Psychological treatments are as effective as pharmacotherapies in the treatment of adult depression: a summary from Randomized Clinical Trials and neuroscience evidence

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Introduction

Several hundred randomized controlled trials have tested the effects of psychological treatments of depression. Although most of these trials have focused on cognitive behavior therapies (Cuijpers et al., 2013; Furukawa et al., 2014), several other types of treatment have been found to be effective in the treatment of depression in dozens of randomized trials, including interpersonal psychotherapy (Churchill et al., 2010; Cuijpers, Donker, Weissman, Ravitz, & Cristea, 2016), behavioral activation (Ekers, Richards, & Gilbody, 2008; Shinohara et al., 2013), problem-solving treatment (Malouff, Thorsteinsson, & Schutte, 2007), life review therapy in older adults (Lan, Xiao, & Chen, 2017), non-directive counseling (Cuijpers et al., 2012), psychodynamic therapies (Driessen et al., 2015; Leichsenring & Rabung, 2008) and third wave therapies (Churchill et al., 2013). What has this large body of research shown about the effects of these therapies? In this Commentary we will give a brief overview of a series of meta-analyses of these randomized trials (Cuijpers, 2017). Because in routine practice most patients still receive antidepressant medication, while the majority of patients prefer psychotherapy (McHugh, Whitton, Peckham, Welge, & Otto, 2013), we will focus specifically on the comparative effects of psychotherapy and pharmacotherapy evaluating the available randomized clinical trials. We also evaluate their comparative effects on brain activity. Given the relatively larger amount of studies on CBT most of the researches are related to this type of therapy. However, when we use the term psychological interventions, especially in meta-analysis it means that different approaches were considered.

We will finish with some recommendations for future research.

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The effects of psychological treatment of depression

The hundreds of randomized trials testing the effects of psychological treatments of depression have not only shown that these treatments are effective. They have also shown that the effects of the different psychological treatments are comparable and there are either no significant differences between them, or these differences are small and clinically not relevant (Barth et al., 2013).

These studies have shown that they are effective in the treatment of specific target groups, such as older adults (Cuijpers, van Straten, Smit, & Andersson, 2009; Gould, Coulson, & Howard, 2012), women with postpartum depression (Cuijpers, Brannmark, & van Straten, 2008), student populations (Cuijpers et al., 2015), and patients with general medical disorders (van Straten, Geraedts, Verdonck-de Leeuw, Andersson, & Cuijpers, 2010). There

are some indication that these therapies result in smaller effect sizes in patients with chronic depression (Cuijpers et al., 2010), subthreshold depression (Cuijpers et al., 2014) and in patients with comorbid alcohol problems (Riper et al., 2014).

These studies have not only shown that these therapies are effective, but it has also been found that they can be delivered in different treatment formats, including individual, group, telephone, internet-based and guided self-help formats (Cuijpers, Donker, van Straten, Li, & Andersson, 2010; Cuijpers, van Straten, & Warmerdam, 2008). When therapies are delivered without any kind of human support the effects are still significant, but considerably smaller than when some human support is given (Karyotaki et al., 2017; Richards & Richardson, 2012). We found no association between the number of treatment sessions and the effect size in individual psychotherapies in which the number of treatment sessions ranged from 4 to 24 (Cuijpers, Huibers, Ebert, Koole, & Andersson, 2013). We also found no association between the total contact time and the effect size.

Psychotherapies for depression have not only found to have effects on depressive symptoms, but also on other, related problems such as quality of life (Kolovos, Kleiboer, & Cuijpers, 2016), social functioning (Renner, Cuijpers, & Huibers, 2014), dysfunctional thinking (Cristea et al., 2015), positive and negative affect (Boumparis, Karyotaki, Kleiboer, Hofmann, & Cuijpers, 2016). There is also a small group of studies in depressed mothers, showing that treatment of depression in mothers results in positive effects on the mental health in their children, the interaction between mother and child and parental functioning (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015). Furthermore the chance of significant deterioration is considerably smaller in patients receiving psychotherapy than in patients in control groups (Cuijpers, Reijnders, Karyotaki, de Wit, & Ebert, 2017).

