Evaluating the combination of medication and psychotherapy in depression treatment:

Conceptual and methodological problems

ABSTRACT

Background
The prevailing opinion among psychotherapy practitioners/clinicians is that a combination of psychotherapy and pharmacotherapy is the most effective treatment for Major Depressive Disorder (MDD). Available research does not support this opinion. The authors propose that this discrepancy is mainly due to specific problems encountered in this type of research.

Aim of the study
To summarize which specific problems have important repercussions on studies in this area.

Methods
On the basis of the published literature on combination treatment and their own experience, the authors describe the conceptual and methodological problems encountered in these studies. Based on available literature and the opinions of the authors a description of the conceptual and methodological problems encountered in the studies is given.

Results
Research in this area presents many specific problems. Nine recommendations are made for conducting future studies in this area. The number of participants to achieve sufficient statistical power, the composition of the population, researcher expertise in pharmacotherapy and psychotherapy, the use of outcome measures other than the usual depression rating scales, and a sufficient duration in the follow-up period are the most important recommendations for future studies.

Conclusion
Most studies do not satisfy the recommendations put forward in this article. This may very well explain the discrepancy found between the opinion of clinicians and the
results of the studies in this area. If future studies take into consideration the recommendations given in this article, a more definitive conclusion about the relative value of combination therapy could then be made.
**Introduction**

There are several efficacious treatments available for patients suffering from major depressive disorder (MDD). The efficacy of medication is well established. Several forms of psychotherapy, in particular cognitive therapy (CT) (Beck et al., 1979), behavior therapy (BT) (Lewinsohn, Sullivan et al., 1982), and interpersonal psychotherapy (IPT) (Klerman, Weissman et al., 1984), have also been found to be efficacious. Generally speaking, medication and psychotherapy seem to be equal in efficacy in the treatment of mild to moderate depression (APA, 2000; Robinson, Berman et al., 1990). While these various forms of treatment help around 50% of patients, there is clearly room for improvement (Casacalenda, Perry et al., 2002). One obvious possibility is to combine medication and psychotherapy. Clinicians generally prefer this strategy (McIntyre, Zarin et al., 1996) but despite its popularity, research has failed to substantiate its efficacy (Blom et al., 2000a). The lack of evidence has not kept APA guidelines from designating this combination therapy as the treatment of choice for severe forms of depression (APA, 2000). In this chapter we will discuss the major conceptual and methodological problems encountered in the study of combination treatment, and explain why the lack of evidence may be inherent in the specific difficulties encountered in this type of study.

**Conceptual problems**

**Type of psychotherapy**

When one studies the combination of two forms of treatment and tries to prove that the combination is more efficacious than either treatment alone, each treatment must of course have to been shown to be so on its own. Not every therapy used in the treatment of depression has been sufficiently proven to be efficacious. For instance, the Depression Guideline Panel review (1993) found the efficacy of cognitive therapy (CT) to be 46.6%, interpersonal psychotherapy (IPT), 52.3%, behavior therapy (BT), 55.3%, and brief psychodynamic therapy, 34.8%. Clearly there are differences in the
efficacy of psychotherapies used in the treatment of MDD. The same meta-analysis found the efficacy of all antidepressant medications to be 57.8%. Pill-placebo efficacy is usually estimated to be between 20 and 50%.

Although these percentages suggest sufficient knowledge of the efficacy of psychotherapy, their primary weakness lies in the small number of studies upon which the estimates are based. The conclusion for IPT for instance was based on two randomized clinical trials (RCT), those for psychodynamic psychotherapy on five. While the conclusions must be treated with caution, they do give an indication of the relative efficacy of treatments used in depression.

To date the largest trial comparing psychotherapy, medication, and pill-placebo in the treatment of MDD was the Collaborative Treatment of Depression Program. Two forms of psychotherapy were included in this study. For a psychotherapy to be included, it had to fulfill only three relatively simple criteria: 1. it had to be specifically applicable to depression, 2. it had to be easily taught to other therapists (preferably with a manual), and 3. there had to be prior proof of efficacy (Elkin et al., 1985). Only CBT and IPT met these three criteria. That only two forms of psychotherapy were able to comply with these rather simple criteria is surprising.

In the ensuing study, no differences were found among any of four conditions: imipramine plus clinical management, IPT alone, CBT alone, and pill-placebo and clinical management (Elkin et al., 1989). In a separate analysis of patients suffering from more severe illness at baseline, both imipramine plus clinical management and IPT were found to be more efficacious than CBT and pill-placebo (Elkin, Gibbons et al., 1995).

Of the psychotherapies currently in existence, only IPT, CBT, and BT have been found to be effective in treating acute MDD (NICE, 2003). In one trial (Keller, McCullough et al., 2000) on chronic forms of depression, the cognitive behavioral analysis system of psychotherapy (CBASP) has been found efficacious. It is not known if CBASP is equally efficacious in acute depression.

If one accepts the conditions listed above, that in research into the efficacy of combination treatment each treatment in the combination must have been proven to be
effecacious on its own, then research on combination therapy is currently only feasible with IPT or CBT, and to a lesser extent, BT.

