Psychotherapy combined with pharmacotherapy and other medical interventions

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1. Pharmacotherapy and psychotherapy

A young female patient was admitted to the Psychiatric and Psychotherapeutic Clinic in Budapest with agoraphobia and increasingly frequent panic attacks. She had 5–6 panic attacks per week, lasting 20–30 minutes. She said that during the attacks she sweated and felt hot flushes, shortness of breath, palpitations, chest pain, dizziness, nausea and fear of death. She was afraid of fainting, although this had never actually occurred. She was very afraid of the attacks. They were provoked by being in enclosed spaces, crowds and public transport (but not cars, especially if she was driving), and could also happen spontaneously. Alprazolam treatment brought immediate termination of spontaneous panic attacks, but she did not dare to use public transport or even go down the escalator of on the Metro. Neither would she go across bridges. Her drug treatment had to be supplemented with selective serotonin reuptake inhibitors. Later, during the psychotherapeutic treatment, her dosage of alprazolam was gradually reduced and eventually terminated. Hospital treatment was followed by several months of outpatient psychotherapy involving systematic desensitization. Afterwards, she started to travel independently, even by Metro, and had only 1–2 brief panic attacks a year, and only in the Metro (e.g. if it was busy and the train stopped between stations.)

Treatment with psychotropic drugs during psychotherapy is very common. It has long been recognized (e.g. Haase, 1980), and high-quality studies have proved, that where indicated (e.g. medium to severe depression, schizophrenia, agoraphobia with panic attacks), combined drug and psychotherapy treatments are more effective than either treatment on its own (e.g. Cuijpers, 2010; Frank et al, 1990). Several false beliefs act as barriers to combined treatment, particularly the centuries-old but persistent view that to accept medicinal treatment implies some kind of moral weakness (Gamwell and Thomes, 1995), a view which is sadly perpetuated in today’s media.

In what is now regarded as the “gold standard” reference book, Kaplan and Sadock (2005) summarise the combination of psychotherapy, and pharmacotherapy as follows:

- Combined treatments are more effective than psychotherapy or pharmacotherapy on their own.
- The “either-or” question in the treatment of most psychiatric diseases is now an outdated paradigm.
- Reducing anxiety with drugs does not reduce (existing) motivation to follow psychotherapy.
- The psychotherapy and drug treatment may be administered by two or even more different people, but also by a single doctor. If there is more than one person involved in the two kinds of therapy, they must work in mutual respect and cooperation. For some conditions, it is better to keep the two treatments “in the same hands”. Such are schizophrenia, bipolar I disorder, eating disorders, and conditions requiring constant monitoring of the pharmacological treatment for any reason.
- Among the obstacles to pharmacotherapy are attitudes and false beliefs, for example, that drug treatment is “invasive”, “controlling” and constitutes a “weakness” or that only serious diseases are to be treated with drugs.

Nonetheless, there are several difficulties associated with the combined use of psychotherapy and drugs. Assessing its effectiveness runs into methodological problems: several groups have to be studied in parallel, and psychotherapy cannot be compared with a blind “placebo” as can be done with medicines. Doctors tend to think in terms of diagnosis and treatment, which
involves placing patients in a diagnostic category and then choosing medicine appropriate to the category. In the ideal case, the “given” or correctly chosen drug results in a cure. In psychotherapeutic practice, we tend to concentrate on problems and not diagnostic categories, and the problem can change during therapy. These and potential attitudinal problems are summarized in table 6/1.

<table>
<thead>
<tr>
<th>Table 6/1 Comparison of pharmacotherapy</th>
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<tr>
<td>Pharmacotherapy</td>
<td>Psychotherapy</td>
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<tr>
<td>Diagnosis is categorical.</td>
<td>Diagnosis is problem-oriented.</td>
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<td>Patients are put into defined diagnostic categories.</td>
<td>Patient’s condition is set against desired goal.</td>
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<td>The aim of therapy is to terminate the diagnosed syndrome (”improvement”, “restoration”).</td>
<td>The problems can change with time during therapy.</td>
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| The outcome is a “product” of diagnosis and therapy, and the criteria are general. | The aim of therapy is to improve the patient’s health and “effectiveness”.

Patients’ preferences greatly influence the kind of treatment they will accept, and their doctor has to take this into account. There is very little research data on patients’ preferences. Patients’ opinions on a treatment can be influenced by friends, relatives, expectations, media and attitudes, as well as the information they receive from the doctor.

