Canadian Psychology / Psychologie canadienne
2017, Vol. 58, No. 1, 7–19

0708-5591/17/$12.00 http://dx.doi.org/10.1037/cap0000096

Honorary President / Président d'honneur

Four Decades of Outcome Research on Psychotherapies for Adult Depression: An Overview of a Series of Meta-Analyses

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Abstract

In the past 4 decades about 500 randomized trials have examined the effects of psychological treatments of adult depression. In this article the results of a series of meta-analyses of these trials are summarised. Several types of psychotherapy have been examined, including cognitive behaviour therapy, behavioural activation therapy, interpersonal psychotherapy, problem-solving therapy, nondirective supportive therapy, and short-term psychodynamic psychotherapy. All therapies are effective and there are no significant differences between treatments. Psychotherapies are about equally effective as pharmacotherapy, and combined treatments are more effective than either of these alone. Therapies are also effective in specific target groups, such as older adults, college students, patients with general medical disorders, but may be somewhat less effective in chronic depression, and in patients with comorbid substance use disorders. Treatments are effective when delivered in individual, group, and guided self-help format. The effects of psychotherapies have been overestimated because of the low quality of many trials and due to publication bias. Future research should not be aimed at the development of new psychotherapies for depression, on specific treatment formats or on therapies in specific populations, because the evidence indicates that all types and formats with human involvement are effective in all specific target groups. Future research should instead focus on a further reduction of the disease burden of depression. Specifically, it should focus on the possibilities of preventing the onset of depressive disorders, treatments of chronic and treatment-resistant depression, relapse prevention, and scaling up treatments, for example by using more guided self-help interventions.

Keywords: depression, meta-analysis, psychotherapy, psychological treatment, cognitive behaviour therapy

Depressive disorders are highly prevalent (Alonso et al., 2004; Kessler et al., 1994), have a high incidence (Waraich, Goldner, Somers, & Hsu, 2004), and they are associated with a substantial loss of quality of life for patients and their relatives (Saarni et al., 2007; Ustun, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). These disorders are also associated with increased mortality rates (Cuijpers, Vogelzangs et al., 2014), high levels of service use, and enormous economic costs (Greenberg & Birnbaum, 2005; Smit et al., 2006). Major depression is currently ranked fourth worldwide in disease burden. Depression is expected to rank first in disease burden in high-income countries by the year 2030 (Mathers & Loncar, 2006). It is not surprising therefore that several treatments of depression have been developed in the past decades and that a considerable body of research has examined the effects of these treatments. There are two main categories of treatments for depression: biological treatments (mostly antidepressant medications) and psychological treatments.

I thank all coauthors of the published and in press meta-analyses that have used our database: Allan A. Abbass, Ceren Acarturk, Gerhard Andersson, Randy P. Auerbach, Jacques P. Barber, Jürgen Barth, Aartjan T. Beekman, Matthias Berking, Claudi L. H. Bockting, Ernst T. Bohlmeijer, Nikolaos Boumparis, Jessica G. Brännmark, Ronny Bruffaerts, Gregory N. Clarke, Frans Clignet, James C. Coyne, Ioana A. Cristea, Daniel David, Derek P. de Beurs, Frans de Jonghe, Saskia C. M. de Maat, Jessica de Wit, Leonore de Wit, Jack J. M. Dekker, Keith S. Dobson, Tara Donker, Ellen Driessen, David D. Ebert, David Ekers, Jonathan Flint, Judy Garber, Claudio Gentili, Anna S. Geraedts, Heike Gerger, Simon Gilbody, Lisa M. Hegelmaier, Ulrich Hegerl, Stefan G. Hofmann, Kirsten Holdt Henningsen, Steven D. Hollon, Jeremy Horder, Marcus J. H. Huibers, Sarah B. Hunter, Ilse Jansma, Elise P. Jansma, Robert Johansson, Peter Jüni, Eirini Karyotaki, Ad J. F. M. Kerkhof, Ronald C. Kessler, Annet Kleiboer, Spyros Kolovos, Sander L. Koole, Hans M. Koot, Peter M. Lewinsohn, Juan Li, John C. Markowitz, Roland Mergl, Cathrine Mihalopoulos, David C. Mohr, Marcus R. Munafò, Thomas Munder, Ricardo F. Muñoz, Eveline Nüesch, Mijung Park, Pietro Pietrini, Anne Margriet Pot, Leanne Quigley, Paula Ravitz, Mirjam Reijnders, Fritz Renner, Charles F. Reynolds III, David Richards, Heleen Riper, Jo Robays, Miquel Roca, Josien Schuurmans, Marit Sijbrandij, Filip Smit, Jan H. Smit, Yolba Smit, Niels Smits, Simona I. Stefan, Dan J. Stein, Adrian Taylor, Sven Trelle, Erick H. Turner, Burçin Ünlü Ince, Edith van 't Hof, Wouter van Ballegooijen, Annemiek van Dijke, Henricus L. Van, Berno van Meijel, Patricia van Oppen, Anneke van Schaik, Bregje A.J. van Spijker, Annemieke van Straten, Irma Verdonck-de Leeuw, Waquas Waheed, Lisanne Warmerdam, Lisa Webster, Myrna M. Weissman, Erica Weitz, and Hansjörg Znoj.