**Different outcome measures**
The most widely used outcome measure for depression is the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960). This scale has been criticized for its overrepresentation of somatic symptoms of depression. It could well make this scale less suitable in psychotherapy outcome research. Weissman, Prusoff et al. (1979) pointed out that medication and psychotherapy do not always have effect on the same symptoms. For instance, in the Weissman et al (1979) study medication generated more improvement in somatic symptoms such as sleep and anxiety, whereas IPT generated more improvement in social adjustment (Weissman, Klerman et al., 1981). When evaluating the possible advantages of combination treatment, one cannot only rely on the HAMD but must also use instruments that take into account other measures of outcome, such as social functioning, quality of life, and medical consumption. It may be that the advantages of combination treatment are to be found in those areas.

**One cook or two**
In most if not all studies on combination treatment, medication was administered by psychiatrists, psychotherapy by psychotherapists. Only in the studies by Beck, Hollon et al. (1985) and Murphy, Simons et al. (1984) were both therapies sometimes given by one and the same person and sometimes by different persons. It cannot be ruled out that this fact influenced the final results (Hollon, Shelton et al., 1991). If the combination treatment is carried out by one person, both the therapist and the patient will experience the process as one integrated treatment. With two therapists (a psychopharmacologist and a psychotherapist), the patient is more likely to experience the procedure as two separate treatments. In the latter case, patient and therapists are more inclined to attribute improvement to one of the two treatments in the combination. Also, there is the risk that the patient may choose to continue with half of the combination if one of the two is too taxing or has too many side effects.
On the other hand it seems reasonable to suppose that the best result might be achieved if therapy is provided separately by a specialist in each respective area. We know of no study in which these two alternatives were compared.

A second problem is treatment rationale for combined treatment. Explaining depression for instance as a medical illness (for which one prescribes medication) can undermine a psychotherapeutic rationale of depression. If the two therapists express to the patient different rationales for treatment, this will obviously influence the patient’s choice.

**Sequential or parallel**

In most studies on combination treatment, both treatments were started at the same time. This is not mandatory. One can also start psychotherapy first and add medication later, or vice versa. In fact this is probably what happens in clinical practice. All three forms can have advantages and disadvantages. No studies, to our knowledge, have compared these forms of combination treatment.

**Research domain**

It is assumed that patients who conform to the diagnosis of MDD in the DSM-IV (APA, 1994) make up a homogenous group. This is clearly not the case. Within the category of MDD one can distinguish different subgroups (by length and severity of index episode, number of previous episodes) and disorder characteristics (melancholic, catatonic, atypical). In all of the studies we examined these subgroups were not identified separately so it is not clear if some groups of patients profit more from combination treatment than others. On theoretical grounds one could for instance assume that patients with chronic depression would profit more from combination treatment (Miller & Keitner, 1996). If one takes comorbid conditions into consideration, many more patient subgroup possibilities present themselves. It could well be that for instance patients with comorbid axis II conditions profit more from combination treatment.

If one were to study these subgroups, the population studied would have to be large enough to include each of the groups in significant numbers. Clearly the size and
scope of such an undertaking would make the research more difficult and expensive to perform.

**Methodological problems**

**Ceiling effect**
If one combines an effective treatment with a second, it may be that the former will not add any benefit because the maximum attainable effect has already been achieved with the first treatment. If one wished to determine more subtle, but clinically relevant, effects, again, large numbers of patients would have to be studied.

**Large number of possible conditions**
According to Hollon and De Rubeis (1981), there are 8 cells necessary to describe all the possible treatment permutations (see Table 1).

Placebo-psychotherapy would be a treatment that requires the same amount of therapist time as ‘real’ psychotherapy. Only nonspecific factors would have to be used. It is doubtful whether such a form of treatment can be designed. In fact, because of this, Lambert and Bergin (1994) advise against it. In place of a placebo-psychotherapy, a waiting list (i.e. no psychotherapy) control group or “treatment as usual” is more often used. The disadvantages of the former are clear. Treatment as usual is in most studies badly defined and consists more often than not of no treatment or poorly executed treatment.

One could add a ninth cell to Hollon and DeRubeis’ alternatives, that is, no treatment at all.

Manning and Francis (Manning and Frances, 1990) estimate that to achieve sufficient statistical power, the minimum number of patients per cell should be around 30. They arrive at this number by presupposing that the combination approach has a relative large effect size. A more realistic estimate predicated on a recovery rate for the single conditions of 50% and for combination treatment of 70% would require a larger number of patients per cell, at least 60. This would thus require a large N: at least 250 patients (with 4 conditions) to 800 patients if more conditions were used. Only one
study (Keller et al., 2000) has ever managed to study this number of patients. All other studies in this area have failed to include such a number of patients (see chapter 3).

