination therapy has a positive effect in preventing
relapse (Bockting, Schene et al., 2005; Bockting, Spinhoven et al., 2006; Fava,
Rafanelli et al., 1998; Segal, Williams et al., 2002; Simons, Murphy et al., 1986) and
in the treatment of residual symptoms (Fava, Grandi et al., 1994). In particular, the
detrimental effects of depression on social functioning can be an indication for
combination therapy (Coryell, Scheftner et al., 1993).
In an overview Klerman (1991) sums up some theoretical disadvantages of
combination treatment: that in a combination treatment medication reduces motivation
for therapy by reducing symptoms, that it negatively influences expectations for
psychotherapy, and that it creates a possible symptom shift because medication does
not address the root of problems but merely reduces symptoms. Klerman believed that
most of these objections are based on ideology rather than scientific evidence. As a
practitioner one must however be aware of theoretical differences of opinion between
psychotherapist and pharmacotherapist, because they may influence the way in which
both will cooperate in combination treatment.

Method
A literature search was performed using MedLine, PsychInfo, recent overviews
(Friedman, Detweiler-Bedell et al., 2004; Jarrett, 1995; Manning & Frances, 1990;
Otto, Smits et al., 2005; Pampallona, Bollini et al., 2004), and cross-references. Studies
were included if patients met a diagnosis of non-chronic MDD and were between 18
and 65 years of age. In addition to a combination condition, the study also had to
include at least one single condition as comparison condition. Whenever possible,
follow-up results of the acute studies were consulted. Only randomized clinical trials (RCTs) were included in our overview.

**Comparison criteria**

In recent years the number of trials studying combination treatment has greatly increased. In all we found 24 papers describing 21 studies (Table 1) (the Thase et al. 1997 study is not included in table 1). Many of the older studies suffer from a small sample size (number of patients per condition). If the number of patients who completed the study was smaller than 15 per cell, we did not include that study in our final analysis.

Of the 24 studies found, 3 concern the same patient group (Bellack, Hersen et al., 1981; Bellack, Hersen et al., 1983; Hersen, Bellack et al., 1984). We have included only one paper (Bellack et al., 1981) from that study in our analysis.

The publication by Thase, Greenhouse et al. (1997) will be discussed separately since it isn’t an RCT, but a compilation of three separate RCTs.

In all of the studies, by far the most common form of psychotherapy used is cognitive-behavioral therapy (CBT) (13 studies, (Beck et al., 1985; Blackburn, Bishop et al., 1981; Covi & Lipman, 1987; Hautzinger, de Jong-Meyer et al., 1996; Hollon & De Rubeis, 1992; Murphy et al., 1984; Roth, Bielski et al., 1982; Rush, Kovacs et al., 1981; Rush & Watkins, 1981; Scott, Tacchi et al., 1997; Scott & Stradling, 1990; Stravynski, Verreault et al., 1994; Teasdale, Fennell et al., 1984). Two studies use interpersonal psychotherapy (IPT) (Reynolds, Miller et al., 1999b; Weissman et al., 1979) and 3, supportive psychodynamic psychotherapy (Burnand, Andreoli et al., 2002; de Jonghe, Hendriksen et al., 2004; de Jonghe, Kool et al., 2001). Marital therapy (Friedman, 1975), supportive therapy (Mynors-Wallis, Gath et al., 2000), and behaviour therapy (Bellack et al., 1981) were used once each.

Many of the older studies cited in this chapter are difficult to interpret because of methodological shortcomings. When we apply the criteria defined in Chapter 2 to these studies we find the following:
Use of a form of psychotherapy with proven efficacy
In some of the studies listed on Table 1, it is not clear if an effective form of psychotherapy was used. By effective we mean that there should be some prior evidence, preferably from an RCT, of the psychotherapy being effective compared to a control (e.g. waiting list) or better yet, to an active control group (medication, different form of psychotherapy, supportive treatment). In some studies (Bellack et al., 1981; de Jonghe et al., 2001, 2004) such evidence was not available. As Pampallona et al. (2004) remark, in these instances it is not clear if a combination treatment advantage can be seen as the result of combining two effective treatments or rather as the result of an enhancement of compliance (by psychotherapy) to pharmacotherapy. We have included in our analysis the studies by the Jonghe (2001, 2004), even though no proof has been found that the supportive psychodynamic psychotherapy used is an effective treatment by itself. They were however large studies, and like our own study, carried out in a standard outpatient setting.
Table 1: Acute major depressive disorder studies comparing combination treatment to psychotherapy alone, medication alone, or both alone (studies marked with * are included in the final analysis).