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Both types have been examined extensively. Since the 1970s about 500 randomized controlled trials have examined the effects of psychological treatments on depression.

It is now about 10 years since we started to build a comprehensive database of randomized trials examining the effects of psychological treatments of depression. Since that time we have updated this database every year (Cuijpers, van Straten, Smit, Mihalopoulos, & Beekman, 2008). We have used this database to answer several research questions with meta-analyses. We have published more than 70 of such meta-analyses. We have examined which psychotherapies are effective, whether psychotherapy is as effective as pharmacotherapy, and whether combined treatments are more effective than psychotherapy or pharmacotherapy alone. We have also examined the effects of the therapies in specific target groups, settings and subtypes of depression, as well characteristics of the therapies, such as the format (individual, group, self-help), and the number of sessions. We have examined the quality of the trials and how this affects their outcomes of the therapies, as well as the problem of publication bias. In this article we will give an overview of the results of these meta-analyses. We already provided an overview in an earlier article (Cuijpers, Andersson, Donker, & Van Straten, 2011). However, since then a considerable number of new meta-analyses have been published. This article can be seen as an update of this earlier overview.

A Database of Randomized Trials of Psychotherapies for Adult Depression

The methods used for building the database and the analyses used in the meta-analyses have been published in a methods article (Cuijpers, Van Straten, Smit et al., 2008). The general methods we used in these meta-analyses have been described in a manual that is freely available (Cuijpers, 2016b). In brief, the database was developed through a comprehensive literature search (of works dating from 1966), and is updated every year. We searched major bibliographical databases (PsycINFO, PubMed, Embase, Cochrane Central Register of Controlled Trials). We include all randomized trials in which at least one arm is a psychological treatment for adults (>18 years) with a depressive disorder according to a diagnostic interview or an elevated level of depressive symptomatology (as indicated by a score above a cut-off score on a validated self-report depression scale like the Beck Depression Inventory).

We calculate standardized mean effects (Cohen's d or Hedges' g) for each comparison between a psychotherapy and a comparison group, indicating the difference between these groups in terms of standard deviations. Effect sizes of 0.8 can be assumed to be large, while effect sizes of 0.5 are moderate, and effect sizes of 0.2 are small (Cohen, 1988). An effect size is, however, still a statistical concept with no direct indication for clinical relevance. Elsewhere we have argued that an effect size of $d = 0.24$ may be a threshold for clinical relevance in depression.

Because effect sizes are difficult to interpret for patients and clinicians we also calculate in most meta-analyses the numbers-needed-to-treat (NNT). The NNT indicates how many patients should receive the treatment to have one more positive outcome compared with the comparison group (Kraemer & Kupfer, 2006; Laupacis, Sackett, & Roberts, 1988).

In all meta-analyses we pool the individual effect sizes according to the random effects model. We calculate the level of heterogeneity with I^2 and its 95% confidence interval (CI). We also calculate in all meta-analyses the small sample bias (usually considered to be an indicator for publication bias), by examining the asymmetry of the funnel plot (showing that more small studies with large effect sizes are published than small studies with small or negative effect sizes). Details of these methods can be found elsewhere (Cuijpers, 2016b).

In Figure 1 the 400 randomized trials on psychotherapy that were included up to January 1, 2014 are presented in 5-year intervals. In the 1970s and 1980s almost all trials were conducted in the United States. Since the second half of the 1990s, the number of trials in Europe has increased considerably. In recent years more trials are conducted in Europe than in North America. Since 2000 an increasing number of trials has also been conducted

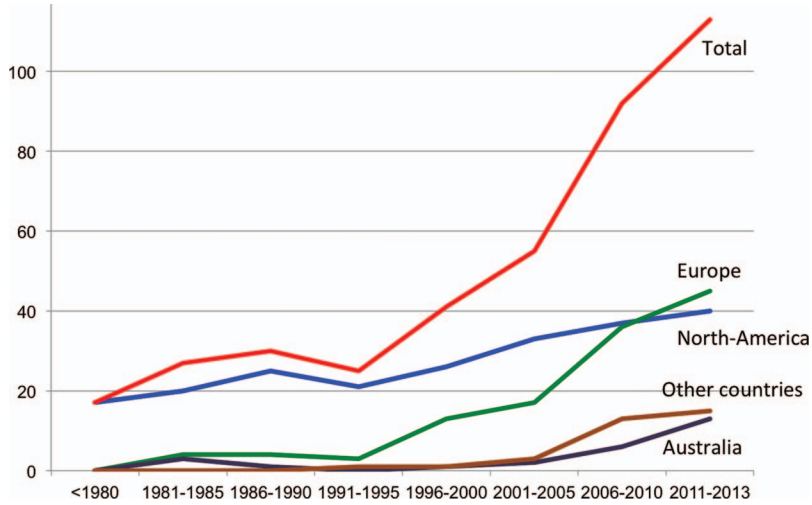

Figure 1. Randomized controlled trials examining the effects of psychotherapies for adult depression (N = 400; published previously in Cuijpers, 2015). See the online article for the color version of this figure.

in non-Western countries. The total number of trials has increased sharply since the 1990s.

