

# Psychotherapy Versus Pharmacotherapy of Depression: What's the Evidence?

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## Zusammenfassung

*Psychotherapie versus Pharmakotherapie der Depression: Wie ist die Evidenzlage?*

**Fragestellung:** Depressive Störungen können mit Psychotherapie, Pharmakotherapie oder ihrer Kombination behandelt werden. Ob einer dieser Ansätze überlegen ist, ist Gegenstand einer fortgesetzten Debatte. Eine kürzlich erschienene Meta-Analyse berichtete Vorteile für Pharmakotherapie.

**Methoden:** Originalstudien und Meta-Analysen zum Vergleich von Psychotherapie und Pharmakotherapie wurden gesichtet.

**Ergebnisse:** Die vorliegende Evidenz spricht dafür, dass Psychotherapie und Pharmakotherapie bei den kurzfristigen Ergebnissen gleich wirksam sind, Psychotherapie im Langzeitverlauf aber effektiver ist. Für die kürzlich vorgebrachte Hypothese, dass Pharmakotherapie in Studien überlegen ist, die keine Placebo-Bedingung einschlossen, bei denen also beide Behandlungen gleichermaßen von einem positiven Erwartungseffekt profitierten, konnte keine überzeugende Evidenz gefunden werden.

**Diskussion:** Depressive Störungen können mit gleichwertigen Ergebnissen im kurzzeitigen Verlauf sowohl mit Psychotherapie als auch mit Pharmakotherapie behandelt werden und mit Vorteilen im Langzeitverlauf für die Psychotherapie. Da die Raten für Remission und Response in beiden Therapien immer noch begrenzt sind, ist eine weitere Verbesserung der Behandlung erforderlich.

*Z Psychosom Med Psychother 62/2016, 190–195*

## Keywords

Psychotherapy – Pharmacotherapy – Depression – Meta-analysis – Blinding – Placebo

## Summary

**Objectives:** Depression may be treated by psychotherapy or pharmacotherapy or their combination. There is an ongoing debate whether one of these approaches is possibly superior. A recent meta-analysis reported results in favour of pharmacotherapy.

**Methods:** Individual studies and meta-analyses on the comparative efficacy of psychotherapy vs. pharmacotherapy were reviewed.

**Results:** Evidence suggests that psychotherapy and pharmacotherapy are equally efficacious in the short-term, but psychotherapy is superior in the long-term. For the recently stated hypothesis that pharmacotherapy is superior to psychotherapy in studies without a pill placebo con-

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dition, which implies equally including a positive expectancy effect for both pharmacotherapy and psychotherapy no evidence was found.

**Conclusion:** Depression may be treated by psychotherapy or pharmacotherapy with equivalent results in the short-term and advantages for psychotherapy in the long-term. As the rates of response and remission are still limited in both treatments, further improvement of treatments is required.

## 1. Introduction

There is evidence from a large number of randomized controlled trials (RCTs) that psychotherapy is effective in depressive disorders (e.g., Barth et al. 2013). Psychotherapy was found to be as efficacious as pharmacotherapy in the short-term but superior in the long-term especially with regard to relapse prevention (Cuijpers et al. 2013; Dobson et al. 2008; Forand et al. 2013; Hollon et al. 2005; Imel et al. 2008; Spielmanns et al. 2011; Vittengl et al. 2007). Only compared to tricyclic antidepressants a small but significant advantage of psychotherapy was reported (Cuijpers et al. 2013). In dysthymia, a small but significant advantage of pharmacotherapy was found (Cuijpers et al. 2013; Imel et al. 2008). Whereas the combination of psychotherapy and pharmacotherapy was reported to be superior to monotherapies by small to medium effect sizes in the short-term (Cuijpers et al. 2009a, 2009b; Hollon & Beck 2013), no superiority was found with regard to long-term effects (Cuijpers et al. 2009b; Forand et al. 2013). With rates of relapse between 40% and 85%, the risk of relapse after pharmacotherapy is relatively high (Hughes & Cohen 2009). Maintenance pharmacotherapy has shown moderate efficacy in preventing relapse (Forand et al. 2013; Geddes et al. 2003). Although psychotherapy and pharmacotherapy are beneficial, the rates for response and remission are still limited (e.g., Cuijpers et al. 2014).

For the treatment of depression in adults, the present guidelines recommend the use of antidepressant medication or psychotherapy or their combination (American Psychiatric Association 2010; DGPPN et al. 2015; National Institute for Health and Clinical Excellence 2010). For patients with subthreshold depressive symptoms or mild depression, the NICE guidelines and the German S3 guidelines, however, do not recommend a routine treatment with pharmacotherapy (DGPPN et al. 2015; National Institute for Health and Clinical Excellence 2010). For moderate or severe depression, the NICE guidelines recommend the combination of pharmacotherapy and psychotherapy (National Institute for Health and Clinical Excellence 2010), whereas the American guidelines recommend the use of pharmacotherapy alone or the combined treatment (American Psychiatric Association 2010). For moderate to severe depression the German S3 guidelines recommend the equivalent use of psychotherapy or pharmacotherapy (DGPPN et al. 2015). For severe depression a combined therapy is recommended (DGPPN et al. 2015).

These recommendations are based on the evidence available at the time of formulating the guidelines. In this context, it is of interest that Cuijpers et al. (2015)

recently presented a meta-analysis on the outcome of psychotherapy and pharmacotherapy for adult depression, reporting in part deviating results. For this reason, this meta-analysis deserves a closer inspection.