<table>
<thead>
<tr>
<th>Study</th>
<th>Conditions(^2) (N completers)</th>
<th>Length (weeks)</th>
<th>Follow up (months)</th>
<th>Blood level taken?</th>
<th>Rating scales(^3)</th>
<th>Mean HAMD score start of trial</th>
<th>Dropout (%) per cell</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck, 1985</td>
<td>Pt(14) vs. C (11)</td>
<td>12</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>20.5</td>
<td>22 vs. 27</td>
<td>ND</td>
<td>Very small N</td>
</tr>
<tr>
<td>Bellack, 1981, 1983 Hersen, 1984</td>
<td>M (8) vs. C (13) vs. Pt+Pp(17) vs. Pt2 + Pp(13)</td>
<td>12</td>
<td>6</td>
<td>-</td>
<td>+</td>
<td>24.7</td>
<td>50 vs. 67 vs. 50 vs. 54</td>
<td>ND</td>
<td>Only female patients. Small N</td>
</tr>
<tr>
<td>Blackburn, 1981(^3)</td>
<td>Pt (22) vs. M(20) vs. C (21)</td>
<td>12-16</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>18.9</td>
<td>18 vs. 19</td>
<td>C&gt;Pt&gt;M</td>
<td>Medication not optimal</td>
</tr>
<tr>
<td>Burnand, 2002(^*)</td>
<td>C (35) vs. M (39)</td>
<td>10</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>24.1</td>
<td>26 vs. 19</td>
<td>C&gt;M</td>
<td>Psychotherapy performed by nurse.</td>
</tr>
<tr>
<td>Covi &amp; Lipman, 1987(^*)</td>
<td>Pt(27) vs. C (23) vs. Pt2 (20)</td>
<td>14</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>18</td>
<td>16 vs. 32</td>
<td>C=Pt=Pt2</td>
<td></td>
</tr>
<tr>
<td>De Jonghe, 2001(^*)</td>
<td>M (33) vs. C (59)</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>20.4</td>
<td>61 vs. 29</td>
<td>C&gt;M</td>
<td>Very low response on AD</td>
</tr>
<tr>
<td>De Jonghe, 2004(^*)</td>
<td>Pt(75) vs. C (79)</td>
<td>24</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>18.1</td>
<td>29 vs. 24</td>
<td>ND</td>
<td>Trend for combination</td>
</tr>
</tbody>
</table>

\(^1\) C= combination; M= medication; Pt = psychotherapy; Pp= pill-placebo; TAU= treatment as usual; WL=waitlist

\(^2\) + means a rating scale used other than a depression severity rating scale (e.g. Social Adjustment Scale)