The Effects of Psychotherapies for Depression

Several different types of psychotherapy have been developed and tested. All have been found to be effective compared with waiting list, care-as-usual, and placebo control conditions. The therapies that have been compared with a control group in at least 10 randomized trials are listed in Table 1. These therapies are cognitive behaviour therapy (CBT), behavioural activation therapy, interpersonal psychotherapy (IPT), problem-solving therapy, nondirective supportive therapy, and short-term psychodynamic psychotherapy (the definitions for each of these therapies are given in Cuijpers, Van Straten, Andersson, & van Oppen, 2008). For each of these therapies we conducted separate meta-analyses. As can be seen in Table 1, the effect sizes for these therapies range from g = 0.58 for nondirective counselling to g = 0.83 for problem-solving therapies, with NNTs from 2 to 3. CBT is by far the most studied type of psychotherapy for depression.

The effect sizes found for these therapies do not significantly differ from each other (Barth et al., 2013). However, the effect sizes are dependent on the type of control group. Waiting list control groups typically have the largest effect sizes (usually g > 0.8; Barth et al., 2013), care-as-usual has an effect size of about g = 0.5, and pill placebo has an effect size of 0.25 (Cuijpers, Turner et al., 2014).

Although these outcomes were examined at posttest, directly after the therapy, there is also evidence that the effects of psychotherapy are longer lasting. In one meta-analysis we found that the odds of a positive outcome at 6 months after randomization was significantly better for those who received the therapy compared with the odds in the control groups (*OR* = 1.92; 95% CI [1.60, 2.31]; Table 2; Karyotaki et al., 2016). In another meta-analysis we found that the odds of a positive outcome was also better at 12 months postrandomization (*OR* = 1.59; 95% CI [1.14, 2.21]; Karyotaki et al., 2014).

Most trials have focused on depression as primary outcome. However, a considerable number of trials have examined other, secondary outcomes of psychotherapy for depression. The results of the meta-analyses in which we examined these secondary outcomes are summarised in Table 1. As can be seen, psychological treatments seem to also have positive effects on quality of life

Table 1
Psychological Treatments of Adult Depression: Comparisons With Control Groups, Comparisons Between Different Types of Psychotherapy and Comparisons With Pharmacotherapy

	N	g	95% CI	I^2	95% CI	NNT	Reference
Different types of psychotherapy versus control groups							
• Cognitive behavior therapy	94	.71	[.62, .79]	57	[44, 65]	3	(Cuijpers, Berking et al., 2013)
• Behavioral activation therapy	31	.74	[.56, .91]	41	[11, 62]	3	(Ekers et al., 2014)
• Interpersonal psychotherapy	31	.60	[.45, .75]	63	[43, 74]	3	(Cuijpers, Donker et al., 2016)
• Problem-solving therapy	13	.83	[.45, 1.21]	83	[71, 88]	2	(Cuijpers, van Straten, & Warmerdam, 2007)
• Nondirective supportive therapy	18	.58	[.45, .72]	0	[0, 44]	3	(Cuijpers et al., 2012)
• Short-term psychodynamic psychotherapy	10	.61	[.33, .88]	54	[0, 76]	3	(Driessen, Hegelmaier et al., 2015)
Direct comparisons of different types of psychotherapy[a]							
• Cognitive behavior therapy vs. all other therapies	46	.02	[−.07, .11]	14	[0, 41]	83	(Cuijpers, Berking, et al., 2013)
• Nondirective supportive therapy vs. all other therapies	30	−.20	[−.32, −.08]	29	[0, 54]	9	(Cuijpers et al., 2012)
• Behavioral activation therapy vs. all other therapies	21	.14	[−.02, .30]	0	[0, 41]	13	(Cuijpers, van Straten, Andersson et al., 2008)
• Psychodynamic therapy vs. all other therapies	15	−.25	[−.49, −.02]	63	[24, 77]	7	(Driessen, Hegelmaier et al., 2015)
• Problem-solving therapy vs. all other therapies	7	.40	[−.07, .88]	73	[23, 86]	5	(Cuijpers, van Straten, Andersson et al., 2008)
• Interpersonal psychotherapy vs. all other therapies	14	.06	[−.14, .26]	52	[0, 72]	29	(Cuijpers, Donker et al., 2016)
Psychotherapy versus pharmacotherapy and combined treatments[a]							
• Psychotherapy vs. pharmacotherapy	48	−.03	[−.14, .08]	52	[0, 47]	63	(Cuijpers, Sijbrandij et al., 2013)
• Psychotherapy vs. combined treatment	19	.35	[.24, .45]	0	[0, 43]	5	(Cuijpers, van Straten, Warmerdam et al., 2009)
• Pharmacotherapy vs. combined treatment	32	.41	[.28, .54]	50	[25, 67]	4	(Cuijpers, Sijbrandij et al., 2014)
• Combined vs. psychotherapy plus placebo	16	.25	[.03, .46]	57	[13, 74]	7	(Cuijpers, van Straten, Hollon et al., 2010)
Effects of psychotherapies compared with control groups on other outcomes than depressive symptoms							
• Quality of life	31	.33	[.24, .42]	21	[0, 49]	5	(Kolovos et al., 2016)
• Suicidality	4	.12	[−.20, .44]	31	[0, 77]	15	(Cuijpers, de Beurs, et al., 2013)
• Hopelessness	18	1.10	[.72, 1.48]	77	[62, 84]	2	(Cuijpers, de Beurs, et al., 2013)
• Dysfunctional thinking	21	.51	[.39, .62]	6	[0, 45]	4	(Cristea et al., 2015)
• Social functioning	39	.46	[.32, .60]	71	[58, 78]	4	(Renner, Cuijpers, & Huibers, 2014)
• Positive affect	8	.37	[.13, .60]	39	[0, 73]	5	(Boumparis et al., 2016)
• Negative affect	8	.40	[.31, .68]	73	[44, 87]	5	(Boumparis et al., 2016)
• Social support	15	.38	[.29, .48]	0	[0–54]	5	(Park et al., 2014)
• Mental health children	7	.40	[.22, .59]	1	[0, 71]	5	(Cuijpers et al., 2015)
• Mother–child interaction	8	.35	[.17, .52]	0	[0, 68]	5	(Cuijpers et al., 2015)
• Parental functioning	5	.67	[.30, 1.04]	51	[0, 82]	3	(Cuijpers et al., 2015)

