Psychotherapy Theory, Research, Practice, Training
2008, Vol. 45, No. 3, 329–339


0033-3204/08/$12.00 DOI: 10.1037/a0013309

# TREATMENT OF DEPRESSION WITH ANTIDEPRESSANTS IS PRIMARILY A PSYCHOLOGICAL TREATMENT

PETER ANKARBERG
*Child and Adolescent Psychiatry Clinic, Nyköping, Sweden*

FREDRIK FALKENSTRÖM
*Young Adults Counselling Centre, Nyköping, Sweden*

*Depression treatment with antidepressants is generally described as evidence-based. However, generalizations to practice recommendations seem to us to rest on the tacit assumption that treatment outcome in research trials is the sum of three factors: specific effects of the drug, expectancy effects (placebo), and spontaneous recovery. Because randomization isolates the specific effects of the drug, trials showing significant drug effects are used as evidence for prescribing the drug regardless of context. Drawing on Wampold's (2001) description of two metamodels of psychotherapy, the authors argue that available empirical evidence indicates that depression treatment with antidepressants is primarily a psychological treatment. This conclusion has far-reaching consequences for the scientific status of contemporary treatments for depression. It also affects what the doctor should focus on in a treatment with antidepressants and how to act when the patient is treatment resistant. In order to achieve the results obtained in clinical trials, the quantity and quality of support from the doctor is more important than pharmacological concerns, such as adequate doses of medicine. When faced with a treatment resistant patient, relationship factors rather than pharmacological factors should be in focus.*

*Keywords:* antidepressants, placebo, psychological factors, evidence-based treatment

Guidelines on the treatment of depression generally stress both the need for adequate levels of medication and some form of follow-up visits for medication monitoring and support. In this, they at least implicitly accept that the treatment of depression with antidepressants has both pharmacological and psychological components that are important. At the same time, the guidelines go into considerably more detail on the antidepressants per se than on the support. There also is a general agreement on dosage levels but not on how often the patient should be seen or on what the doctor should do when he or she meets the patient. Often the guidelines only stress the need to see the patient at regular intervals. Since the guidelines uniformly are more detailed concerning the antidepressants per se than the support, it seems that they assume that the antidepressants per se are the most important part in the pharmacological treatment of depression. This becomes obvious when the guidelines move on to what steps to take when a patient is treatment resistant, that is, does not improve after approximately four to eight weeks. The guidelines then recommend practitioners to increase dose, switch medication, add another medication, or add psychotherapy. None recommend changing what the practitioner does when seeing the patient, seeing the patient more often, or changing practitioner (American

Peter Ankarberg, Clinical Psychologist, Licensed Psychotherapist, Child and Adolescent Psychiatry Clinic, Nyköping, Sweden; Fredrik Falkenström, Clinical Psychologist, Licensed Psychotherapist, Young Adults Counselling Centre, Nyköping, Sweden.

Correspondence regarding this article should be addressed to Peter Ankarberg, Barn- och ungdomspsykiatrin, Tullportsgatan 8, 611 33 Nyköping, Sweden. E-mail: peter.ankarberg@dll.se

Psychiatric Association Work Group on Major Depressive Disorder, 2000; Institute for Clinical Systems Improvement, 2007; National Institute for Clinical Excellence, 2004; Royal Australian and New Zeeland College of Psychiatrists Clinical Practice Guidelines Team for Depression, 2004; ). That the guidelines uniformly focus on changing the pharmacological technique when a patient is treatment resistant instead of recommending changing the psychological context in which the medication is prescribed show that they assume that effectiveness of a pharmacological treatment of depression primarily depends on the treatments pharmacological component per se.

This conclusion seems to be based on the fact that antidepressants consistently have shown a small but statistically significant advantage over placebo treatment in randomized controlled trials (RCTs). Because randomization is used to control for all possible confounds, thereby isolating the therapeutic ingredient of interest, researchers and authors of treatment guidelines are of course correct in the conclusion that antidepressants are somewhat more effective than placebo. However, we would add that this has only been shown when antidepressants are given in a very specific psychological context.

What we find more questionable is the fact that those results from clinical trials are interpreted in such a way that it seems to be taken for granted that the most important part of an antidepressant treatment is the antidepressants per se. There seems to be at least two tacit assumptions behind this assumed primacy of pharmacological effects: First, authors of treatment guidelines seem to take for granted that the chemical substance causes the specific effect of antidepressants and that this is more important than the context in which it is prescribed. Second, improvement in control groups is thought to be mostly the result of patient expectations (placebo) embedded in receiving the medication and spontaneous recovery due to the passage of time and not to the context in which the placebo is prescribed. Given that these assumptions are met, it is logical to conclude that treatment with antidepressants in clinical practice will be as effective as in clinical trials as long as the patient continues his or her medication. If they are not met, and it is the main argument of the present paper that they are not, this casts doubt on the effectiveness of some of the most common ways of treating depression in clinical practice.

In the present review of antidepressant treatment of depression, we challenge the assumption about antidepressant treatment being primarily pharmacologic by extending the common factors hypothesis (e.g., Lambert & Ogles, 2004; Wampold, 2001) from psychotherapy research to treatment with antidepressants. In the field of psychotherapy research, there is an ongoing debate over what contributes to positive therapeutic outcomes. Two major orientations, or metamodels, have been identified: Simply put, there are those who believe that specific techniques are efficacious for specific patients or disorders, and those who believe that the efficacy of psychotherapy is best explained by therapeutic factors that are common across treatments (Frank, 1961; Wampold, 2001).