\(^3\) Although Blackburn et al (1981) report on one study, in fact two different groups of patients were studied. In the first section patients referred by an outpatient department, the bottom group were patients referred by their GP. The former group tended to have more severe symptoms.
<table>
<thead>
<tr>
<th>Study</th>
<th>Conditions¹ (N completers)</th>
<th>Length (weeks)</th>
<th>Follow up (months)</th>
<th>Blood level taken?</th>
<th>Rating scales²</th>
<th>Mean HAMD score start of trial</th>
<th>Dropout (%) per cell</th>
<th>Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedman, 1975</td>
<td>M (34) vs. C (36) vs. Pp+Pt (36) vs. Pp (34)</td>
<td>12</td>
<td>-</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>19 vs. 17 vs. 16 vs. 15</td>
<td>ND</td>
<td>Low dose of AD. AD was tapered before end of study</td>
</tr>
<tr>
<td>Hautzinger, 1996*</td>
<td>Pt(54) vs. M(46) vs. C(52)</td>
<td>8</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>24.4</td>
<td>17 vs. 16 vs. 16</td>
<td>ND</td>
<td>Study also compared in- and outpatients.</td>
</tr>
<tr>
<td>Hollon, 1992*</td>
<td>M(32) vs. Pt(16) vs. C(16)</td>
<td>14</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>24.1</td>
<td>44 vs. 36 vs. 36</td>
<td>ND</td>
<td>Trend in favor of combination</td>
</tr>
<tr>
<td>Mynors-Wallis, 2000</td>
<td>Pt-GP (34) vs. Pt-N(36) vs. M(34) vs. C(31)</td>
<td>12</td>
<td>12</td>
<td>-</td>
<td>+</td>
<td>20.3</td>
<td>10 vs. 12 vs. 0.1 vs. 13</td>
<td>ND</td>
<td>Medication not optimal</td>
</tr>
<tr>
<td>Murphy, 1984*</td>
<td>Pt(19) vs. M(16) vs. C(18) vs. Pt + Pp(17)</td>
<td>12</td>
<td>12</td>
<td>+</td>
<td>-</td>
<td>19.9</td>
<td>21 vs. 33 vs. 23 vs. 0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Reynolds, 1999*</td>
<td>M(25) vs. C (16) vs. Pt + Pp(17) vs. Pt (22)</td>
<td>16</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>19.9</td>
<td>0 vs. 24 vs. 25 vs. 0</td>
<td>C&gt;M&gt;Pl</td>
<td>Only elderly (&gt; 55) patients.</td>
</tr>
<tr>
<td>Roth, 1982</td>
<td>Pt(13) vs. C (13)</td>
<td>12</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>Unknown</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Rush &amp; Watkins, 1981</td>
<td>Pt(23) vs. Pt(2) vs. C (7)</td>
<td>10-12</td>
<td>12</td>
<td>-</td>
<td>+</td>
<td>Unknown</td>
<td>18 vs. 11 vs. 0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Scott &amp; Strandling, 1990</td>
<td>Pt + TAU(10) vs. Pt2+TAU(19) vs. WL+TAU</td>
<td>12-15</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>Unknown</td>
<td>41 vs. 30 vs. 17</td>
<td>OCT+TAU =CT+TAU =TAU</td>
<td>Medication prescribed by GP and not optimal</td>
</tr>
<tr>
<td>Study</td>
<td>Conditions^1 (N completers)</td>
<td>Length (weeks)</td>
<td>Follow up (months)</td>
<td>Blood level taken?</td>
<td>Rating scales^2</td>
<td>Mean HAMD score start of trial</td>
<td>Dropout (%) per cell</td>
<td>Results</td>
<td>Remarks</td>
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<td>-----------------------------------------</td>
</tr>
<tr>
<td>Scott, 1997</td>
<td>Pt+TAU(16) vs. TAU (18)</td>
<td>6</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>33 vs. 25</td>
<td>CT+TAU &gt;TAU</td>
<td>Medication not optimal</td>
<td></td>
</tr>
<tr>
<td>Stravynski, 1994</td>
<td>Pt vs. C</td>
<td>15</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>24</td>
<td>Unknown</td>
<td>ND</td>
<td>No N given</td>
</tr>
<tr>
<td>Teasdale, 1984</td>
<td>TAU(17) vs. Pt + TAU(17)</td>
<td>16</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>18.5</td>
<td>15 vs. 29</td>
<td>ND</td>
<td>Medication not optimal</td>
</tr>
<tr>
<td>Weissman, 1979; DiMascio, 1979*</td>
<td>Pt(17) vs. M(20) vs. C (23) vs. WL(21)</td>
<td>16</td>
<td>12</td>
<td>-</td>
<td>+</td>
<td>52 vs. 67 vs. 24 vs. 70</td>
<td>C&gt;IPT=M&gt;WL</td>
<td>Only female patients</td>
<td></td>
</tr>
</tbody>
</table>

C= combination; M= medication; ND = No difference; Pt = psychotherapy; Pp= pill-placebo; TAU= treatment as usual; WL=waitlist
^1 + means use of a rating scale other than a depression severity rating scale (e.g., Social Adjustment Scale)
^2 Although Blackburn et al (1981) report one study, in fact two different groups of patients were studied. In the first group patients were referred by an outpatient department, the second group consisted of patients referred by their GP. The former group tended to have more severe symptoms.
**Measurement of outcome**