The effect sizes of psychotherapies for adult depression when compared to control conditions typically are in the range of d=0.5 to 0.8 (Cuijpers, 2017), which corresponds with a numbers-needed-to-be-treated (NNT) between 4 and 6 (Furukawa, 1999). Unfortunately, these effect sizes are considerably overestimated because the quality of many trials is not optimal and because of publication bias. The association between the effect size and the quality of studies on psychotherapy for depression has been well-established (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010). Only a small part of the trials meet all basic quality criteria and these studies find considerably smaller effect sizes than lower-quality studies (d=0.22 versus d=0.74; Cuijpers, van Straten et al., 2010). We also examined whether trials on psychotherapy for depression funded by the US National Institutes of Health resulted in publications (Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015). We found that about one quarter of these trials did not result in a published paper. We also found that when the data of these unpublished trials were pooled with the published data, the effect size dropped about 25% (Driessen, Hollon et al., 2015).

Comparing psychotherapy with pharmacotherapy and combined treatments

There are several dozens of studies directly comparing psychotherapies and pharmacotherapies for depression (Cuijpers, Sijbrandij et al., 2013). Meta-analyses of these trials indicate that there are no major differences between psychotherapies and pharmacotherapies and that they result in comparable effect sizes. The largest meta-analysis of these studies included 48 trials and found a differential effect size of g=0.03, which was neither statistically nor clinically significant. It was found that pharmacotherapy was significantly more effective than psychotherapy in dysthymia, but that was based on only 5 studies and the quality of these studies was not optimal.

These trials may be affected by several specific features of the trials. One of these features is that in some trials comparing psychotherapy with pharmacotherapy there is also a placebo condition, while there is no placebo condition in other trials. However, when there is a placebo condition, patients are blinded and do not know whether they receive the medication or the placebo. Because patients in the psychotherapy conditions are not blinded they may have higher expectations and more hope for improvement than the blinded patients receiving pharmacotherapy. We examined whether trials with a placebo condition differed from studies without a placebo condition (Cuijpers & Cristea, 2015). Although the difference between the group of studies with placebo and those without was not significant, we did find that the studies without a placebo condition (so both conditions were not blinded) resulted in a small but significant effect in favor of pharmacotherapy (g=0.13). In the studies with a placebo condition there was no significant difference between psychotherapy and pharmacotherapy.

Another feature of the trials that may affect outcomes is whether they are sponsored by the pharmaceutical industry. In one meta-analysis it was explored whether this sponsorship was related with the outcomes of the trials (Cristea, Gentili, Pietrini, & Cuijpers, 2016). No significant difference was found between the group of studies that were funded and the ones that were not funded by the industry. However, industry-funded trials did result in a significantly larger effect size in favor of pharmacotherapy than studies that did not receive funding from the industry. However, again the effect size was significant but very small (g=0.11).

When taken together, the results of these meta-analyses suggest that there are no or at least no major differences between the effects of psychotherapy and pharmacotherapy for depression. However, that only concerns the short-term effects. There is some evidence that

the effects of psychotherapy last longer than those of pharmacotherapy. There is a small group of studies comparing patients receiving either CBT or pharmacotherapy in the acute phase of treatment, and then examine what happens in the follow-up period of 12 to 24 months (Cuijpers, Hollon, et al., 2013). In eight studies, the patients who had received CBT in the acute phase did receive no or almost no further treatment. The patients who had received pharmacotherapy in the acute phase discontinued the pharmacotherapy in the follow-up period. The odds for a positive outcome (response or remission) was significantly larger in the CBT group compared to the pharmacotherapy group (OR=2.61; 95% CI: 1.58 to 4.31). In 5 studies patients continued to take medication during follow-up, while the patients in the CBT group did not receive treatment. The odds for a positive outcome was OR=1.62 (95% CI: 0.97 to 2.72) in favor of CBT. This was not significant (P=0.07) but it does indicate that CBT without continuation may be as effective as pharmacotherapy with continuation treatment.

Although psychotherapy and pharmacotherapy are probably about equally effective at the short term, there is considerable evidence that at the short term the combination of psychotherapy and pharmacotherapy is more effective than either psychotherapy (Cuijpers, van Straten, Warmerdam, & Andersson, 2009) or pharmacotherapy alone (Cuijpers et al., 2014). At the longer term, the odds for a positive outcome at 6 months or longer after randomization is higher in combined treatment compared to pharmacotherapy only (OR=2.72; 95% CI: 1.83 to 4.04; 12 studies) and that is also true at 12 months or longer (OR=2.72; 95% CI: 1.50 to 4.96; 8 studies). However, there is no evidence that at the longer term combined treatment is more effective than psychotherapy alone at 6 months or more post-randomization (OR=1.30; 95% CI: 0.76 to 2.22; number of studies: 7). This may be related to low statistical power because of the small number of studies.

Psychotherapy or pharmacotherapy: does the brain matter?