In our review of common versus specific effects in antidepressant treatment, we challenge the assumption that the specific technique of antidepressant medication per se is responsible for most of the treatment outcome. In our analysis, we use the framework created by Wampold (2001) to analyze the issue of common versus specific factors in psychotherapy. He identified two different metamodels that both attempt to explain what factors are responsible for psychotherapeutic effects. The metamodels are roughly equivalent to specific versus common factors, but are named the "medical model" and the "contextual model," respectively. The reasons for choosing Wampold's model rather than the more widespread common factors model are that we find the term "contextual model" to be better suited for explaining the effect of pharmacological treatment and that Wampold has created a framework that enables a systematic analysis of which model best explains the data.

According to Wampold, the medical model stipulates that the therapist's role is to provide an explanation for the client's problem or disorder and a treatment that contains specific therapeutic ingredients that are in accordance with the theoretical explanation for the specific problem.The critical aspect of the medical model is that these specific ingredients are thought to be responsible for the major part of positive outcomes. In the contextual model, on the other hand, specific therapeutic techniques are seen as beneficial because both therapist and patient believe that they are rational and efficacious. Wampold concludes that the available empirical evidence on the outcome of psychotherapy, taken together, overwhelmingly

favors the contextual model relative to the medical model of psychotherapy.

When it comes to psychopharmacological treatment, it is easy to see that researchers subscribe to a medical model in that a biological explanation is given for a specific disease, and a specific pharmacological agent is prescribed that is meant to correct a chemical imbalance causing the disorder. It is usually taken for granted that it is the specific technique of the antidepressants that in itself is responsible for all or most of the treatment effects.

However, there is an extensive debate as to how effective and/or specific antidepressants are in the treatment of depression as well as in other conditions. There appears to be a growing consensus that antidepressants does not have a much greater effect than placebo and that the earlier hopes for the new generation of antidepressants were overly optimistic (Kirsch, Moore, Scoboria, & Nicholls, 2002; Storosum et al., 2001). Many have also pointed out that factors, such as the patient-doctor relationship and contextual factors, appear to play as great or a greater part than antidepressants per se in the patient recovery (Blatt, Sanislow, Zuroff, & Pilkonis, 1996; Krupnick et al., 1996; McKay, Imel, & Wampold, 2006; Moncrieff & Cohen, 2006). Some have also criticized the way the placebo concept is used in most current antidepressant research on the grounds that it discounts psychological mechanisms as a potential treatment pathway in its own right (Wolfaardt, Reddon, & Joyce, 2005).

As far as we know, the most explicit challenge of the medical model of therapeutic action when it comes to pharmacological treatments is that made by Blatt and Zuroff (2005). Using data from the Treatment of Depression Collaborative Research Program (TDCRP), they conclude that there is little support for the assumption that the type of treatment, be it antidepressants or a specific psychotherapy, is a primary factor in determining treatment outcome. They state that it is the therapeutic alliance and patient characteristics that matters the most in predicting outcome both in antidepressant and psychotherapeutic treatments.

In the following, we expand the analysis made by Blatt and Zuroff using other data sources besides data from TDCRP. In reviewing the literature on treatment with antidepressants, we use Wampold's (2001) outline of the two metamodels of psychotherapy as a blueprint for organizing research results.

## Pharmacological Versus Psychological Models of Depression Treatment With Antidepressants

Wampold (2001) outlined six hypotheses concerning the medical and contextual models of psychotherapy, five of which differentiate between the two models. We have adopted his hypotheses in order to answer the question whether there is scientific support for the assumption that the specific technique of taking antidepressants per se is responsible for most of the effect of antidepressant treatment. In doing this, we have changed the term "medical model" to "pharmacological model" and "contextual model" to "psychological model" since those terms better describe the differing assumptions regarding antidepressants. This is then a test between the pharmacological model and the psychological model for antidepressants. The six hypotheses are:

1. *Absolute Efficacy:* Antidepressant treatment is efficacious. This hypothesis is the same for both models.
2. *Relative Efficacy:* The pharmacological model postulates that some psychopharmacological treatments produce better outcomes than others, while the psychological model predicts that all treatments intended to be therapeutic regardless of specific ingredients included are efficacious (assuming that they are theoretically coherent and plausible to both patient and therapist).
3. *Specificity of Effects:* The pharmacological model stipulates that beneficial effects of treatment are mostly due to specific ingredients, that is the medication in itself. In the psychological model, the specific medication is not seen as crucial in and of itself.
4. *General Effects:* The psychological model predicts that the largest part of treatment efficacy consists of general effects, that is, effects that are common to all pharmacological treatments. The pharmacological model also posits that there are general effects, but specific effects of the medication per se are thought to be larger and more important than nonspecific effects.
5. *Adherence and Allegiance:* The pharmacological model postulates that adherence to a

specific therapeutic protocol is critical, and that adherence to some protocols is more effective than adherence to others. In the psychological model, the therapeutic protocol needs to be coherent and in line with the doctor's and patient's worldviews, but some protocols are not inherently more effective than others. The doctor's allegiance to his or her treatment is unimportant within the pharmacological model as long as the doctor delivers treatment correctly, while in the psychological model allegiance is crucial because belief in treatment is a central element of this model.

