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Cuijpers, Pim

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COMMENTARY

Research on Negative Effects of Psychotherapies: The Next Steps

Pim Cuijpers
Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam

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"First, do no harm" is an important injunction that has been acknowledged widely in the broader biomedical field since the 1860s. In the field of psychotherapy and psychological interventions, this decree has only relatively recently been considered as one of the core issues in research and practice. For a long time it has been assumed that negative effects are not so relevant in psychological interventions. Because psychotherapy is "only talking," it was assumed that no possible harm could be done and patients rarely raise such issues. Although the importance of negative effects of psychotherapies has been described for several decades, it is relatively recent that this is considered an important subject for research and clinical practice of psychotherapies. The study on negative effects in a guided, web-based intervention for mild to moderate depression in this issue (Oehler et al., 2021, p. 131) shows that negative effects are taken more seriously in recent years by researchers, and it fits in a trend to focus more research on these negative effects. It also shows that negative effects, when broadly defined, are quite common in psychological interventions, at least in web-based psychological interventions.

In this article, I will focus on the lack of reporting of negative effects in trials on psychotherapy, lack of consensus of what negative effects are, and how "individual participant data" meta-analyses can help in moving the field forward.

Statistical Power to Show Significant Negative Effects

Most studies on negative effects focus on specific outcomes, such as clinically significant deterioration or serious adverse effects. However, these specific negative outcomes are relatively rare. For example in one meta-analysis of trials on psychotherapies for depression, we found that deterioration rates in therapies was lower than 5% (Cuijpers et al., 2018). At the same time, these trials were relatively small, with about 80 participants in an average trial, and more than 70% of trials having less than 100 participants. That means that these studies usually do not have enough statistical power to find a significant difference between treatment and control group in terms of deterioration rates.

A simple power calculation shows that to demonstrate that the deterioration rate is reduced with 50% from 5% in the control group to 2.5% in the intervention group, 984 participants are needed per condition (assuming a power of 0.80 and an alpha of 0.05; calculations in Stata/SE 16.1 for Mac). So, to show a substantial reduction of a rare negative effect, such as deterioration, a trial of about 2,000 participants is needed. Such trials are hardly ever done in the field of psychological interventions for mental health outcomes and are extremely costly.

Authors of studies reporting the results of randomized trials are not inclined to report such data of deterioration rates, probably because these rates do not even come close to a significant difference. In our meta-analysis of deterioration rates in psychotherapies for depression (Cuijpers et al., 2018), we found that only 6% of trials reported deterioration rates. It is important, however, that such rates are reported. Even when individual studies do not have sufficient statistical power to find significant differences in deterioration rates between treatment and control groups, meta-analyses can integrate these results statistically and at some point sufficient statistical power will be realized. That does require, however, that studies do report deterioration rates, even though the numbers are small and differences do not get close to significance.

Individual Participant Data Meta-Analyses and Negative Outcomes

Individual participant data (IPD) meta-analyses are well suited to examine deterioration rates in psychotherapy trials. In IPD meta-analyses, the primary data of randomized trials are merged into one big dataset. IPD meta-analyses are often used to examine moderators and predictors of outcome of interventions, so that we get more knowledge about who benefits from which intervention. This is important because individual trials are typically designed to examine the effects of an intervention but do not have the statistical power to examine moderators and predictors. However, another important advantage of IPD meta-analyses is that the combined dataset has sufficient statistical

Pim Cuijpers https://orcid.org/0000-0001-5497-2743
Correspondence concerning this article should be addressed to Pim Cuijpers, Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Van der Boechorststraat 7-9, 1081 BT Amsterdam, the Netherlands. Email: p.cuijpers@vu.nl

power to examine rare outcomes, such as deterioration rates. In recent years, the number of IPD meta-analyses on psychological interventions is increasing, despite the considerable effort to collect the datasets, harmonize the relevant variables, and conduct analyses of the pooled datasets.