Note. CI = confidence interval; *N* = number of comparisons; NNT = numbers-needed-to-treat.
[a] In these comparisons a positive sign indicates that the first treatment of column one is more effective than the second one.

Table 2
Long-Term Effects of Psychotherapies for Depression: Odds Ratios

	N	*OR*	95% CI	I^2	95% CI	Reference
Therapy vs. control						
• Response at > 6 months	55	1.92	[1.60, 2.31]	65	[53, 74]	(Karyotaki et al., 2016)
• Response at > 12 months	11	1.59	[1.14, 2.21]	55	[17, 75]	(Karyotaki et al., 2014)
Combined vs. pharmacotherapy						
• Response at > 6 months	13	2.93	[2.15, 3.99]	0	[0, 57]	(Karyotaki et al., 2016)
• Response at > 12 months	8	2.23	[1.43, 3.41]	0	[0, 68]	(Karyotaki et al., 2016)
Combined vs. psychotherapy						
• Response at > 6 months	8	1.42	[.97, 2.0]7	0	[0, 68]	(Karyotaki et al., 2016)
• Response at > 12 months	7	1.33	[.88, 2.14]	0	[0, 71]	(Karyotaki et al., 2016)

Note. CI = confidence interval; *N* = number of comparisons.

(Kolovos, Kleiboer, & Cuijpers, 2016), hopelessness (Cuijpers, de Beurs et al., 2013), on dysfunctional thinking (Cristea et al., 2015), on positive and negative affect (Boumparis, Karyotaki, Kleiboer, Hofmann, & Cuijpers, 2016), and on social support (Park, Cuijpers, van Straten, & Reynolds, 2014). There is also a small group of studies examining the effects of psychotherapy for depressed mothers on the mental health of their children (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015). These studies show an overall effect on the mental health of these children, on the mother–child interaction and on parental functioning in general. Unexpectedly, very few studies have examined the effects of psychotherapy for depression on suicidality (Cuijpers, de Beurs et al., 2013). The effects of psychotherapy on suicidality remains therefore unclear. In the meta-analyses examining these secondary outcomes we typically find a strong association between the effects of therapies on depression and those on the secondary outcomes.

In a recent meta-analysis conducted by another group (Johnsen & Friborg, 2015) it was suggested that the effects of CBT have been falling over time. However, this meta-analysis had several serious methodological and conceptual problems. Therefore, we decided to redo this study (Cristea et al., in press). We used the same inclusion criteria as the original meta-analysis, but limited these to randomized trials. We identified 30 additional trials that had been missed in the original meta-analysis. In this larger sample, we did confirm the significant association between year of publication and the effect size (although this was based on prepost effect sizes, which are known to have many methodological problems; Cuijpers et al., 2016). However, the heterogeneity in these analyses was so high (>90%) that these outcomes can hardly be interpreted. Furthermore, this drop in effects over time was only found in the United States where early studies showed very high effect sizes. Studies from other parts of the world and more recent studies in the U.S. did not point at such an association. Year of publication does not appear to be a stable, reliable, and independent moderator of the effectiveness of CBT for depression. The temporal trend that was suggested in the original study is most likely a statistical artifact.