Neurobiological alterations have been described in patients with mood disorders (Cole, Costafreda, McGuffin, & Fu, 2011; Donofry, Roecklein, Wildes, Miller, & Erickson, 2016; Jesulola, Sharpley, Bitsika, Agnew, & Wilson, 2015; Mears & Pollard, 2016; Zhang et al., 2016). In this sense it has been proposed that the normalization of such alterations may represent the neurobiological correlate of treatment effects. Several studies have evaluated the effect of antidepressant therapy at a neurobiological level. A recent meta-analysis of neuroimaging findings shows that medications have a widespread modulation activity in the brain that can be summarized, as they tend to normalize neural responses by increasing neural responses to positive stimuli and decreasing activity to negative ones within the limbic system and by increasing the recruitment of the dorsolateral prefrontal cortex which is involved in emotional regulation process (Ma, 2015). In the same way, several systematic reviews evaluated the effects of psychotherapies on brain activity (Frewen, Dozois, & Lanius, 2008; Messina, Sambin, Palmieri, & Viviani, 2013). The first was a systematic review of the studies on neuroimaging correlates of psychotherapy, while the other is a neuroimaging-based meta-analysis using the same approach of Ma (2015). Despite, the methodological differences both highlighted a wide modulation of brain activity. Particularly, Frewen and colleagues reported how limbic middle structures (*i.e.*, cingulate cortices) and dorsolateral prefrontal cortex could be considered a biological signature of psychotherapy effects (while Messina and colleagues failed in described similar results at a meta-analytic approach). A part from the typical limitations of the neuroimaging-based meta-analysis (including lack of control for biases and lack of use of reliable measures of effect size), all these reviews involving both drugs and psychotherapies had the supplementary issue that they consider both RCT and non-RCT studies: indeed, the great majority of the studies took in considerations are studies where only a group of depressed patients was considered and the brain activity measured before and after the intervention. Regarding psychotherapy for depression, only few studies have RCT design comparing psychotherapy against pharmacotherapy or two forms of psychotherapy. For instance, Kennedy and colleagues (2007), reported that response to both CBT and venlafaxine was correlated to a decreased brain activity in orbitofrontal cortex, medial prefrontal cortex, occipital-temporal cortex. Metabolism in the subgenual cingulate and the caudate differentiated between groups. In another study, using SPECT to assess the effect of IPT *vs* escitalopram showed dissimilar results (Martin, Martin, Rai, Richardson, & Royall, 2001) since IPT responders had an increased blood flow both in the posterior cingulate and in basal ganglia (this latter also shared with escitalopram responders). However in both studies is possible to underline a partial common pattern: regions that are modulated both by pharmacological and psychological interventions.

To summarize the literature on brain activity changes related to effective psychological intervention is still small. Studies are typically underpowered and conducted in uncontrolled designs. However, a few preliminary claims can be made: i) psychological interventions can be studied in terms of their neurobiological correlates not differently than drugs; ii) the few available RCTs and the conclusions of at least one systematic review suggest that the effect of drugs and psychotherapies on brain activity is, at least partially, overlapping and involves a normalization of brain activity of depressed patients who became more *similar* to healthy non-depressed controls. Despite the putative different mechanisms of action which may

insist on different neural patterns (Mayberg, 2003), the brain recovering from a depressive episode seems to recover in similar ways despite the type of effective intervention in use.

Discussion and Conclusions

The effects of psychological treatment of adult depression have been tested in several hundreds of randomized controlled trials. There is no doubt that these treatments can be considered as evidence-based. The effects are comparable to those of antidepressant medication and probably last longer. A limited, but promising, evidence of comparable effects of psychotherapies and pharmacotherapies on brain activity has been documented as well. Of course this body of research has several limitations that have to be taken into account when interpreting the results. The most important limitation is that the quality of much of this research is not optimal, and the effects may be overestimated because of this. However, there is little doubt that the effects of psychotherapies are comparable to those of pharmacotherapies, even after taking these limitations into account.

The question is how these therapies can be applied in routine practice. Stepped-care interventions are an excellent way to provide these treatments. There is considerable evidence that low-intensity psychological treatments, such as guided self-help or internet-based treatments are effective and can be offered as a first step in such stepped-care models. When these treatments are not effective, or when there is a clear reason not to use low-intensity therapy, the patient can step up to high-intensity face-to-face therapy or pharmacotherapy. This model has been found to be successful in the IAPT program and it used more and more in other countries and settings as well.

Psychological treatments of depression are the preferred type of treatment for the majority of patients with depression, they are effective, have comparable effects as pharmacotherapy, and they are probably more effective at the longer term. The next step is to implement these therapies and make them available for as many patients as possible.

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