6. *Therapist Effects:* The pharmacological model predicts that outcome variance due to treatment effects is greater than the variance due to doctor, particularly if the doctors adhere to the treatment protocol. The psychological model, on the other hand, predicts that outcome variability due to doctors within the same treatment will be greater than variability due to treatments.

In sum, the psychological model explains results of treatment in terms of the personality of the doctor, the personality of the patient, and the relationship that they develop, while the pharmacological model explains results of treatment in terms of biological changes in the brain caused by the specific pharmacological agent. In the following, we will go through the available empirical evidence concerning these hypotheses when it comes to treatment of depression using antidepressant medication.

## Evidence for Pharmacological and Psychological Models

### *1. Absolute Efficacy*

Absolute efficacy is the efficacy of an active treatment compared to no treatment. The established research standard in medicine is to compare an active treatment with a placebo treatment in a randomized double-blind design. Thus, we have not been able to identify any studies that directly compare treatment with antidepressants with an untreated group. However, the absolute efficacy of depression treatment using antidepressants can be deducted from research on short-term psychotherapy. In RCTs that compare antidepressants to psychotherapy, the treatments tend to be equally effective, although both are only slightly better than pill placebo (Elkin et al., 1989; Keller et al., 2000; Leff et al., 2000; Markowitz et al., 1998; Miranda et al., 2003; Mynors-Wallis, Gath, Day, & Baker, 2000; Mynors-Wallis, Gath, Lloyd-Thomas, & Tomlinson, 1995; Schulberg et al., 1996).

Since the effect of antidepressants and short-term psychotherapy are about equal, it is possible to use the difference between short-term psychotherapy and no-treatment controls to make a fairly accurate approximation of the absolute efficacy of antidepressants. Working along these lines, one meta-analysis estimated the mean effect sizes for different treatments of depression to be 1.55 for antidepressants, 1.16 for placebo medication, 1.60 for psychotherapy, and 0.37 for no-treatment controls (Kirsch & Sapperstein, 1998). Treatment with antidepressants thus seems to be marginally more effective than placebo medication but substantially more effective than no treatment. The conclusion that antidepressants are substantially more effective than no treatment is in line with both pharmacological and psychological models of therapeutic action. However, the conclusion that this is also true for treatment with placebo medication is more in line with the psychological model than with the pharmacological model.

### *2. Relative Efficacy*

Relative efficacy answers the question "Does treatment A produce better outcomes than treatment B?" and is deduced from comparative outcome studies in which active treatments are contrasted with one another (Wampold, 2001). The pharmacological model predicts differential efficacy among treatments, because specific ingredients theoretically connected with a given disorder vary between different treatments. If treatment effects were due to specific ingredients, then some ingredients would be more efficacious than others. On the other hand, the psychological model predicts that there are no differences in efficacy between specific treatments for a particular disorder.

The research comparing different pharmacological treatments of depression can be divided into two groups: comparisons between antidepressants with differing mechanisms of action and comparisons between substances assumed to be antidepressant and other psychoactive substances. Another test of the relative efficacy of

antidepressants would be to study how antidepressants work in depression as compared to how they work in other specific psychiatric disorders.

Meta-analyses of comparisons between antidepressants with differing pharmacological effects show similar rates of improvement regardless of type of medication. Freemantle, Anderson, and Young (2000) summarized the results of 105 studies with altogether 11537 patients treated with tricyclics, SSRI and SNRI meta-analytically, and found no differences in outcome. A recent meta-analysis of 14 studies with altogether 2283 patients comparing conventional antidepressants with hypericum extracts also showed no differences in outcome (Linde, Berner, Egger, & Mulrow, 2005). Thus, the situation in pharmacological treatment of depression in similar to the "dodo-bird verdict" situation in psychotherapy research in that no specific treatment can be shown to be superior in outcome to another.

It is important to note that several studies have also shown similar rates of improvement in depression as with antidepressants using psychoactive compounds that are not thought to be primarily antidepressant, such as neuroleptics (Robertson & Trimble, 1992), barbiturates (Blashki, Mowbray, & Davies, 1971), and some stimulants (Rickels et al., 1970).

Taken together, these results are quite strong evidence against a marked specific pharmacological efficacy of antidepressants. A psychological explanation of treatment results seems more plausible.

### *3. Specific Effects*

Specific effects are those effects that are produced by the unique characteristics of the active treatment in question. When it comes to antidepressant medication, specific effects are those that are thought to arise from, for example, the change in serotonin levels in the nervous system produced by the active chemical agent. Specificity of effects is investigated by comparing active medication to placebo in double-blind randomized controlled trials (RCTs). The pharmacological model predicts that specific effects are substantial and larger than general effects, while the psychological model predicts the opposite.