As already mentioned, laypeople often have a negative view of drug therapy, associating it with ideas like “invasive,” “control”, “weakness” and “serious condition”. They often also have specific ideas regarding the side-effects they will accept, and preferences regarding types of drugs and the way they are administered. There is little objective data on this, but our own experience is that if a patient is satisfied with the form of the drug (the shape or colour of a tablet or how quickly it dissolves in the mouth), it is not advisable to change to a different form (Bitter et al, 2010).

Changes in the pharmaceutical industry in recent decades have had a negative effect on pharmacotherapy. Drug research passed from universities to industry in the late 19th and early 20th centuries. By end of the 20th century, over-aggressive marketing seriously had weakened the confidence in the pharmaceutical industry among patients, doctors and even investors, and this phenomenon is much more perceptible in the psychiatric field than in areas such as cardiology and oncology. The crisis of confidence has led to increased official control and almost irrationally vehement demands for evidence-based medicine (Smith and Pell, 2003). This has affected pharmaceutical research and several large companies have abandoned development of psychiatric drugs in the recent past.

In summary, the influences on selecting medication include the doctor’s training and background, the patient’s preferences, and the characteristics of the drug – particularly its efficacy and tolerability/safety. It is important to bear in mind that efficacy and tolerability/safety have different implications for adherence in different branches, such as oncology, infectology and psychiatry. There are also major variations among diseases within psychiatry. Studies of schizophrenia, for example, have found that the main reason for breaking off anti-psychotic treatment is lack of efficacy rather than side effects (Lieberman et al, 2005; Kahn et al, 2008). The situation is different with patients suffering from anxiety. A review of studies involving comparison of quetiapine-XR 300 mg/day treatment and a placebo determined the rate of discontinuation due to adverse events. It used the measure “number needed to harm” (NNH), in this case the number of patients treated for very patient who drops out, so that the smaller the number the higher the dropout rate. The study found NNH to be 9 for bipolar depression, 8 in refractory major depression disorder and 5 for generalized anxiety disorder (Gao et al, 2010). These results confirm a frequent observation in clinical practice that anxious patients are – understandably – more worried about the side effects of drugs than patients being treated for bipolar disorder or schizophrenia. We can
improve adherence by discussing the type and likelihood of side effects with the patient. Indeed, the occurrence of a side effect can actually convince some patients that a drug is working.

One explanation of the greater effectiveness of combined pharmacological and psychotherapeutic treatment is the improvement of adherence brought about by psychotherapy, so that actual efficacy is due to patients taking the medicine more correctly. Psychotherapy also provides an opportunity to detect lack of adherence and analyze its extent and reasons, so that we can help to correct it. One of the commonest reasons for relapse in psychiatric diseases is taking medicines irregularly or abandoning them (e.g. in schizophrenia and bipolar disorder). For schizophrenia, this problem affects about half of all patients (Svestka and Bitter, 2007). Among the causes of non-adherence are the disease itself (e.g. lack of disease insight), aspects of the patient's personality, the health system (e.g. doctor accessibility, price of medicines) and the medicine (the form it is administered in, and more importantly, its efficacy and tolerability).

The placebo effect is an important issue in psychotherapy and pharmacotherapy. A severe difficulty for psychiatric research is the strong placebo effect in control groups, a phenomenon which has been growing steadily for several decades. In clinical studies of antidepressants, about 50% of patients in placebo groups experience improvement in the acute period of a few weeks (Walsh et al, 2002). This may be due to the psychotherapeutic effect, which in this case does not mean psychotherapy within a defined, structured framework, but the empathy, helpful attitude and communication of the staff involved in treatment. In some study centres, the placebo response and the proportion of improvers from the placebo are markedly higher than in others. There can also be a “negative placebo” effect. One study of patient reaction to the antidepressant duloxetine looked at the effectiveness of the drug in maintenance treatment following the acute phase. Patients were randomized to placebo or duloxetine on a double-blind basis after they had completed acute treatment. Figure 6/1 clearly shows that even the patients who continued to receive the drug experienced an – albeit temporary – deterioration in their condition after randomization (Perahia et al, 2006).

For some diseases (e.g. schizophrenia and medium or severe depression), the data shows that the effect of the placebo is not sustained, and deterioration and relapse occur much more quickly among patients treated with placebo than those treated with the active drug. A classic paper by Montgomery et al (1993) nicely illustrates this phenomenon in the treatment of depressive patients with antidepressants and placebo.

