Combining pharmacotherapy and psychotherapy - the example of depressive disorders

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ABSTRACT

The debate about whether to use psychopharmacology or psychotherapy has shifted from an "either / or" debate to a rational discussion of combination therapy or sequential therapy. This paper discusses the reasons for this academic shift.

The implications of this scientific debate are the choice of modality in a particular clinical condition, augmentation effects, prevention of relapse and recurrence with continuation treatment, the sequential application of psychotherapy and pharmacotherapy, improvement of compliance.

Major depression is used as an example of a disorder where the combination of psychotherapy and pharmacotherapy offer great advantages. The evidence for the efficacy of this combination reviewed and discussed.

The studies looking at the neurobiological effects of psychotherapy is reviewed and discussed. The practical aspects of combination therapy are presented and problems inherent are indicated and the effectiveness presented.

Finally the Canadian Psychiatric Association's comprehensive evidence based clinical guideline for the treatment of depressive disorders is discussed as it relates to combination treatment.

The conclusion is that an expanding body of evidence in the use of psychotherapy and psychopharmacology in combination is guiding us. As further studies are done, clearer guidelines will emerge leading to improve evidence-based practice of these modalities.

Keywords: *Pharmacotherapy, Psychotherapy, Depression*

Introduction

The debate has been raging for years now: "To pill or to talk"! Proponents of either side assume almost religious positions at times. Psychopharmacologists have mostly pointed out the non-empirical nature of psychotherapy - no evidence exists to guide the psychotherapist. Psychotherapists stated that giving only medication does not lead to personality growth or resolution of deep-seated conflicts.

However, in recent years the academic debate has shifted. No longer can an "either, or" question be asked. Recent developments in both fields have created a rapprochement that is leading to rational academic questions being asked about when to treat whom with what, and how and when to combine treatments. These advances in thinking have been initiated by several important advances in the field of psychotherapy:

- The "empiricalization" of psychotherapy. Psychotherapy has benefited tremendously from the advent of psychotherapies that are manualized and standardized. The practitioners of these psychotherapies (e.g. cognitive behavioral therapy (CBT) and interpersonal therapy (IPT)) have begun to demonstrate empirical evidence for the efficacy of the therapies.
- At the same time, and following on the empiricalization, a rapid onset of the effect of psychotherapy has been demonstrated.
- The particular methods of these psychotherapies have been refined. Practices and techniques are no longer applied with "religious fervor" but rather grounded in empirical evidence collected through well designed research protocols.
- The neurobiological effects of psychotherapy have been demonstrated in several excellent near-imaging studies.

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All of these factors have combined and heralded the scientific era in the debate. The issues are now about setting the limits of combined treatments, comparing effects through well designed research trials, defining the advantages of and delineating the indications for combination therapy.

The implications of combination

The issue has moved beyond the "either, or" question.

Firstly, it is about the choice of modality in a particular clinical condition. The advent of acceptable diagnostic systems has led to the recognition of clinically defined disorders. Following on this the question of what to use for whom and in which combination is now important i.e. indications for either pharmacotherapy or psychotherapy or the combination. Comparable effects of CBT and psychopharmacology have been demonstrated for the following conditions:

- Major depressive disorder;
- Dysthymia / chronic depression;
- Panic Disorder;
- Social Phobia;
- Obsessive compulsive disorder;
- Generalized anxiety disorder.

Secondly, the question of augmentation arises - can the effect of combination be better than either alone?

Thirdly, psychopharmacological studies have demonstrated prevention of relapse and recurrence with continuation treatment. The same questions are being asked of psychotherapy continuation treatment.

Fourthly, the sequential application of psychotherapy and pharmacotherapy is important - which one should be applied first and which one should follow, or should combinations be used throughout.

Fifthly, practitioners of psychotherapy have noticed improvement of compliance with pharmacotherapy especially if compliance is made part of the psychotherapeutic process.

In summary, most authors on the subject are now in agreement that combination therapy offers several benefits. The most important of these are:

- Improved treatment response;
- Reduced relapse and recurrence rates;
- Enhanced quality of life;
- Facilitation of lower medication dosages;
- Enhanced compliance.

The example of major depression

The treatment of major depressive disorder became one of the earliest examples of a growing body of research demonstrating the aforementioned aspects. In a so-called "mega-analysis" Thase et al[1] pooled 6 studies done from 1982 - 1992 on the treatment of major depression in which psychotherapy (CBT- or IPT-studies) and pharmacotherapy was used alone or in combination. This analysis included 595 depressed out patients, (non-bipolar / non-psychotic) aged 18 to 60 years. On average the treatment lasted for 16 weeks. CBT or IPT alone was given versus IPT in combination with antidepressants.