Are All Psychotherapies Equally Effective in the Treatment of Depression?

We can conclude that effect sizes from types of psychotherapy (compared with control groups) do not significantly differ from each other, suggesting that all therapies have comparable effects. However, a much better way to examine whether different types of psychotherapy are actually equally effective is to examine studies in patients who are randomly assigned to two (or more) different types of psychotherapy. If there are differences after treatment this can be considered direct evidence that therapies are indeed not equally effective.

In several meta-analyses we have examined these studies with direct comparisons between therapies (Barth et al., 2013; Cuijpers, Berking et al., 2013; Cuijpers, Donker, Weissman, Ravitz, & Cristea, 2016; Cuijpers et al., 2012; Cuijpers, van Straten, Andersson et al., 2008; Driessen, Hegelmaier et al., 2015). We have summarised the differential effect sizes found in these meta-analyses in Table 1. Overall we found few indications that there are significant and clinically relevant differences between studies. We did find that nondirective counselling was somewhat less effective than other therapies. However, in a more detailed study, we found that studies comparing counselling with another therapy often use counselling as a "nonspecific" control group. Furthermore, many of these studies suffer from researcher allegiance against counselling (Cuijpers et al., 2012). In studies with no researcher allegiance the difference between counselling and other therapies was not significant. We also found that brief psychodynamic therapies were somewhat less effective than other therapies (Driessen, Hegelmaier et al., 2015). This difference was also small and may not be robust when more research is done in this area.

Some researchers consider this absence of a difference between therapies to be evidence that the effects are not realised by therapy-specific mechanisms but by the so-called "common factors." A well-known example of such a common factor is the alliance between therapist and patient (Wampold & Imel, 2015). It is beyond the scope of the current article to list all arguments why this conclusion cannot be drawn from these studies. However, one important issue in this debate is that both the statistical power and the methodological quality is usually far too low in almost all studies directly comparing different therapies (Cuijpers, 2016a). In one article, we showed that in the studies examining CBT, IPT, and psychodynamic therapies, none of the individual trials had enough power to detect an effect size smaller than g = 0.34 (while the threshold for a clinically relevant effect is g = 0.24; Cuijpers, Turner, Koole, van Dijke, & Smit, 2014). Pooling of these studies in meta-analyses may help with solving the problem of low sta-

tistical power. However, after exclusion of studies of low quality even pooling these studies in meta-analyses does not result in sufficient power to find clinically relevant effect sizes.

Psychotherapy and Pharmacotherapy

Our meta-analyses of trials directly comparing psychotherapies and pharmacotherapy for depression indicate that there are no major differences between these two types of treatment (Cuijpers, Sijbrandij et al., 2013; Cuijpers, Van Straten, van Oppen, & Andersson, 2008, 2010). In the largest and most recent meta-analysis of these trials directly comparing psychotherapy and pharmacotherapy (Cuijpers, Sijbrandij et al., 2013), we found a differential effect size of g = −0.03 (in favour of pharmacotherapy), which was neither significant nor clinically relevant.

One problem is that in some trials directly comparing therapy with pharmacotherapy there is also a placebo condition. Such a placebo condition is not present in other trials. In these trials, the patients in the pharmacotherapy condition are blinded and do not know whether they are using the medication or the placebo. This is not the case in psychotherapy, because patients always know they are receiving that. Patients in the therapy conditions may therefore have expectations of positive effects and hope that the therapy will work. Patients in the medication condition on the other hand do not have these hopes and expectations to the same extent because they are uncertain whether they received medication or placebo. In a meta-analysis we therefore examined studies comparing psychotherapy with pharmacotherapy in which a placebo was used separately from those in which no placebo was used. The ones in which no placebo was used (and patients in both conditions) is probably the best comparison. It was found that pharmacotherapy was a little more effective than psychotherapy (g = 0.13) and this was significant.

On the other hand, however, many medication trials are sponsored by the industry and this may affect outcomes. That may also be true for trials comparing psychotherapy and pharmacotherapy. In a meta-analysis in which we explored the influence of sponsorship on the outcomes of these trials, we found that in the industry-funded trials pharmacotherapy was significantly more effective than psychotherapy (g = 0.11; Cristea, Gentili, Pietrini, & Cuijpers, 2016). In the trials that were not funded (and are therefore probably more independent) there was no significant difference between the two treatments (g = 0.10 in favour of psychotherapy).

So, overall it seems pretty robust that psychotherapy and pharmacotherapy are about equally effective, although some factors like blinding and sponsorship may result in small, clinically irrelevant differences in outcomes.