During the last 30 years, much research has been done comparing antidepressants to placebo in the treatment of depression. Looking back at the results from such RCTs, it is clear that antidepressants perform somewhat better than placebo, but the difference is not impressive. In a large meta-analysis of altogether 19639 patients with moderate to severe major depressive disorder, depressed patients given antidepressants achieved a symptom reduction of 40.7% compared to 30.9% with placebo (Khan, Warner, & Brown, 2000). This meta-analysis was based on pools of studies where all positive and negative studies were included. The results from Khan, Warner, and Brown (2000) are similar to the results from other meta-analyses also using pools of studies where all positive and negative studies are included. Taken together, the results of meta-analyses show that depressed patients tend to achieve a symptom reduction of approximately 40% during an average 8-week trial. Placebo has between 70 and 80% of the effect that antidepressants have and thus gives a symptom reduction of approximately 30%. In 40% to 70% of the studies, antidepressants does not perform better than placebo (Khan et al., 2000; Kirsch, Moore, Scoboria, & Nicholls, 2002; Kirsch, Scoboria, & Moore, 2002; Storosum et al., 2001).

However, even the conclusion of a small specific effect of antidepressants is uncertain. This conclusion rests on the assumption that trials of antidepressants are double-blind, so that neither patient nor doctor knows if the patient is taking placebo or antidepressants. This assumption is not supported by empirical evidence. One review found 26 reports of psychotropic drug studies that evaluated whether or not the double-blind design was broken. In 88% of the reports, both patients and doctors were able to guess correctly more often than chance if the patient was on active medication (Fisher & Greenberg, 1993). For antidepressants, the breaking of the blind can to a large extent be explained by the side effects of the drug. Patients experiencing more side effects and their doctors are more accurate in guessing that they are receiving antidepressants than patients not having any side effects, and independent evaluators can correctly guess what treatment the patients receives solely based on information regarding the side effects (Bystritsky & Waikar, 1994; Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994; White, Kando, Park, Waternaux, & Brown, 1992).

That the breaking of blind inflates the difference between placebo and antidepressants is shown when studies using ordinary placebo are compared to studies using active placebos (placebo with similar side effects as antidepressants).

A review of studies comparing a tricyclic antidepressant with either ordinary placebo or active placebo showed that tricyclics were superior to ordinary placebo in 63% of the studies. In studies using active placebo, tricyclics were superior in only 14% of the studies (Thomson, 1982). Thus, active placebo was as effective as antidepressants and consequently more effective than ordinary placebo. The most likely explanation for this difference between ordinary placebo and active placebo is that in trials using active placebo neither patient nor doctor are able to guess if the patient is receiving active medication or not and such knowledge can thus not influence the patient's change or the doctors perception of this change. The most likely conclusion from these studies is that the small difference between antidepressants and placebo is due mainly to an enhanced placebo effect caused by the breaking of blind and not to a specific pharmacological antidepressant effect. This is more in support of the psychological than of the pharmacological model.

### *4. General Effects: Expectancy Effects or Social Support?*

General effects are those effects that are produced by aspects of treatment that are common across treatments and are usually distinct from the theoretically specified therapeutic ingredients. The pharmacological model predicts that there are general effects, although these are smaller and less important than the specific effects, in this case the effect of antidepressants per se. The psychological model predicts that the context of treatment is vital to therapeutic success, and that treatment effects are mostly due to general psychological effects.

In pharmacological research on antidepressants, general effects tend to be treated as synonymous with expectancy (placebo) effects. That is, all treatment effects in the placebo treated group is assumed to be the result of natural improvement over time and expectations tied to the belief that one is taking a potent medicine, and thus not primarily dependent on the context in which the medication is prescribed. It is this assumption that makes it possible to generalize the effects from clinical trials to treatment with antidepressants in general care without any contextual demands other than adequate diagnosis and dosage. The assumption is that antidepressants in clinical practice will produce the same effect as antidepressants in controlled trials since the pill in itself carries the full effect of placebo plus specific effect. This is of course a central assumption for the current practice of prescribing antidepressants under conditions that in many ways differ from those in controlled trials.

Placebo is by definition something that occurs without any active treatment. However, in antidepressant research the assumption that improvement in the placebo group occurs without any active treatment is not supported by empirical facts. On the contrary, we argue that patients in RCTs are given a psychosocial treatment with large effect: Patients in RCTs generally meet with a doctor or nurse weekly or biweekly during the first two months and at the same intervals or perhaps every third or fourth week for the remainder of the study (e.g., Croft et al., 1999; Elkin et al., 1989; Gelenberg et al., 2003; Keller et al., 1998; Lepola, Loft, & Heldbo Reines, 2003; Wagner et al., 2004). In a fairly average 3-month RCT, every patient thus meets with a doctor or nurse at six to eight separate times. The most common intervention is some kind of structured assessment of symptoms. This is an intervention that in itself has been shown to reduce symptoms of depression and anxiety (Scarvalone et al., 1996).

In RCTs that compare antidepressants given together with sparse contact with a doctor to antidepressants given together with approximately the same amount of support as in RCTs in general show that added support has a great impact on symptom reduction. In fact, the difference in symptom reduction between patients given added support and those given a sparse contact is greater than the difference typically reported between patients given antidepressants and those given placebo in RCTs. (Gilbody, Whitty, Grimshaw, & Thomas, 2003; Hunkeler et al., 2000; Katon et al., 1995; Rost, Nutting, Smith, Werner, & Duan, 2001). The psychosocial interventions given in RCTs thus seem to have a greater effect than antidepressants per se. The effect of antidepressants in RCTs thus cannot be equated with only a combination of natural improvement over time, expectations regarding the medication (placebo), and specific effects of the antidepressant. Most of the effect is dependent on the amount of support given during the trial.