The following results were found: in less severe depression, as defined by a score of 19 or less on the 17-Item Hamilton depression rating scale (HAM-D-17), all modalities were equally effective (p=0,1). In the more severe depression, as defined by a score of 20 or more on the HAM-D-17, combination therapy was significantly more effective (p=0.001). Time to recovery was equal for all groups but faster in the more severe - combination treatment group. Combination therapy resulted in response in 9 weeks in contrast to 13 weeks for psychotherapy alone.

Thase[1] concludes, "the current study provides the strongest empirical evidence ever marshalled to indicate that combined therapy is superior to psychotherapy alone for treatment of more severely depressed outpatients, in terms of both overall recovery rates and shorter time to recovery."

Jarrett et al[2] conducted a randomized clinical trial in the prevention of recurrent depression using cognitive therapy (CT) with and without a continuation phase. They recruited 156 patients aged 18 - 65 years old. All 84 responders (defined as a HAM-D of 9 or less) were randomized to continuation- or control CT. The result was that over an 8-month period continuation-CT significantly reduced relapse over the controls (10% vs 31%). In patients with early onset major depressive disorder continuation-CT significantly reduced relapse and recurrence rates to 37% versus 62% in controls. In the 24 month analysis it was shown that patients with higher risk for relapse, (e.g. early onset of first depressive episode, unstable remission late in acute phase), continued to have lower relapse rates even after discontinuation of CT. This indicated that the effects of CT continued to endure and this distinguished CT from pharmacotherapy. Higher risk patients who received continuation-CT had comparable relapse rates to low risk patients who only had acute phase CT, indicating the positive response and lowering of risk of relapse to those of low risk patients. The study indicates that CT offers safe, tolerable and effective relapse prevention after acute phase response for treatment of major depressive disorder has been documented. Continuation-CT has also demonstrated replaces prevention in acute phase pharmacotherapy responders, acute phase CT-responders and acute phase combination responders.

The neurobiological effects of psychotherapy

The neurobiological effects of psychotherapy have been demonstrated in several excellent neuro-imaging and neurochemistry studies. The rationale for these studies extends beyond the obvious statement about the need for demonstrating an effect on brain functioning. The biggest revenue from these studies lies in the demonstration of the exact way that the brain is changed as well as the specific areas involved. This is then contrasted with the mechanisms of action of the neuropharmacological agents. As a consequence there is the future promise of better defining the indications for either therapy in different disorders.

Thase et.al.[3] give an excellent review of these findings given in summary as follows:

A reduction of thyroid-stimulating hormone levels was found after CBT treatment. A reduction in postdexamethasone plasma cortisol levels was found among patients randomly assigned to treatment with CBT. The effects of psychotherapy on HPA-activity are not different from effects of amitriptyline. Almost 50% of the dexamethasone "nonsuppressors" in both CBT and amitryptyline groups normalized after treatment. Both IPT and venlafaxine were associated with increased blood

flow to the left temporal or right basal ganglia regions. Both IPT and paroxetine treatment normalized metabolism in the prefrontal cortex and left anterior cingulate gyrus. Neither study found much evidence of differential treatment effects. Patients with more pronounced polysomnographic disturbances were less responsive to CBT or IPT than patients with more normal sleep patterns indicating that more severe forms of major depression might not respond as well to psychotherapy. Poor response to psychotherapy was seen in patients with increased limbic activity on PET scans. Pharmacotherapy, by contrast, may be more efficacious for such patients by virtue of more direct effects on neural circuits or gene activity. Depression associated with more marked, perhaps autonomous disturbances of limbic-brainstem circuitry may be relatively less responsive to psychosocial interventions (i.e. CBT) because of associated impairments in cognitive, hedonic, and mood regulatory capacities.

Practical issues of combination

Three methods of combination have been described:

- Both drug treatment and psychotherapy initiated at the same time;
- The second treatment added after the first;
- The first treatment is discontinued and a second started.

Should both pharmacotherapy and psychotherapy be provided by a single clinician? The obvious answer is that skills in both are required if the clinician is planning to provide both.

If the clinician however does not possess the required skill in psychotherapy, referral to a psychotherapist is essential. This implies good communication and teamwork. The patient also needs to be supplied with a rationale of how the two therapies are complementary and needs to be assured of the open channels of communication between psychiatrist and psychotherapist.

How effective is combined treatment?