**Table 1: Theoretical possible conditions in combination therapy studies**

<table>
<thead>
<tr>
<th>Med only</th>
<th>Psyth only</th>
<th>Pill-plac only</th>
<th>Psyth-plac only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med + Psyth</td>
<td>Med + Psyth-plac</td>
<td>Pill-plac + Psyth</td>
<td>Psyth-plac + Pill-plac</td>
</tr>
</tbody>
</table>

Plac = Placebo; Psyth = Psychotherapy; Med = medication

**Optimal dosage**
In the medication condition it is relatively simple to ascertain the dosages used and patient compliance with the medication regime. Although seemingly simple to do, in many studies this has not been done.
What is more complicated is to define the “dosage” and integrity of the psychotherapy used. So called ‘dose finding’ studies in psychotherapy have been few. For historical reasons a frequency of 50 minutes once a week is commonly used. For most psychotherapies it is not known if changes in frequency and/or length of therapy matter.
A second issue in this regard is whether the psychotherapy protocol is actually implemented. In most of the older studies it is not clear whether the therapists actually did what they were meant to do. Most recent trials have taped sessions and rated them for treatment adherence.

**Selective dropout**
Dropout in combination studies is generally high. Manning and Francis (1990) and Jarret (1995) found 25 to 50% in the medication condition. Especially when almost half of the subjects drop out, questions about the validity of the findings must be raised. With such a high dropout rate in one of the conditions, it may well be that only a certain selection of patients could be maintained in the study. Preventing dropout is
a major concern for researchers. Frank, Kupfer et al. (1995), for instance state that by
making the patient more of a partner in therapy and research, dropout can be
substantially reduced. Training physicians in compliance enhancement is seldom
done. This may be because most studies on combination treatment are carried out by
researchers whose main interest is in psychotherapy.

**Home team advantage**

Much of the research to date has been carried out by researchers who invented the
psychotherapy form themselves (eg, Beck and Klerman & Weissman). The first
publications about new psychotherapies were without exception positive (Gaffan,
Tsaousis et al., 1995). It would be advisable for the research to be carried out at a
distance from the founding fathers and mothers. Ideologically neutral researchers can
avoid possible biases.

**Patient selection**

In almost every study on combination treatment, patients with comorbid conditions
such as alcohol/drug abuse, personality disorders, and other comorbid disorders
(somatic disorders!) are excluded. The relevance for clinical practice is hereby
reduced. It is common for clinicians to state that the patients they see are not the ones
included in clinical trials. This seems to be particularly to be true for pharmacotherapy
trials (Zimmerman, Mattia et al., 2002).

Many patients seen in studies are not referred but are solicited through advertisements.
Some clinicians argue that this biases results. In most randomized clinical trials
mainly higher income, Caucasian, and less comorbid patients tend to participate. A
recent study confirmed this (Balslev Jorgensen, Dam et al., 1998). If combination
treatment is particularly advantageous for the more severely or chronically depressed,
it would be problematic if these groups were excluded. Possible benefits would be
missed.
**Statistical problems**

In most studies the primary outcome measure is a percentage drop in the HAMD score (Hamilton, 1960). By comparing differences between conditions, the effect on severity of depression for a group of patients can be established. This type of analysis can however cause important results to be missed (Balkom & van Dyck, 1995; Hollon et al., 1991). For example, if combined treatment particularly benefited a subgroup of more ill patients, this effect would be masked when analyzing the group as a whole. When analyzing results of a study using combination treatment, at least two separate possible advantages of the combination should be examined, that is, whether (a) combination treatment as a whole is more effective for all patients, and (b) combination treatment is more effective for a certain group of patients.

**Discussion**

There exists a remarkable division between the opinion of clinicians and the findings of most researchers about the efficacy of combination treatment. The relevance of this issue is considerable. Depression is one of the most common illnesses and very debilitating. The treatments available today are efficacious in only 30 to 50% of patients. More effective methods of treatment need to be found. Given the difficulties outlined here, it is not surprising that researchers have not been able to establish advantages for the combination. To establish definitively whether combination therapy is more effective, future studies should satisfy at least the following conditions:

1. The form of psychotherapy used must have been shown to be effective in prior studies.
2. The primary outcome measure should be an internationally recognized measure (HAM-D, MADRS or IDS). In addition, secondary measures measuring interpersonal relationships, health costs, and other psychosocial parameters should be used.
3. For the combination therapy, responsibility for administering the pharmacotherapy and psychotherapy should be assigned to two different persons, or be delivered by the same person throughout the entire study.

4. The statistical power of the study should be large enough to allow conclusions to be drawn. Because the advantage of combination treatment may be discrete, a large number of patients are needed.

5. The total number of conditions should not be too large. In view of the statistical power needed, a study using four conditions would need at least 200 patients.

6. The study should be performed by a group with expertise in pharmacotherapy as well as in psychotherapy.

7. The research population should resemble the clinical population as much as possible and selection of patients should be kept to a minimum. This means that patients who have received prior treatment, patients with chronic depression, and patients with comorbid personality disorders should be included. It may well be that combination treatment has particular advantages for these subgroups.

8. Some of the advantages found for combination treatment became evident in the follow-up after the trial. Especially a reduction of the risk of relapse has been found to be an advantage for combination therapy over medication only. Studies with a sufficiently long follow-up period are needed.

9. In view of the especially high dropout rates among medication cells reported in prior studies, use of one of the modern antidepressants, with fewer side effects, may well have an advantage in this area, and should be used.