This is supported by the fact that no consistent relationship has been demonstrated between either dosage or the level of plasma concentration

of antidepressants and therapeutic response (Amsterdam et al., 1997; Freemantle et al., 2000). In fact, it seems that almost all difference in effect between different antidepressant trials depends not on the type or dose of antidepressant but on the placebo characteristics of the study, that is the characteristics of the support given. The correlation between placebo effect and drug effect in a meta-analysis of 19 studies were 0.9 (Kirsch & Sapperstein, 1998)!

How the support or assessment is done also seems to be important. Successful doctors get better result with support plus placebo than unsuccessful doctors get with support plus antidepressants (see section on Therapist Effects below). Again, it seems that it is not the antidepressants per se that have effect but rather the doctor's skill and the quality of the alliance between doctor and patient.

What this shows is that it is inaccurate to call RCTs of antidepressants comparisons between antidepressants and placebo. They are comparisons between a form of clinical management that usually includes a stringent assessment of symptoms and adverse effects combined with either antidepressants or pill placebo. The amount and quality of this clinical management and structured assessment explains more of the variance in treatment effect than the antidepressants per se. This is in line with the psychological model of therapeutic action and goes against the pharmaceutical model assumption that the antidepressants in themselves cause most of the treatment effects.

### *5. Adherence*

Adherence refers to how well the treatment provider follows the guidelines for the specific treatment method. According to the pharmaceutical model, the doctors' adherence to a specific treatment would have a strong impact on treatment outcome. According to the psychological model, doctors' adherence would be at most weakly related to outcome.

In antidepressant research, adherence according to the pharmaceutical model would primarily concern the doctor prescribing the correct dosage and the patient following the prescribed dosage. The difference in outcome between doctor-patient dyads showing good adherence and dyads showing poor would be expected to be large. According to the psychological model, dyads showing good adherence would also be expected to show better results than dyads showing poor adherence, but the explanation would be different. In the pharmaceutical model, the difference would be attributed to the patients in the adherent dyads receiving more adequate dosage than patients in nonadherent dyads. In the psychological model, the difference would be attributed to a better relationship between doctor and patient in the adherent dyads. This better relationship would cause both the better outcome and the better adherence, in that the patient who feels understood and supported by his or her doctor is more prone to comply with prescriptions. Since, as mentioned before, there is no consistent relationship between dosage and/or plasma levels of antidepressant and outcome (Amsterdam et al., 1997; Freemantle et al., 2000), and a good relationship between doctor and patient has a stronger impact on outcome than antidepressants per se (Blatt & Zuroff, 2005), the evidence is more in favor of the psychological model in regard to adherence.

### *6. Therapist Effects*

According to the pharmaceutical model of therapeutic action, doctor effects are only important in the sense that treatment should be delivered correctly. When it comes to medication, the doctor needs to provide correct information to the patient about the medicine and motivate the patient to follow the doctor's prescription. Thus, the doctor needs to ensure compliance with treatment on the patient's part, but as long as the patient takes the medicine in the correct dose and at the right times, therapist effects would be negligible. On the other hand, the psychological model predicts therapist effects to be substantial and important in their own right—that is, not just to get the patient to comply with treatment.

Therapist effects have been studied in treatment with antidepressants. As mentioned before, successful doctors have been shown to get better result with clinical management and structured assessment plus placebo than unsuccessful doctors get with clinical management and structured assessment plus antidepressants (Blatt et al., 1996; Krupnick et al., 1996). In one study examining nine psychiatrists treating 112 patients randomized to antidepressants or placebo, it was shown that the psychiatrist effect was greater than the effect of antidepressants (McKay et al.,

2006). Another study showed that the outcome of treatment with antidepressants for patients of doctors who were experienced as lacking in communicative skills deteriorated—at least when it came to disability and activity limitation—while patients of doctors experienced as good communicators improved (Van Os et al., 2005).

Those results can be seen as evidence for the psychological model, in that prescription of antidepressants are only effective in the context of a relationship with a doctor who is experienced as empathic and understanding. Proponents of the pharmacological model might argue that the relationship with the doctor is only effective because it makes it more likely that the patient complies with treatment, but it would be difficult to explain within the pharmacological model the fact that doctors who are competent at establishing a therapeutic alliance with their patients do better with placebo than other doctors are doing with active medication. This finding is more in line with the psychological model, in that the doctor-patient relationship is more important than if the patient gets an active medication or not.

Although more studies are needed to settle this issue, it seems that therapist/doctor effects affect outcome to a great extent in their own right and not only as a way to make the patient accept the medication. Available evidence thus supports the psychological model more than the pharmaceutical model.

## Conclusions and Implications for Research and Practice

Available evidence supports a psychological model of therapeutic action when it comes to antidepressant medication, and there is not much support for the pharmaceutical model. Although evidence in some areas is sparse, we think that the burden of proof rests on those who continue to hold onto the pharmaceutical model of therapeutic action. In the absence of evidence for the pharmaceutical model, we propose to provisionally accept the psychological model of therapeutic action for antidepressants. Doing so has far-reaching consequences both for what can be called evidence-based treatments of depression and for where the focus in pharmacological treatment of depression should be in clinical practice.