2. Combined pharmacotherapeutic and psychotherapeutic treatment of depression

There has been an upsurge in publications on combined pharmacotherapeutic and psychotherapeutic treatment in recent years. The emphasis has been moving away from general principles and frameworks of treatment towards specific treatments and their outcomes. At the time of writing (2010), the most, and perhaps highest-quality, research results concern combined treatment of depression. The redrafting of diagnostic systems has led to the abolition of “neurosis” as a category, and its replacement with several smaller categories. Studies of combined pharmacotherapeutic and psychotherapeutic treatment thus do not cover neurosis, which has been one of the central issues of the classic psychotherapeutic literature. Personality disorders, also very important in psychotherapy, feature very little in combined treatment studies, mainly because there are very few, if any indications for treatment of personality disorders in the authorized summary of product characteristics of most medicines. “Off-label” use is well known in international practice, but is difficult to research because of strict legal and ethical restrictions.

Each year, 7% of the total adult population suffer from depression requiring treatment. In Hungary, there are about 3000 (30/100,000) deaths due to suicide, and about ten times as many suicide attempts. In line with international data, studies have confirmed that two thirds to three quarters of these were connected with diagnosable depression. About 15% of depressives die of suicide. Depression is a disease of great significance in every branch of medicine, because it has a high comorbidity with every chronic and/or serious disease (e.g. chronic pain, diabetes mellitis,
tumours, myocardial infarction). Depression exacerbates these, and degrades the outcome of treatment. One independent predictor of death after myocardial infarction is a diagnosis of major depression in the period when it could be successfully treated (e.g. Bush et al, 2005). For these reasons, we will look in detail at the combined treatment of depression.

The placebo response in clinical studies of depression is high, but is followed by a relatively high relapse rate. Anti-depressant treatment has a significant advantage in preventing relapse: there is a 30–40% higher rate of relapse with placebo treatment (Hirschfeld, 2001). Combined treatment must be planned to incorporate the optimum period of drug treatment, which is the period up to approximately one year after cessation of symptoms. According to Hirschfeld (2001), discontinuation of anti-depressant treatment too early – within one year – correlates with high relapse rates.

We will present the methodology and outcome of the combined treatment through one excellent study (Frank et al, 1990). This was a controlled study of 128 patients treated for recurrent depression. In the acute phase, the patients received combined pharmacotherapy (imipramin) and psychotherapy (interpersonal), and those who reacted to it were randomized into five groups (n=128) and followed for three years. The drug dosage was maintained at a high level (on average 200 mg/day) after the acute phase. This is frequently reduced in practice, and insufficient dosage can be a cause of relapse. The patients in all five groups were told whether they would receive tablets or not, but not whether the tablet was the active drug or a placebo. They were also told whether they would receive further psychotherapy or only medication. The average times to relapse in each of the groups are shown in Table 6/2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Average time to relapse (weeks)</th>
<th>Median time to relapse* (weeks)</th>
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<tbody>
<tr>
<td>Interpersonal psychotherapy and imipramin treatment</td>
<td>131</td>
<td>–</td>
</tr>
<tr>
<td>Medication with imipramin alone (without psychotherapy)</td>
<td>124</td>
<td>–</td>
</tr>
<tr>
<td>Interpersonal psychotherapy and placebo</td>
<td>74</td>
<td>61</td>
</tr>
<tr>
<td>Interpersonal psychotherapy alone (without imipramin or placebo tablets)</td>
<td>82</td>
<td>54</td>
</tr>
<tr>
<td>Medication with placebo alone (without psychotherapy)</td>
<td>45</td>
<td>21</td>
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*The median is the number of weeks which passed until 50% of patients relapsed. Where there is no value, fewer than 50% of patients relapsed during the 3 years.

Frank and his co-workers summarized the analysis of the times to relapse by saying that imipramin had a highly significant prophylactic efficacy in treating depression, and interpersonal psychotherapy somewhat lesser efficacy. They stressed that 200 mg/day was the effective dose of imipramin. Interpersonal psychotherapy lengthened the time to relapse among those who did not receive active imipramin treatment. It is interesting to note that the study was continued for another two years after the end of the third year. The patients remaining in the study were randomized into two groups: one continued with treatment of daily 200 mg of imipramin and the other received a placebo. There was a very convincing difference between the two groups to the advantage of imipramin (Kupfer et al, 1992).

3. Efficacy of combined medication and psychotherapy treatment

Meta-analyses provide a higher level of evidence than one or even several single studies, but there have been very few studies of combined pharmacotherapy and psychotherapy treatment to date. The study by Frank et al (1991) indicated the methodological difficulties, because it needed 5
study cells. The meta-analysis published by Cujpers et al in 2010 identified only 16(!) studies involving a comparison of psychotherapy and active medication vs. psychotherapy and placebo, between 1966 and 2009. It is interesting to note that that the Frank study, otherwise regarded as a classic, was omitted from the meta-analysis, probably because of a technical search and data identification error, which neither the readers nor the editor corrected.