Reduction of the severity of MDD is seen by most studies as the primary outcome measure. In later studies it has become more common to use remittance as outcome criterion. Remittance is most often defined as a score of 9 or less on the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) at the end of the study. In all but very few studies, the HAMD is used as primary measure of outcome despite its being criticized (Bagby, Ryder et al., 2004; Zimmerman, Posternak et al., 2005). Particularly in trials comparing psychotherapy to medication, the use of the HAMD is said to favor medication because of its relative overscoring of somatic symptoms in MDD. However, use of other rating scales to measure severity of depression, such as the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) or the Inventory of Depressive Symptoms (IDS) (Rush, Gullion et al., 1996), is rare. It is noteworthy that when another outcome measure (the Social Adjustment Scale (SAS) (Weissman & Bothwell, 1976) was used, (Weissman et al., 1981), an incremental benefit in favor of the combination was found. It is not clear whether only IPT has this effect or whether other forms of psychotherapy would show the same benefit. Some studies (see Table 1) have used the SAS, but results were not reported. It is therefore an open question whether CBT has an effect comparable to IPT on social functioning.

**Size of the treatment group**

The older studies in particular suffer from a small N. In some studies (Bellack et al., 1981; Blackburn et al., 1981; Rush et al., 1981; Stravynski et al., 1994) cells even contained 10 patients or less. Though the more recent studies are far better in this regard, it is very rare for a study to reach the minimum size of 30 patients per cell necessary to ascertain a statistical difference as described by Manning et al. (1990). As indicated in Chapter 2 these small numbers make the chance of a type II statistical error a real possibility. For this reason we have excluded studies with an N smaller than 15 subjects per cell from our final analysis.
**Study design**

As explained in Chapter 2, the optimal design for a study of combination treatment would encompass 7 or 8 different conditions, though for practical reasons we do not think such a design is feasible. None of the studies came close to meeting this number of conditions. Yet if too few conditions are included, not all research questions can be answered. In particular, a psychotherapy-pill-placebo condition is missing in all but a few studies. This is unfortunate because by adding this condition one can control for the non-specific therapeutic effects of medication. The combination of psychotherapy and pill-placebo was used in 4 studies (Bellack et al., 1981; Beutler, Scogin et al., 1987; Murphy et al., 1984; Reynolds et al., 1999b). Three of the 4 studies found no difference between the 2 (combined) conditions. The only exception here was the study by Reynolds et al. (1999), but it cannot be ruled out that this was due in part to the specific way in which the trial was conducted: patients in the IPT – pill-placebo condition received significantly fewer sessions of psychotherapy than patients in the IPT-nortriptyline condition.

**Attrition**

In many of the studies, attrition, especially in the pharmacotherapy condition, was high (19 to 67%). It is not clear what the exact reasons are. Regrettably a high dropout is a common finding in depression research, not just in studies comparing combination treatment (Anderson & Tomenson, 1995). It has been suggested that modern antidepressants, notably the selective serotonergic re-uptake inhibitors (SSRIs), have a better track record in this respect (Anderson & Tomenson, 1995), although the advantages are small. (Paykel, 1995) states that combination treatment may have specific advantages for enhancing compliance. In all of the studies we examined this seems to be the case. The dropout rate in medication cells is between 19 and 67%, in the combination cells between 0 and 36%.
**Researcher allegiance**

Four out of the 21 studies were carried out by the inventor of the psychotherapy under consideration (Beck et al., 1985; Bellack et al., 1981; Rush et al., 1981; Weissman et al., 1979) or by a researcher closely associated with the inventor (Hollon & De Rubeis, 1992). Interestingly these researchers all note a clear advantage for the psychotherapy under study compared to the control condition(s). That researcher allegiance is a powerful predictor of success has been noted before (Gaffan et al., 1995). None of the more recent studies, with the exception of the studies by de Jonghe et al. (2001, 2005), suffer from researcher alliance.