In the current debate, the most common definition of an evidence-based psychological treatment is that the treatment has to have shown superiority over some control condition in randomized controlled trials. As we have shown, the evidence strongly supports that treatment of depression with antidepressants is, in fact, primarily a psychological treatment. It then seems reasonable to have the same demands on an evidence-based treatment with antidepressants as we have on other psychological treatments, such as psychotherapy. The fact that patients given clinical management and structured assessment plus antidepressants improve somewhat more than patients given clinical management and structured assessment plus pill placebo is then not enough to support the conclusion that treatment with antidepressants in itself is either effective or evidence-based. An analogy from psychotherapy research illustrates this. Suppose that several RCTs would show that patients given eight biweekly sessions of psychotherapy plus biweekly telephone calls improve significantly more than patients given only biweekly psychotherapy. From this, we can conclude that psychotherapy plus phone calls are more effective than only psychotherapy. However, we cannot conclude that this makes biweekly phone calls an evidence-based treatment. Yet, this is exactly what is done when treatment with antidepressants without a similar form and amount of clinical management and structured assessment as in clinical trials is seen as an evidence-based treatment.

This logical error seems to us to be based on the faulty assumption that the pharmacological model best explains the effect of an antidepressant treatment. Since this is not the case, proponents of evidence-based practice in psychiatry should have similar demands on the clinical management and structured assessment as they do on psychotherapy. That is the clinical management and structured assessment use in clinical trials would have to be manualized and doctors' adherence to the manual would have to be controlled. This form of manualized clinical management and structured assessment would then have to be tested against some kind of control condition, such as friendly contact or sparser contact. Only types of clinical management and structured assessment that could show superiority over control conditions would then be evidence-based. In clinical practice, this would mean that only treatments where antidepressants are combined with the same amount and type of clinical management and structured assessment that has been

tested with good results in clinical trials would be deemed evidence-based.

When looking at treatment with antidepressants from a perspective building more on the common factors model and Wampold's contextual model all treatments with antidepressants that in general follow the treatments tested in RCTs would be accepted as having a scientific support. Such treatment would have to include at least as much time with the doctor as that generally given in RCTs, but it would not be necessary for the doctor to replicate the content of the sessions so that it is the same as in clinical trials. The reason for this is that the time spent with the doctor is essential for relationship factors and other contextual factors to work and that it is the doctors' and patients' mutual understanding and belief in the model that is essential, rather than the exact content. The scientific support is then limited to treatments allowing at least biweekly sessions with the doctor during the first two to three months of treatment and at least monthly or bimonthly thereafter. Treatment with antidepressants in ordinary clinical practice that allows for much less time with a doctor or nurse thus lack scientific support regardless of if we use criteria from evidence-based medicine or from the common factor model.

In clinical practice, the strong support for the psychological model of antidepressant treatment makes it necessary for doctors to change focus. Instead of focusing mostly on the pharmacological details of treatment, focus should be on creating a context that provides the best opportunities for symptom reduction. This means allowing enough time with the patient, at least every other week. It also means paying attention to how the patient experiences the doctor and the relationship. The goal would be for the individual doctor to be seen as someone who understands the patient's dilemmas and to create a good therapeutic alliance. It probably is possible for another health worker than the doctor to handle the clinical management and structured assessment and achieve similar results as if the doctor does this. If this model is used, it is of course important that everyone involved know that how this relationship works is more important than the antidepressants per se.

Another important consequence for clinical practice would be the handling of patients who do not improve after several weeks or months of antidepressant medication. Current practice (following the pharmacological model) is to increase dosage, add other medications, or change medication. If, as we conclude, the evidence is more in favor of the psychological model, this situation should be handled differently: Since relationship factors are mostly responsible for the effects of antidepressant treatment, the first step to take should be to attend to the therapeutic alliance. The goal would be to change the relationship so that the patient would feel better understood, supported, or engaged in treatment than before. As a second step, the amount of time with the doctor could be increased. If this has no effect, the next logical step would then be to change doctor and evaluate the effect of this before considering changing or adding medication. As shown in the beginning of this article, current guidelines on the pharmacological treatment of depression give recommendations on how to act when a depressed patient is treatment resistant based on the pharmacological model. After reviewing the evidence, it seems to us that the guidelines recommendations do not follow the empirical evidence in this respect.

## References

American Psychiatric Association Work Group on Major Depressive Disorder, (2000). *Practice guideline for the treatment of patients with major depressive disorder* (2nd ed.). Washington DC, APA. Retrieved May 2007 from http://www.psych.org/psych_pract/treat/pg/MDD2e_05_15_06.pdf

Amsterdam, J. D., Fawcett, J., Quitkin, F. M., Reimherr, F. W., Rosenbaum, J. F., Michelson, D., et al. (1997). Fluoxetine and norfluoxetine plasma concentrations in major depression: A multicenter study. *American Journal of Psychiatry, 154,* 963–969.

Blashki, T. G., Mowbray, R., & Davies, B. (1971). Controlled trial of amitryptiline in general practice. *British Medical Journal,* 133–138.

Blatt, S. J., Sanislow, C. A., Zuroff, D. C., & Pilkonis, P. A. (1996). Characteristics of effective therapists: Further analyses of data from the National Institute of Mental Health treatment of depression collaborative research program. *Journal of Consulting and Clinical Psychology, 64,* 1276–1284.