## 2. Does blinding favour psychotherapy over pharmacotherapy?

Cuijpers et al. (2015) recently examined the effects of blinding on the outcome of psychotherapy and pharmacotherapy for adult depression by a meta-analysis. The study is based on the plausible hypothesis that patients in placebo-controlled trials treated with pharmacotherapy cannot be sure to receive an active drug and may therefore not benefit from the typical and well-documented effects of positive expectancies to the same degree as patients treated with psychotherapy who usually know that they are receiving the verum. As a consequence, studies including a pill placebo condition may result in overestimating the effects of psychotherapy and underestimate those of pharmacotherapy (Cuijpers et al. 2015, p. 686). For these reasons Cuijpers et al. (2015, p. 686) aimed at testing the hypothesis that "... studies that also included a placebo condition (blinded pharmacotherapy) differed significantly from the studies in which no placebo condition was included (unblinded pharmacotherapy)." When the authors directly compared studies with and without a placebo condition, however, no significant difference ( $p = 0.15$ ) was found for the effects of psychotherapy vs. pharmacotherapy in depression (Cuijpers et al. 2015, p. 689). Thus, the authors' hypothesis was not confirmed. Despite this insignificant result, the authors carried out another statistical analysis comparing the effects of psychotherapy and pharmacotherapy separately for studies with and without a placebo condition. For the first condition (blinded pharmacotherapy) they reported a non-significant difference ( $g = 0.02$ ), for the second condition (unblinded pharmacotherapy) a significant but very small difference of  $g = -0.13$ . Surprisingly, the authors now concluded to have corroborated their initial hypothesis (Cuijpers et al. 2015, p. 689): "The 31 comparisons in which no placebo control was used, resulted in line with the hypothesis, in a small, but significant effect in favour of pharmacotherapy ...". For a strict test of the authors' hypothesis, however, a *direct* comparison of studies with and without placebo is mandatory. As noted above, this test yielded an insignificant result ( $p = 0.15$ ). Performing a less strict test when a stricter test already failed to corroborate the hypothesis is questionable. In the discussion section, the authors interpret their results once more in an inconsistent way. While they concede that the effect in favour of pharmacotherapy they found was very small and not clinically relevant (Cuijpers et al. 2015, p. 691), they still conclude (Cuijpers et al. 2015, p. 619): "These results could suggest that in the acute treatment of depression, pharmacotherapy is somewhat more effective than psychotherapy, and this may be a reason for clinicians and patients to prefer pharmacotherapy over psychotherapy."

Furthermore, it is puzzling that a study which generally used highest methodological rigor for its meta-analytical procedures, failed to define any quality criteria for "psychological treatments," e.g., by including only *empirically supported* methods

of psychotherapy. Instead, the meta-analysis included studies using, for example, non-directive counselling which is not an empirically supported treatment of depression and has been found to be inferior to pharmacotherapy in a previous meta-analysis by the authors (Cuijpers et al. 2013). The inclusion of less efficacious methods of psychotherapy critically affected the results by Cuijpers et al. (2015): As shown by Cuijpers et al. (2015, p. 690) themselves in a sensitivity analysis, no significant differences in favour of pharmacotherapy were found when only CBT was compared to pharmacotherapy in studies without placebo controls. Thus, the difference the authors found in their secondary analysis ( $g = -0.13$ ) which included all forms of psychotherapy is likely due to the fact that some forms of psychotherapy were somewhat less efficacious than CBT (compared to pharmacotherapy). As a consequence, the difference found in the authors' secondary analysis cannot be attributed to unblinding of pharmacotherapy but rather reflects the inclusion of less efficacious treatments in the psychotherapy conditions. Thus, the authors' (generalizing) conclusion that in the acute treatment of depression pharmacotherapy may be somewhat more effective than psychotherapy (Cuijpers et al. 2015, p. 619) is once again not consistent with the authors' own analyses – i.e., when only efficacious psychotherapies of depression are included in the analysis.

Finally, as another limitation the authors did not include data on follow-up studies examining the long-term effects of psychotherapy and pharmacotherapy. There is evidence that psychotherapy (CBT) is superior to pharmacotherapy in the long-term (Hollon & Beck 2013).

### 3. Discussion

For the treatment of depression there is evidence from a substantial number of RCTs that psychotherapy is as efficacious as pharmacotherapy in the short-term but superior in the long-term. The hypothesis that including a placebo condition would lead to underestimating the effects of pharmacotherapy and overestimating those of psychotherapy was not corroborated in a convincing way. In sum, Cuijpers et al. (2015) discussed their findings in an inconsistent and potentially misleading way which we tried to counterbalance.

In this context, it is important to take the recent discussion on low replicability of research into account (Ioannidis 2005a; Lehrer 2010; Nuzzo 2015; Open Science Collaboration 2015). Low replicability of clinical research is particularly alarming because of the implied consequences for clinical practice, e.g., questionable treatment recommendations. Ioannidis (2005b) discussed several factors that may contribute to low replicability. Small effect sizes such as the very small effect ( $g = -0.13$ ) reported by Cuijpers et al. (2015) are one of the risk factors (Ioannidis 2005b; Leichsenring & Steinert in press). Some small effects may just represent randomness or nothing but noise. Flexibility in design, definitions, outcome and data analysis are another factor contributing to low replicability (Ioannidis 2005b). Performing a less strict statistical test when a stricter test failed to confirm the authors' hypothesis before represents a

form of flexibility in data analysis. Furthermore, the meta-analysis by Cuijpers et al. (2015) contained further threats to replicability (unclear definitions) as it neither differentiated for different levels of severity of depression nor methods of psychotherapy.

In order to enhance replicability of research, a more open and transparent attitude in all stakeholders involved in the process of research was recently recommended (Nuzzo 2015; Open Science Collaboration 2015). On the side of journal editors this requires, for example, that critical comments to articles published in the respective journal are welcomed and not rejected for whatever reasons.

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