**Chronic versus non-chronic MDD**

Miller and Keitner (1996) argue that combination treatment is especially indicated for treating chronic depression. When analyzing data on combination treatment it is best to separate non-chronic from chronic forms of depression. For example in their review, Pampallona et al. (2004), cite 5 studies of chronic depression (Browne, Steiner et al., 2002; Hellerstein, Little et al., 2001; Keller et al., 2000; Miller, Norman et al., 1989; Ravindran, Anisman et al., 1999). While this is less than the number of studies on non-chronic depression (11), they are large studies encompassing 919 patients, almost 50% of the total number of patients (1842) included in all of the studies Pampallona et al. found. Four out of these 5 studies (Hellerstein et al., 2001; Keller et al., 2000; Miller et al., 1989; Ravindran et al., 1999) show an advantage for the combination treatment. For IPT, the small pilot study by de Mello, Myczcowisk et al. (2001) found a small, non-significant advantage of combination treatment over medication alone in dysthymic patients. The study by Browne et al. (2002), thus far the largest using IPT, showed no advantage for IPT over medication, nor for the combination of medication (sertraline) and IPT. Markowitz also did not find an advantage for combination treatment (Markowitz, Kocsis et al., 2005).
For an overview of studies on psychotherapy in chronic depression see (Blom & Jonker, 2005a).

**Follow-up**

Regrettably there are only a few published studies which include a significant follow-up period. We have summarized the findings on Table 2. Considering only the studies with a follow-up period of a year or longer (Beck et al., 1985; Blackburn et al., 1981; Murphy et al., 1984; Rush et al., 1981; Scott et al., 1997; Weissman et al., 1979), then the patients who received psychotherapy are clearly better off. There is a caveat though: in contrast to modern guidelines stipulating that when remission of symptoms has been achieved, medication should be continued at least 6 months to a year. In all of the studies medication was discontinued at the end of the acute phase.

**Results**

Of the 24 studies found we discarded 16. Seven studies because the N was smaller than 15 (see table 1), which we considered the minimum necessary to rule out the possibility of a type II statistical error. Five studies (Blackburn et al., 1981; Friedman, 1975; Mynors-Wallis et al., 2000; Scott et al., 1997; Teasdale et al., 1984) were discarded because the medication dosage prescribed was not high enough or because it was not clear how the medication was prescribed. Three papers reported on the same sample (Bellack et al., 1981; Bellack et al., 1983; Hersen et al., 1984), of which only one was included. Again two papers (DiMascio et al., 1979; Weissman et al., 1979) also reported on the same study. In all, that leaves 9 studies with which useful comparisons can be made. We will discuss separately the study by Thase et al. (1997) which is a ‘mega-analysis’ of six separate studies by the same treatment group, each with a slightly different design.
Combination versus psychotherapy alone
This comparison was made in 7 studies. Only 2 studies (DiMascio et al., 1979; Reynolds et al., 1999) found an advantage for combination over psychotherapy. IPT was the psychotherapy used in both studies. One wonders if the psychotherapy in the study by Reynolds et al (1999) was given in a sufficient dose (see above). Also, patients were over 55 years of age in this study, making it less generalizable. This would leave only the study by DiMascio et al. (1979) showing an advantage for combination therapy over psychotherapy alone for treating acute depression. None of the studies included in our analysis found an advantage for the combination over CBT alone.
The study by Thase et al. (1997) found no advantage of the combination over psychotherapy (CBT or IPT). Only for one subgroup of more severely depressed patients (HAMD > 20) did they find an advantage for the combination over psychotherapy alone.

Combination versus medication alone
This comparison was made in 7 studies. Five (Burnand et al., 2002; Covi & Lipman, 1987; de Jonghe et al., 2001; DiMascio et al., 1979; Reynolds et al., 1999) found an incremental benefit for combination over medication alone. Three studies did not find a difference. Of the 5 positive studies, 2 (de Jonghe et al., 2001; Weissman et al., 1979) were hampered by high attrition in the medication condition. Since attrition is also an outcome, one can view this as a recommendation for combination therapy over medication only. It remains however unclear if this outcome really is the result of a true advantage of a combination of 2 active therapies or is simply the effect of enhancing compliance by the addition of psychotherapy to medication.
As noted earlier, the design of the study by Reynolds et al. (1999) was inappropriate.
In only one study (Burnand et al., 2002) did the combination have an unequivocal advantage over medication alone. However there is a problem with
the Burnand study too, namely that the form of psychotherapy (psychodynamic-supportive) used had not been tested separately.