Blatt, S. J., & Zuroff, D. C. (2005). Empirical evaluation of the assumptions identifying evidence based treatments in mental health. *Clinical Psychology Review, 25,* 459–486.

Bystritsky, A., & Waikar, S. V. (1994). Inert placebo versus active medication: Patients blindability in clinical pharmacological trials. *Journal of Nervous and Mental Disease, 182,* 485–487.

Croft, H., Settle, E., Houser, T., Batey, S. R., Donahue, R. M., & Ascher, J. A. (1999). A placebo-controlled comparison of the antidepressant efficacy

and effects on sexual functioning of sustained-release bupropion and sertraline. *Clinical Therapeutics, 21,* 643–658.

Elkin, I., Shea, M. T., Watkins, J. T., Imber, S. D., Sotsky, S. M., Collins, J. F., et al. (1989). National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. *Archives of General Psychiatry, 46,* 971–982.

Fisher, S., & Greenberg, R. P. (1993). How sound is the double-blind design for evaluating psychotropic drugs? *Journal of Nervous and Mental Disease, 181,* 345–350.

Frank, J. D. (1961). *Persuasion and healing: A comparative study of psychotherapy.* Oxford: John Hopkins Press.

Freemantle, N., Anderson, I. M., & Young, P. (2000). Predictive value of pharmacological activity for the relative efficacy of antidepressant drugs: Meta-regression analysis. *British Journal of Psychiatry, 177,* 292–302.

Gelenberg, A. J., Trivedi, M. H., Rush, J., Thase, M. E., Howland, R., Klein, D. N., et al. (2003). Randomized, placebo-controlled trial of nefazodone maintenance treatment in preventing recurrence in chronic depression. *Biological Psychiatry, 54,* 806–817.

Gilbody, S., Whitty, P., Grimshaw, J., & Thomas, R. (2003). Educational and organizational interventions to improve the management of depression in primary care: A systematic review. *Journal of the American Medical Association, 289,* 3145–3151.

Greenberg, R. P., Bornstein, R. F., Zborowski, M. J., Fisher, S., & Greenberg, M. D. (1994). A meta-analysis of fluoxetine outcome in the treatment of depression. *Journal of Nervous and Mental Disease, 182,* 547–551.

Hunkeler, E., Meresman, J., Hargreaves, W., Fiureman, B., Berman, W., Kirsch, A., et al. (2000). Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care. *Archives of Family Medicine, 9,* 700–708.

Institute for Clinical Systems Improvement. (2007). *Health care guideline: Major depression in adults in primary care* (10th ed.). Retrieved May 2007 from http://www.icsi.org/depression_5/depression_major_in_adults_in_primary_care_3.html

Katon, W., Von Korff, M., Lin, E., Walker, E., Simon, G., Bush, T., et al. (1995). Collaborative management to achieve treatment guidelines: Impact on depression in primary care. *Journal of the American Medical Association, 273*(13), 1026–1031.

Keller, M. B., Kocsis, J. H., Thase, M. E., Gelenberg, A. J., Rush, A. J., Koran, L., et al. (1998). Maintenance phase efficacy of sertraline for chronic depression: A randomized controlled trial. *Journal of the American Medical Association, 280,* 1665–1672.

Keller, M. B., McCullough, J. P., Klein, D. N., Arnow, B., Dunner, D. L., Gelenberg, A. J., et al. (2000). A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New England Journal of Medicine, 342,* 1462–1470.

Khan, A., Warner, H. A., & Brown, W. A. (2000). Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: An analysis of the Food and Drug Administration database. *Archives of General Psychiatry, 57,* 311–317.

Kirsch, I., Moore, T., Scoboria, A., & Nicholls, S. (2002). The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention & Treatment, 5*. Retrieved January 29, 2003, from http://www.journals.apa.org/prevention/volume5/pre0050023a.html

Kirsch, I., & Sapperstein, G. (1998). Listening to Prozac but hearing placebo? A meta-analysis of antidepressant medication. *Prevention & Treatment, 1.* Retrieved March 10, 2007, from http://www.journals.apa.org/prevention/volume1

Kirsch, I., Scoboria, A., & Moore, T. (2002). Antidepressants and placebos: Secrets, revelations, and unanswered questions. *Prevention & Treatment, 5.* Retrieved March 24, 2003, from http://www.journals.apa.org/prevention/volume5/pre0050033r.html

Krupnick, J. L., Sotsky, S. M., Simmens, S., Moyer, J., Elkin, I., Watkins, J., et al. (1996). The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: Findings in the National Institute of Mental Health treatment of depression collaborative research program. *Journal of Consulting and Clinical Psychology, 64,* 532–539.

Lambert, M. J., & Ogles, B. M. (2004). The efficacy and effectiveness of psychotherapy. In M. J. Lambert (Ed.), *Bergin and Garfield's handbook of psychotherapy and behavior change* (5th ed.; pp. 139–193). New York: Wiley.

Leff, J., Vearnals, S., Brewin, C. R., Wolff, G., Alexander, B., Asen, E., et al. (2000). The London Depression Intervention Trial. Randomised controlled trial of antidepressants v. couple therapy in the treatment and maintenance of people with depression living with a partner: Clinical outcome and costs. *British Journal of Psychiatry, 177,* 95–100.