The meta-analysis by Cujpers et al (2010) covers studies of clinically very heterogeneous groups, so that it provides no help in determining areas of indication, but does give an overall evaluation. Their conclusion on the basis of the 16 studies was that the combination of an active drug combined with psychotherapy has a significant but small advantage over combination with a placebo (NOT over a “no pill” cell!). The number needed to treat (NNT) was 7, which means that an average of 7 patients (under clinical study conditions) have to be given active medication instead of placebo for one patient to show a positive outcome. Many internal medicine studies have ended up with similar results. The NNT for asthma corticosteroid treatment for a similar period of combined pharmacotherapy and psychotherapy treatment was found to be 9, according to the Cochran database (Rowe et al, 1998).

There are several considerations involved in judging efficacy: the setting of the study (e.g. inpatient or outpatient department, private practice), the clinical characteristics of the patients in the study, the qualifications of the therapists, the phase of treatment (acute or maintenance), and the period of treatment (a few weeks, several months, a year). Anecdotal evidence has to be handled with care, especially if adduced to support an extreme opinion.

Finally, we should look at two very important considerations. One is that some conditions (e.g. extreme anxiety, violent behaviour) are obstacles to psychotherapy, so that medication helps patients to receive psychotherapy at all. The other is that both pharmacotherapy and psychotherapy carry risks. Many papers and even books deal with adverse and dangerous drug-drug interactions. We know nothing of the risks of combined pharmacotherapy and psychotherapy, and have only a little indirect knowledge based on high-level evidence (e.g. conclusions on the effects of drugs on psychotherapy from their effects on attention and memory).

The risks of psychotherapy itself have been little studied, which further hampers an assessment of the risks of combined treatment. The frequency of suicide attempts among depressive patients treated with both psychotherapy and medication decreased after starting treatment, but some risk remained (Simon et al, 2007). The application guidelines for antidepressants also draw attention to the risk of suicide during treatment, especially among young people. There is no such official warning for psychotherapy.

Just as with pharmacotherapy, suicidal thoughts and intentions often occur during psychotherapy of depressed young people, according to a study by Bridge et al, (2005), which detected the occurrence of suicidal thoughts and intentions in 11 (12.5%) of 88 depressed adolescents given psychotherapy. As well as showing up the methodological problems of combined treatments, this result underlines that depression is a high-risk disease, and this risk cannot be reduced to zero by psychotherapy or any other method.

4. Psychotherapy with medical interventions

<table>
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<th>Psychotherapy and surgery</th>
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<td>As a second-year medical student, I spent a summer placement in an ear, nose and throat department. I often assisted in preparation for tonsillectomies. Two surgeons worked in parallel in different operating theatres. In one, patients often collapsed before reaching the operating chair, and in the other, there was hardly a single occurrence of this during the month of my placement. The first doctor was himself anxious. He spoke somewhat aggressively with his patients and did not maintain conversation with them when they arrived in the theatre. The other doctor spoke kindly and reassuringly with his patients and showed understanding towards their fear.</td>
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This small sample of cases conveys the power of the doctor-patient relationship even without a formal psychotherapeutic setting, as well as the severe anxiety that medical interventions can cause.

Nearly every disease, and symptoms like pain and dizziness, cause anxiety and can lead to avoidance behaviour. The more painful or life-threatening the disease, the more severe these effects are. Doctors often underestimate the anxiety caused by medical examinations and interventions. Fear of pain caused by medical intervention and fear of the outcome of an examination (serious or incurable disease) are particularly common. Many patients also spend several weeks in fear before they are taken for examination.

One of our patients said: “When I was waiting for stomach endoscopy I could not sleep, I was living on sleeping pills, and in terror that I had stomach cancer.” She went to her GP to ask for sleeping pills because she could not get to sleep because of her anxiety and woke up several times during the night. Reducing anxiety for brief, non-life-saving occasional interventions (such as tonsillectomy) is simpler than in the case of treatment for serious diseases (e.g. combined – surgical, radiological, chemotherapy – treatment of tumours).

Anxiolytics can help, but congruent behaviour, and an understanding and helpful attitude on the part of the doctor, and being accessible, are very important. We cannot be on duty day and night, but even a mild symptom of the side effect of a medicine can provoke serious anxiety, which a competent and understanding doctor can alleviate. A state of anxiety related to physical diseases and examinations most often corresponds to adaptation disorder (American Psychiatric Association, 2000).