There is some evidence that the effects of psychotherapies 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, which then examine what happens in the follow-up period. Almost all studies had a follow-up between 12 and 24 months after the end of the acute phase treatment. In this follow-up period, the patients who had received CBT in the acute phase received no treatment, except for a few booster sessions in some studies. In five of the included studies the patients in the pharmacotherapy condition continued to take medication. The odds of responding to treatment were higher in the CBT condition than in the continued pharmacotherapy condition, but not significantly so (*OR* = 1.62; 95% CI [0.97, 2.72]; NNT = 10; Cuijpers, Hollon et al., 2013). In eight studies in this meta-analysis, the patients in the pharmacotherapy condition discontinued treatment during follow-up (while patients in the CBT condition did not receive any treatment). In these studies the odds of responding were significantly better in the CBT conditions at follow-up than in the pharmacotherapy conditions (*OR* = 2.61; 95% CI [1.58, 4.31]; Cuijpers, Hollon et al., 2013).

Although psychotherapy and pharmacotherapy are probably about equally effective in the short-term, it is clear that the combination of the two is more effective than either of them alone (see Table 1). In meta-analyses of trials examining these comparisons we found that combined treatment is significantly more effective than pharmacotherapy alone with an effect size of g = 0.41 (NNT = 4; Cuijpers et al., 2014), and than psychotherapy alone with g = 0.35 (NNT = 5; Cuijpers, van Straten, Warmerdam, & Andersson, 2009).

There is also a group of studies comparing combined treatment with the combination of psychotherapy and placebo (Cuijpers, van Straten, Hollon, & Andersson, 2010). These studies indicate the exact contribution of the medication to the effects of combined treatments. As can be seen in Table 1, medication contributes to the effects of combined treatments by an effect size of g = 0.25 (NNT = 7).

Characteristics of Patients

We have conducted several meta-analyses in specific groups of patients, such as older adults (Cuijpers, Karyotaki, Pot, Park, & Reynolds, 2014; Cuijpers, van Straten, & Smit, 2006), college students (Cuijpers, Cristea et al., 2016), and patients with general medical disorders, such as diabetes, heart diseases, or cancer (van Straten, Geraedts, Verdonck-de Leeuw, Andersson, & Cuijpers, 2010; see Table 3). In general, these studies show that the effects of psychotherapies in specific subgroups are comparable with those in adult populations in general.

In two meta-analyses we have compared the effects of psychotherapies in such specific groups (older adults, Cuijpers, van Straten, Smit, & Andersson, 2009; and college students, Cuijpers, Cristea et al., 2016) to studies of adults in general. We conducted metaregression analyses, in which we compared these two groups of studies, while controlling for other characteristics of the trials. In both metaregression analyses we found no indication that the effects differed between the specific populations and adults in general.

We also conducted some meta-analyses in specific settings. In one meta-analysis we examined the effects of psychotherapies in inpatient settings and found an effect size of g = 0.29 (95% CI [0.13, 0.44]; Cuijpers, Clignet et al., 2011). This is somewhat smaller than the effects found for therapies in other settings. The reason is probably that in these trials a structured psychotherapy is compared with usual care that typically involves quite intensive care in inpatient settings, including psychological support and therapy.

In another meta-analysis we examined the effects of psychotherapy in primary care patients (Cuijpers, van Straten, Van Schaik, & Andersson, 2009). In this meta-analysis we found that the effects were also somewhat smaller than in other settings (g =

Table 3
Characteristics of Participants and of the Psychotherapies

	N	g	95% CI	I^2	95% CI	NNT	Reference
Psychotherapy for specific target groups versus control groups							
• Older adults	40	.64	[.47, .80]	80	[73, 85]	3	(Cuijpers, Karyotaki et al., 2014)
• Student populations	22	.89	[.66, 1.11]	57	[23, 72]	2	(Cuijpers, Cristea et al., 2016)
• Patients with general medical disorders	18	1.00	[.57, 1.44]	93	[90, 94]	2	(van Straten et al., 2010)
Settings							
• Patients in primary care	20	.31	[.17, .45]	46	[0, 67]	6	(Cuijpers, van Straten, van Schaik et al., 2009)
• Inpatients	15	.29	[.13, .44]	0	[0, 46]	6	(Cuijpers, Clignet et al., 2011)
Subtypes of depression							
• Patients with subthreshold depression	14	.35	[.23, .47]	13	[0, 51]	5	(Cuijpers, Koole et al., 2014)
• Patients with chronic depression	8	.23	[.06, .41]	0	[0, 56]	8	(Cuijpers, van Straten, Schuurmans et al., 2010)
• Women with postpartum depression	19	.61	[.37, .85]	65	[37, 77]	3	(Cuijpers, Brannmark, & van Straten, 2008)
Characteristics of therapies							
• Individual versus group psychotherapies	19	.20	[.05, .35]	0	[0, 43]	9	(Cuijpers, van Straten, & Warmerdam, 2008)
• Guided self-help versus face-to-face therapies	9	−.15	[−.41, .11]	2	[0, 55]	12	(Cuijpers, Sijbrandij et al., 2014)
• Number of sessions[a]							
• 4–6	23	.47	[.30, .65]	45	[9, 66]	4	(Cuijpers, Huibers et al., 2013)
• 7–10	27	.58	[.42, .74]	69	[55, 79]	3	(Cuijpers, Huibers et al., 2013)
• 12–16	22	.68	[.50, .85]	57	[30, 73]	3	(Cuijpers, Huibers et al., 2013)
• 18–24	20	.61	[.41, .81]	42	[1, 66]	3	(Cuijpers, Huibers et al., 2013)
• Sessions per week ($p < .001$)							
• <1	10	.44	[.19, .69]	64	[29, 82]	4	(Cuijpers, Huibers et al., 2013)
• 1	46	.58	[.46, .70]	53	[35, 67]	3	(Cuijpers, Huibers et al., 2013)
• >1	22	.71	[.52, .91]	53	[24, 71]	3	(Cuijpers, Huibers et al., 2013)