Lepola, U. M., Loft, H., & Heldbo Reines, E. (2003). Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *International Clinical Psychopharmacology, 18,* 211–217.

Linde, K., Berner, M., Egger, M., & Mulrow, C. (2005). St. John's Wort for depression: Meta-analysis of randomized controlled trials. *British Journal of Psychiatry, 186,* 99–107.

Markowitz, J. C., Kocsis, J. H., Fishman, B., Spielman, L. A., Jacobsberg, L. B., Frances, A. J., et al. (1998). Treatment of depressive symptoms in human immunodeficiency virus-positive patients. *Archives of General Psychiatry, 55,* 452–457.

McKay, K. M., Imel, Z. E., & Wampold, B. E. (2006). Psychiatrist effects in the psychopharmacological treatment of depression. *Journal of Affective Disorders, 92,* 287–290.

Miranda, J., Chung, J., Green, B., Krupnick, J., Siddique, J., Revicki, D., et al. (2003). Treating depression in predominantly low-income young minority women: A randomised controlled trial. *Journal of the American Medical Association, 290*(1), 57–65.

Moncrieff, J., & Cohen, D. (2006). Do antidepressants cure or create abnormal brain states? (DOI: 10.1371/journal.pmed. 0030240) *PloS Med, 3,* E240.

MYNORS-WALLIS, L. M., GATH, D. H., DAY, A., & BAKER, F. (2000). Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. *British Medical Journal, 320,* 26–30.

MYNORS-WALLIS, L. M., GATH, D. H., LLOYD-THOMAS, A. R., & TOMLINSON, D. (1995). Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. *British Medical Journal, 310,* 441–445.

National Institute for Clinical Excellence. (2004). *Depression: Management of depression in primary and secondary care. Clinical practice guideline No 23.* London: NICE. Retrieved March 5, 2005, from http://www.nice.org.uk/pdf/CG023quickrefguide.pdf

RICKELS, K., GORDON, P. E., GANSMAN, D. H., WEISE, C. C., PEREIRA-OGAN, J. A., & HESBACHER, P. T. (1970). Pemoline and methylphenidate in mildly depressed outpatients. *Clinical Pharmacology and Therapeutics, 11,* 698–710.

ROBERTSON, M. M., & TRIMBLE, M. R. (1992). Major tranquillisers used as antidepressants. A review. *Journal of Affective Disorders, 4,* 173–193.

ROST, K., NUTTING, P., SMITH, B. S., WERNER, J., & DUAN, N. (2001). Improving depression outcomes in community primary care practice: A randomized trial of the QuEST intervention. *Journal of General Internal Medicine, 16,* 143–149.

Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. (2004). Australian and New Zealand clinical practice guidelines for the treatment of depression. *Australian and New Zealand Journal of Psychiatry, 38,* 389–407.

SCARVALONE, P. A., CLOITRE, M., SPIELMAN, L. A., JACOBSBERG, L., FISHMAN, B., & PERRY, S. W. (1996). Distress reduction during the Structured Clinical Interview for *DSM–III–R. Psychiatry Res, 59,* 245–249.

SCHULBERG, H. C., BLOCK, M. R., MADONIA, M. J., SCOTT, C. P., RODRIGUEZ, E., IMBER, S. D., ET AL. (1996). Treating major depression in primary care practice. Eight-month clinical outcomes. *Archives of General Psychiatry, 53*(10), 913–919.

STOROSUM, J. G., ELFERINK, A. J. A., VAN ZWIETEN, B. J., VAN DEN BRINK, W., GERSONS, B. P. R., VAN STRIK, R., ET AL. (2001). Short-term efficacy of tricyclic antidepressants revisited: A meta-analytic study. *European Neuropsychofarmacology, 11,* 173–180.

THOMSON, R. (1982). Side effects and placebo amplification. *British Journal of Psychiatry, 140,* 64–68.

VAN OS, T. W. D. P., VAN DEN BRINK, R. H. S., TIEMENS, B. G., JENNER, J. A., VAN DER MEER, K., & ORMEL, J. (2005). Communicative skills of general practitioners augment the effectiveness of guideline-based depression treatment. *Journal of Affective Disorders, 84,* 43–51.

WAGNER, K. D., ROBB, A. S., FINDLING, R. L., JIN, J., GUTIERREZ, M. M., & HEYDORN, W. E. (2004). A randomised, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *American Journal of Psychiatry, 161,* 1079–1083.

WAMPOLD, B. E. (2001). *The great psychotherapy debate.* London: Erlbaum.

WHITE, K., KANDO, J., PARK, T., WATERNAUX, C., & BROWN, W. A. (1992). Side effects and the blindability in clinical pharmacological trials. *Clin Res Reports, 149,* 1730–1731.

WOLFAARDT, U. B., REDDON, J. R., & JOYCE, A. S. (2005). Assessing the efficacy of antidepressants: The transactional paradigm. *Medical Hypotheses, 64,* 1229–1236.

## CE Credit Announcement

The APA Division of Psychotherapy (Division 29) currently offers its members Continuing Education (CE) credits for reading *Psychotherapy Theory, Research, Practice, Training*. For more information about this and to take the CE examination based on the articles in the current issue or the previous issue's exam, please go to http://www.divisionofpsychotherapy.org/ce.php.