Three randomized controlled clinical trials of CBT versus pharmacotherapy versus combination have been done.[1] Two of these found no differences in the acute effects in major depressive disorder. A third found that combination was superior to pharmacotherapy alone. CBT had lower relapse rates than pharmacotherapy alone. The combination of therapies did as well as CBT alone in relapse prevention. In a study by Thase et al[4], the cognitive behavioral analysis system of psychotherapy was compared to nefazodone in the treatment of dysthymic disorder and found that the combination had a better effect than either alone in the treatment of chronic depression.

Recommendation for psychotherapy in the treatment of depressive disorders

The Canadian Psychiatric Association has published a comprehensive evidence based clinical guideline for the treatment of depressive disorders. The section on psychotherapy in the treatment of mood depressive disorders is comprehensive and presents evidence based treatment recommendations.[5]

Recommendation for concurrent combined acute phase treatment (CCT)

CCT is not recommended, as there is at present no evidence for greater efficacy except in chronic depression as indicated by Thase et al.[4] For the treatment of severe depression, the combination of IPT and pharmacotherapy was found to be more effective than either alone. In the maintenance phase treatment, CCT is not recommended as no evidence exists for greater efficacy except in elderly patients where the combination of IPT and nortriptyline may reduce relapse rates.

Recommendation for sequential combined treatment (SCT)

According to the Canadian[5] guideline there exists limited evidence supporting SCT, that is adding either modality of treatment to the other if patient has not responded or had a partial response to monotherapy. The exception has been found in adding CBT to the treatment of patients with residual symptoms after acute treatment with antidepressants - this improves remission rates and reduces relapse / recurrence rates. Also, adding antidepressants to the treatment of women with partial or no response after acute treatment with IPT may improve remission rates.

Recommendations for crossover psychotherapy for maintenance treatment (CPMT)

According to the Canadian guideline[5], CPMT following pharmacotherapy for acute treatment is not routinely recommended, due to the absence of studies comparing crossover psychotherapy with pharmacotherapy in the maintenance phase of treatment.

However, CPMT may be second-line treatment, especially in recurrent depression where CBT, or modifications of CBT reduce recurrence rates in patients who are not receiving maintenance pharmacotherapy.

CONCLUSION

It is clear that an expanding body of evidence in the use of psychotherapy and psychopharmacology in combination is guiding us. As further studies are done, clearer guidelines will emerge leading to improve evidence-based practice of these modalities. Each disorder and its treatment should be approached based on these developing evidence. At best we can say that there are tremendous benefits in combining these treatments whenever indicated, leading to greater treatment response, relapse prevention and patient treatment compliance.

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Commentary

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Dr. Franco Colin's article provides us with a valuable overview of current recommendations for combining psychotherapy and pharmacotherapy based on empirical evidence. This is in keeping with the trend towards evidence based medicine practice. This trend has brought us much in the way of clarity and standardization but it may introduce bias in treatment of psychiatric patients. For example, one obvious bias would be to favor the use of psychotherapies that can more easily submit to "empiricalisation" such as cognitive behaviour therapy (CBT) and interpersonal therapy (IPT) over other types of psychotherapy.

On a practical level we as clinicians regularly experience difficulty applying what appears to be oversimplistic research outcomes and recommendations into practice. In my unit we encounter these difficulties on a daily basis. I strongly believe that in order to best utilise the conclusions drawn from evidence based research we have to be aware of its limitations as well.

Apples and oranges

The therapeutic effects of combining pharmacotherapy and psychotherapy are extremely difficult to research. As result, decisions regarding the combination of pharmacotherapy and psychotherapy are often based on clinicians' personal observations and perhaps dogma as opposed to empirically validated recommendations. Dr. Colin has presented a succinct overview of a number of important studies and reviews done thus far as well as an optimistic prediction for clearer evidence based medicine guidelines in the future. It should be noted that the evidence based literature regarding the use of psychotherapy is less abundant in other disorders as opposed to depression which has been used as the example.

There has been a clear shift towards evidence based medicine over the past decade. In studying the effects of combining pharmacotherapy and psychotherapy researchers have felt compelled to find a common yardstick with which to measure them. After all, you cannot weigh apples and oranges together.

So psychotherapy has had to submit to the scrutiny of empirical research. As result attempts have been made to manualise and standardise therapies. Whether psychotherapy has benefited tremendously from this, as Dr. Colin suggests, is an ongoing matter of debate.

Developments stemming from the evidence based medicine movement include the generation of therapeutic protocols and standards of care. Consequently specific practice guidelines for the treatment of particular problems have emerged within the past decade. Examples include Practice Guidelines for Major Depressive Disorders in Adults.[1] Training programs in cognitive therapy (CT) have mushroomed over recent years in view of the increased demand for evidence based clinical practice and short term therapies.