Note. CI = confidence interval; *N* = number of comparisons; NNT = numbers-needed-to-treat.
[a] This meta-analysis was conducted only in individual therapies.

0.31; 95% CI [0.17, 0.45]; NNT = 6). In a series of subgroup analyses we found that in studies in which patients were referred by their general practitioner the effects were comparable to those in other settings. When patients were identified through systematic screening of primary care patients, however, the effects were considerably smaller and nonsignificant. The difference between these two groups of studies was significant.

In our database we have included trials in which patients are included if they meet diagnostic criteria for major depression or another mood disorder. However, we have also included trials in which a cut-off on a self-report measure is used as inclusion criterion. In our meta-analyses we typically find no difference between the effect sizes in these two groups of studies (Cuijpers, Berking et al., 2013; Cuijpers, van Straten, Warmerdam, & Smits, 2008).

There is a considerable number of trials examining the effects of psychotherapy in specific types of depression (see Table 3). In one meta-analysis we examined studies in people with subthreshold depression (depressive symptoms but no major depressive disorder). We found that the effects of psychotherapy in this group were moderate but significant (g = 0.35; 95% CI [0.23, 0.47]; NNT = 5). However, these effects were significantly smaller than in patients with a major depressive disorder. This is not surprising because the level of depressive symptoms was low from the start and there was less room for improvement. We also found that these treatments significantly reduced the incidence of major depressive episodes at 6 months follow-up (relative risk [RR] = 0.61) and possibly at 12 months (RR = 0.74).

In another meta-analysis we focused on trials in patients with chronic depression (Cuijpers, van Straten, Schuurmans et al., 2010). We found that psychotherapy had a small but significant effect (g = 0.23; 95% CI [0.06, 0.41]) on depression when compared with control groups. Psychotherapy was significantly less effective than pharmacotherapy in direct comparisons (g = −0.31), especially SSRIs. This finding, however, was fully attributable to dysthymic patients (the studies examining dysthymia patients were the same studies that examined SSRIs). Combined treatment was more effective than pharmacotherapy alone but even more so with respect to psychotherapy alone, although again this difference may have reflected the greater proportion of dysthymic samples in the latter.

In one meta-analysis we examined trials combining CBT and motivational interviewing to treat comorbid depression and alcohol use disorder. We found that the effects of this intervention on depression were small but significant (g = 0.27; 95% CI: 0.13 ~ 0.41; NNT = 7), as were the effects on alcohol (g = 0.17; 95% CI: 0.07 ~ 0.28; Riper et al., 2014). And finally, in another meta-analysis we found that the effects of psychological treatments of women with postpartum depression were large and comparable with those in other populations (g = 0.61; 95% CI [0.37, 0.85]; NNT = 3).

We have examined several other characteristics of patients in our meta-analyses. For example we examined whether the proportion of people from ethnic minorities in the trials was associated with the effect size (Unlu Ince, Riper, van 't Hof, & Cuijpers, 2014). We used subgroup and metaregression analyses. We did not find a significant association between the proportion of people from ethnic minorities and the effect size. In another metaregression analyses we examined whether the mean severity of the population in the trials at baseline predicted outcome (Driessen,

Cuijpers, Hollon, & Dekker, 2010). We found no indication that baseline severity was associated with outcome. This suggests that psychotherapy is also effective in patients with severe depression.

The problem with such metaregression analyses is that they can only be conducted with the aggregated data from each study, and not with the data of individual patients. So, the mean depression score at baseline from one study says very little about the range of severities of depression in that trial. In one of the subprojects of our meta-analysis project, we started to collect the primary data of trials in order to conduct so-called "individual patient data" (IPD) meta-analyses (Riley, Lambert, & Abo-Zaid, 2010). With the individual data from trials it is possible to examine characteristics of individual participants (such as baseline severity) and examine them across trials. One advantage is also that individual trials typically do not have enough statistical power to examine moderators of outcome. However, by combining the data of individual trials the statistical power increases considerably, making such analyses of moderators possible.