The tendency for patients to repeat the question “what is my diagnosis?” is a source of irritation for many doctors. What the question really means is, “what will happen to me?”, i.e. what is the course and outcome of my disease going to be like? Many surgeons and internists encounter some psychiatric conditions of organic origin (e.g. confusion or memory loss after head injuries, or anxiety connected to hyperthyroidism) more often than psychiatrists do. It is the responsibility and obligation of the doctor carrying out the intervention to reduce anxiety caused by interventions, and it is no excuse to say, “I’m not a psychologist” or “I’ve never been interested in psychiatry.” Doctors who alleviate their patients’ anxiety and give them hope have much better clinical outcomes than doctors who are rigid, moralizing and authoritarian, a fact borne out by many studies. Mihály Bálint (1990) stated that the doctor’s personality is a factor in healing. Moreover, a doctor can do harm. “Pull yourself together”, “try to behave”, “act like a man” and similar instructions should be eliminated from doctors’ communication. Even without special training, it is possible to imagine what it is like to be a patient, and what a patient will expect in any situation. Psychotherapeutic effects are not confined to fifty-minute sessions: another of Bálint’s findings is that a brief meeting of doctor and patient, perhaps only a few minutes, can be just as valuable.

It is not always easy to decide when patients need information and when their real need is for understanding. Very often, they expect both. When a patient repeatedly calls by telephone to talk about a completely negative tissue pathology report (e.g. after removal of a melanoma), it is worth saying something like, “you seem to be worried about this”. But when the patient calls first and nervously enquires about the test result, that is the time for giving information, e.g. that it is negative. We must avoid making the mistake of talking with patients about their feelings and anxieties when we should be giving information, such as the results of tests we referred them for, or the outcome of interventions we performed (e.g. an operation). For a worried patient, failure to give information often gives the impression that “something is up” and we are concealing something. Even where there is a psychologist or psychiatrist helping the team in treating non-psychiatric illnesses (e.g. oncology or gynaecology), telling patients about test results or how a wound is healing are the competence and duty of the doctor treating the basic disease. Every school of psychotherapy deals with the need for acceptance, understanding attentiveness and provision of information in the doctor-patient relationship, although for non-psychotherapist doctors, the most useful ideas are those formulated in the person-centred approach founded by Carl Rogers (Tringer, 2005).
Even in such a short overview of the subject, it is worth noting that hypnosis can be effective in alleviating or eliminating some kinds of pain (Bányai and Benzcúr, 2008).

Finally, a few words about psychiatric patients who do not recognize or accept that their symptoms are part of a psychiatric disorder. All branches of medicine have their own examination procedures for characteristic symptoms, and patients suffering from psychiatric diseases often take their symptoms to doctors in other fields: e.g. patients suffering dizziness because of agoraphobia go to an ear, nose and throat specialist, those with delusion of parasitosis practically always go to a dermatologist, panic sufferers to an internist or cardiologist, and those with coenesthopathy or hallucinations to surgeons. It is not unusual for these patients to be unwilling to accept the help of a psychiatrist, and they have to be treated by other specialists or by GPs. An important task with these patients is to protect them from unnecessary tests and interventions. The stigma attaching to psychiatric diseases means that patients are reluctant to talk about their psychological complaints, and prefer to take their physical symptoms (e.g. lack of appetite, losing weight, headaches, insomnia) to a doctor to “get a ticket” for medical testing and treatment. The unfortunate is often a failure to recognize the basic problem, the psychiatric disease, and a long series of unnecessary examinations ensues, not infrequently with mistaken diagnoses. These patients often later do receive psychotherapeutic treatment, but only after treatment for an imagined somatic disease has started.

“Disease-specific” psychotherapy of chronic patients (e.g. diabetes mellitus, tumours and arthritis), and communication with incurable and dying patients require special training, which is covered in later chapters.

Summary

Treatment with psychotropic drugs is very commonly carried out in parallel with psychotherapy. The rules of pharmacotherapy and psychotherapy differ at many points, necessitating careful planning and control of combined treatment. Combined treatments are more effective than using just one kind, but we know little about the magnitude of the benefit. The well-known risks – particularly of attempted suicide and completed suicide – have to be monitored during combined treatment. Combined treatment for anxieties arising from medical interventions is specifically recommended.

Questions

1. What is the efficacy of a placebo in the long- and short-term treatment of depression?
2. Does one drug have the same NNH in different diseases?
3. What are the advantages of combining medication with psychotherapy?
4. What are the links between adherence (compliance) and combined treatment?
5. What links have been found between suicide risk and the start of treatment of depression?