In the ‘mega-analysis’ by Thase et al. (1997) no advantage of the combination over medication only was found, neither for the whole group, nor for the subgroup of more depressed patients.

One can conclude that 4 out of 7 studies found an advantage of combination over medication alone, but that all 4 of these studies were seriously hampered by shortcomings in methodology and in execution of the trial.

Therefore, as Pampallona et al. (2004) have remarked, it remains to be seen whether adding psychotherapy to medication simply enhances compliance (and thereby explains the difference in outcome) or is a true incremental effect of the psychotherapy used.
Table 2: Results follow-up (FU)

<table>
<thead>
<tr>
<th>Author</th>
<th>Length FU (ms)</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackburn (1981) (Blackburn, Eunson, &amp; Bishop, 1986)</td>
<td>12</td>
<td>Significantly more relapse in medication condition.</td>
<td>All treatment was stopped at the end of the acute phase.</td>
</tr>
<tr>
<td>Covi &amp; Lipman (1987)</td>
<td>9</td>
<td>Differences at endpoint were maintained.</td>
<td>Psychotherapy was stopped at the end of acute treatment, medication was tapered but not stopped.</td>
</tr>
<tr>
<td>Hautzinger (1996)</td>
<td>12</td>
<td>No difference in remittance.</td>
<td>Not clear if medication was continued in FU. Psychotherapy was stopped.</td>
</tr>
<tr>
<td>Murphy (1984) (separate publication (Simons, Murphy, Levine, &amp; Wetzel, 1986))</td>
<td>12</td>
<td>Cognitive therapy alone or combined with pill-placebo was more effective.</td>
<td>Medication and psychotherapy were stopped after acute phase.</td>
</tr>
<tr>
<td>Mynors-Wallis (2000)</td>
<td>12</td>
<td>No difference between conditions.</td>
<td>All patients were referred back to GP. Treatment in FU unknown.</td>
</tr>
<tr>
<td>Reynolds (1999)</td>
<td>4</td>
<td>Differences at endpoint were maintained.</td>
<td>Very short FU.</td>
</tr>
<tr>
<td>Scott (1997)</td>
<td>12</td>
<td>Differences were maintained.</td>
<td>Only 33% of patients in control group was seen at FU. Treatment in FU (by GP) was unknown.</td>
</tr>
<tr>
<td>Teasdale (1984)</td>
<td>3</td>
<td>No difference</td>
<td>All patients were referred back to GP. Treatment in FU unknown.</td>
</tr>
<tr>
<td>Weissman et al. (1979, 1981)</td>
<td>12</td>
<td>Significant improvement in social adjustment in patients receiving IPT.</td>
<td>Medication was stopped at end of treatment.</td>
</tr>
</tbody>
</table>
Conclusions
We have tried to answer the question whether combination treatment is more efficacious than either pharmacotherapy or psychotherapy alone. Combination treatment had an advantage over psychotherapy alone in two studies compared to 5 studies that did not show a difference. These two studies both used IPT. One could hypothesize that IPT could be more easily combined with medication because of IPT’s explicit use of the medical model. Clearly there is room for more and larger studies to examine this.

The case for combination treatment over medication only is more intriguing. The problem of attrition is especially large in medication-only conditions. It could well be that attrition is high because of the use of tricyclic antidepressants (TCAs) in most of the studies. TCAs have more, and more serious, side effects than modern antidepressants. It remains to be seen whether the use of modern antidepressants leads to a lower attrition rate. In the only study that did use modern antidepressants (de Jonghe et al., 2001) attrition was very high, so this speculation is uncertain.

Putting the results of all of these studies together, we cannot conclude as yet that combination treatment has an advantage over either psychotherapy alone or medication alone. On the other hand, due to the many methodological problems encountered in most studies so far, it is also difficult to conclude the contrary. Clearly there is a need for larger studies comparing modern psychotherapy with modern antidepressants.