It is important to remember that the motivating force behind empiricalisation has not only come from researchers and practitioners. Various groups have been pressurising psychotherapists to demonstrate that what they do actually works. Such pressures have come from medical aids, managed health care organisations and consumer activist groups. And most of the time the underlying questions asked are economic. Will psychotherapy cost more than medication? Will the addition of psychotherapy reduce the total cost of medicine used? Can psychotherapy be limited to a specified number of sessions in order to contain costs?

Therefore published guidelines and recommendations such as those from the Canadian Psychiatric Association[2], although useful, have their limitations. They are mostly biased towards evidence based medicine and may indirectly be influenced by an economic agenda.

The real world

The first controlled outcome study comparing CT with imipramine was undertaken in 1977.[3] Since then there has been a regular flow of studies of increasing sophistication comparing CT with pharmacotherapy. With time however there has been a curious trend to smaller effect sizes. Gaffan et al (1995) has suggested several reasons for this occurrence.[4] Early results may reflect higher enthusiasm from therapists who were pioneers in CT. With the widespread (and manualised) use of CT, therapists involved in outcome studies may be less expert. Could studies be reflecting the real world less and less?

Clinical trials involve major problems in their generalisability to clinical practice. These include exclusion of co-morbidity and non naturalistic inclusion criteria. Often personality traits/disorders are ignored as complicating factors in treatment and will likely respond better to psychotherapy as opposed to pharmacotherapy. Excluding subjects with DSM IV personality disorders from studies has various ramifications. In my opinion it reinforces the dichotomy in thinking of patients as either having Axis I or II disorders. It also downplays the importance of personality traits and defences in maintaining Axis I conditions even in the absence of a DSM IV personality disorder. Such longstanding individual characterological factors cannot be addressed by manualised and standardized short term therapies yet they will affect prognosis and compliance on medication.

Persons[5] attempted to elucidate why therapists have failed to

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adopt and integrate empirically validated treatments into clinical practice. It was pointed out that philosophical differences often underpin different psychotherapeutic approaches. Opponents of empirical research and manualised protocols argue that while behavioural and cognitive therapies value symptom reduction, other approaches such as psychodynamic therapies value insight and increased understanding. Which dependent measure should we use to define effectiveness ? Therapist and client variability and factors common to all psychotherapies may play a major role in treatment effectiveness.[6]

Towards a more integrated and naturalistic approach

It is clear, as Dr. Colin has stated, that psychotherapy has been demonstrated to be an essential tool in the treatment of psychiatric conditions. However, in deciding when and how to combine it with medication we need to use an integrative approach taking into account the specific patient's individual needs, expectations and underlying personality structure.

Valuable recommendations and insight can be gained from clinical research but patients in practice cannot be approached as subjects in research studies. At a practical level we can start by looking beyond the DSM IV[7] as a starting point in formulating a treatment plan. The DSM was developed more as a research tool rather than a practice aid, and even in research it has its limitations. Subcategories of depressive disorder as defined by DSM fulfill a useful role in ensuring that outcome studies are concerned with comparable groups of patients. However, as well as using categorical systems, future progress may lie in the study of the response of key symptoms to different treatment approaches. Symptoms such as retardation and anhedonia, for example, may respond differently to cognitive therapy and pharmacotherapy. Such an approach may help to resolve the ongoing heated debates relating to the severity of depression and the differential response to psychotherapy or medication.

In formulating a treatment plan note should be taken of the patient's individual beliefs and expectations regarding medication. My experience is that patients occasionally view medication as interfering with their autonomy and feel more in control of their own treatment in psychotherapy. This is especially prominent in those with marked dependency issues. In cases like this, provided the depression is only mild to moderate, it could be justified to attempt psychotherapy on its own before considering antidepressants.

An assessment should also be made of the patients predominant coping skills and defences as these can guide the clinician not only in deciding whether to combine psychotherapy and pharmacotherapy, but also in deciding which particular form of psychotherapy to use. Psychodynamic therapies should not be overlooked merely because they are not as prominent in research as the manualised therapies. The quality of the therapeutic relationship in CT is important and may be a nonspecific factor common to all therapies and predicting outcome. Several studies have also found a positive relationship between level of competence and outcome.[8] Interestingly Blatt and coworkers (1996) found that pretreatment high levels of perfectionism had a significant negative outcome on patients treated with CT, IPT, pharmacotherapy or placebo.[9]

In conclusion a commonsense and holistic approach is required integrating research findings as well as individual needs of the patient. There may even be times that an emphasis on psychotherapy is more useful than pharmacotherapy[10]. Not to be overlooked is the psychotherapy we do when we are not doing psychotherapy. The importance of listening, educating, re-assuring, empathizing and facilitating a trusting and constructive therapeutic relationship cannot be underestimated.

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