For example, one IPD meta-analysis included trials that compared cognitive behavioral therapy (CBT) with antidepressants in adult depression and included 16 trials with 1,700 patients (Vittengl et al., 2016). About 5% to 7% of patients showed any deterioration (an increased score on the 17-item Hamilton Rating Scale for Depression [HAM-D-17] or Beck Depression Inventory [BDI] of one point), 1% showed reliable deterioration (an increase of more than 8 points on the HAM-D-17 or more than 9 points on the BDI), and 4% to 5% showed extreme nonresponse (had a post-treatment HAM-D score of 21 or higher or a BDI score of more than 31). No significant difference between CBT and antidepressants was found on any of these rates. Two other IPD meta-analyses showed that the reliable deterioration rates was 3% in internet-based CBT for depression with support and 6% in unguided internet-based CBT, and in both IPD meta-analyses these rates were significantly higher in the control conditions (Ebert et al., 2016; Karyotaki et al., 2018).

IPD meta-analyses are not only capable to calculate average deterioration rates of interventions, but they also have enough statistical power to examine which participants have a increased risk to deteriorate. For example, one IPD meta-analysis found that the risk for deterioration was higher in guided internet-based CBT for depression among people with lower levels of education (Ebert et al., 2016).

One disadvantage of IPD meta-analyses is that only moderators and predictors can be examined that are examined across all or most included trials. Otherwise, there is still not enough statistical power to examine such moderators and predictors. The same is true for negative outcomes. It is possible to examine deterioration rates in IPD meta-analyses, because the main outcome measure can be used to examine the proportion of participants who experienced clinically significant deterioration. But other negative outcomes can only be examined in IPD meta-analyses when enough studies have reported it. And unfortunately, there is no consensus on what the most important negative outcomes are, which limits progress on more knowledge about negative effects considerably.

Towards a Consensus on the Definition of Negative Effects

The study on negative effects in this issue of *Clinical Psychology: Science and Practice* (Oehler et al., 2021, p. 131) shows that negative effects can take many different forms. According to the Inventory of Negative Effects of Psychotherapy (INEF) that was used in this study to assess negative effects, these can vary from "feeling worse" and "changing for the worse" to new symptoms, relationship problems with family or friends, and suicidal ideation for the first time. Each of these negative effects was experienced by only a limited number of participants, but the number of participants who experienced one or more effects was quite considerable.

For the future study on negative effects, it is very important to develop some kind of consensus on what the most important potential negative effects are. It is clear that, for example, clinically significant deterioration and serious adverse events, such as suicide attempts, are important negative effects. But it is not clear what other negative effects should be considered core negative outcomes. One could, for example, also consider nonresponse and drop-out as negative effects, because they could have prevented the patient from receiving adequate care or spontaneous remission (Dimidjian & Hollon, 2010). But there is very little consensus on what other negative effects are relevant.

However, to increase knowledge on negative effects it is important to define what the most important ones are. With the rise of IPD, meta-analyses research is not necessarily limited by small studies and lack of statistical power. But, to make progress, it is important that some kind of consensus is reached about the most important negative effects and that studies report these outcomes, regardless of the significance of the findings.

One solution could be that all trials include a questionnaire on negative effects, such as the INEF. Another solution would be that a selection of the most common negative effects would be selected from such a questionnaire. It would already help considerably if all studies would report rates of clinician significant deterioration. It would also be a good development if all trials would include a paragraph on adverse effects, as is common in trials on drugs. Without such a consensus and improvements in reporting of studies, research on negative effects will not be able to make much progress.

Conclusion

Negative effects are not as uncommon as often assumed, and more research on these effects is very important from a clinical perspective. In this article it was shown that most individual negative effects are, fortunately, relatively rare. Only few studies report negative effects, also because differences in negative effects between treatment and control groups are hardly ever significant, because of power problems. It is, however, for further research on negative effects, very important that negative effects are reported in trials. It is also important to reach some consensus across trials of what the most important negative outcomes are. Then we will be able to pool these outcomes in (IPD) meta-analyses and get more clarity about what the most important negative effects are and who is most at risk for experiencing these. Then our field will also be able to take the "first, do no harm" injunction seriously.

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