We are currently in the process of collecting the data of trials for several comparisons. However, we have already successfully collected the data of 16 randomized trials comparing CBT with pharmacotherapy for depression with more than 1,700 patients. The first articles about these data have now been published. We have shown that, contrary to what is thought by many clinicians, baseline severity is not a significant predictor of outcome and CBT is as effective in severe depression as pharmacotherapy (Weitz et al., 2015). In another article based on these data we showed that deterioration of patients and extreme nonresponse in trials comparing CBT and pharmacotherapy is rare, and not significantly different in the two treatment modalities. (Vittengl et al., 2016) Finally, we showed that gender is not a predictor or moderator of outcome in CBT and pharmacotherapy (Cuijpers, Weitz et al., 2014). We also found that there is no difference in effects between CBT and pharmacotherapy in patients with melancholic depression or with atypical depression (Cuijpers et al., in press).

Characteristics of Therapies

In several meta-analyses we examined whether characteristics of therapies are associated with the effect sizes. Previously we already saw that type of therapy does not seem to be very strongly related to outcome of therapies. In an early meta-analysis we found that professionally trained therapists did not appear to realise higher effect sizes than trained students who delivered the therapies (Cuijpers, van Straten, Warmerdam et al., 2008). However, this meta-analysis is already somewhat older and was based on only a limited number of studies, so this finding has to be verified in future research.

We have also examined in several meta-analyses whether treatment format is related to outcome. In one meta-analysis we included trials in which individual and group therapies were directly compared with each other (Cuijpers, van Straten, van Oppen et al., 2008). Individual therapy seemed to be somewhat more effective than group therapy ($g = 0.20$; 95% CI [0.05, 0.35]; NNT = 9). Furthermore drop-out from treatment seemed to be somewhat smaller in individual therapy. However, the quality of these studies was low. Therefore, the results have to be considered with caution and may very well reflect a chance finding. This is especially true because this finding was not confirmed in moderator analyses of controlled trials in which typically no indication is found that individual or group treatment differ significantly from each other (Cuijpers, Berking et al., 2013; Cuijpers, van Straten, Warmerdam et al., 2008).

In general it seems that the treatment format is not or not strongly related to outcome, whether that format is individual, group, or guided self-help (through a book or through computerized therapy). In one meta-analysis we found that Internet-based guided self-help interventions are effective compared with control conditions with an effect size that is comparable with those of face-to-face therapies ($g = 0.61$; 95% CI [0.45, 0.77]; Andersson & Cuijpers, 2009). In another meta-analysis we selected trials in which face-to-face therapies were directly compared with guided self-help therapies. In guided self-help interventions patients apply a written psychological treatment to themselves. The therapist only helps the patient to work through the materials. The meta-analysis comparing face-to-face therapies with guided self-help found no significant difference between the two treatment formats ($g = -0.15$; 95% CI [−0.41, 0.11]).

In general we can say that treatment format is not or only to a limited extent associated with the effects of treatment. However, this is only true for the individual, group, and guided self-help formats. Because the Internet is becoming increasingly integrated in societies, several unguided interventions for depression have become available. A growing number of trials have examined the effects of these treatments. In a meta-analysis of such trials we found that unguided treatment of depression has significant effects on depression ($g = 0.28$; 95% CI [0.14, 0.42]), but these effects are considerably smaller than those of individual, group, and guided self-help interventions (Cuijpers, Donker et al., 2011).

In another meta-analysis we examined whether the amount, frequency, and intensity of therapy was related to the effect sizes (in this meta-analysis we only included studies on individual therapies; Cuijpers, Huibers, Ebert, Koole, & Andersson, 2013). There was only a small association between number of therapy sessions and effect size. Furthermore, this association was no longer significant when the analysis adjusted for other characteristics of the studies. In metaregression analyses we also found no significant association with the total contact time or duration of the therapy. However, there was a strong association between number of sessions per week and effect size. An increase from one to two sessions per week boosted the effect size by $g = 0.45$, while keeping the total number of treatment sessions constant. We are currently verifying in a randomized trial whether this association is indeed robust (Bruijniks et al., 2015).

Causes of Overestimation of the Effects

In most meta-analyses described to date psychotherapy has been found to have moderate to large effects on depression. However, we also found indications that these effects are considerably overestimated (Cuijpers, Andersson et al., 2011).

In one meta-analysis we examined the association between quality of trials and the effect size (Cuijpers, Andersson et al., 2011; Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010). We assessed eight quality criteria: participants met diagnostic criteria for a depressive disorder, a treatment manual was used, the therapists were trained, treatment integrity was checked, intention-to-treat analyses were used, $N > 50$, randomization was

conducted by an independent party, and assessors of outcome were blinded. Out of the 115 trials, only 11 (with 16 comparisons between therapy and control) met all eight quality criteria. The effect size found for the high-quality studies (g = 0.22; 95% CI [0.14, 0.31]; NNT = 8) was significantly smaller than in the other studies (g = 0.75; 95% CI [0.66, 0.84]; NNT = 2). That was even true after restricting the sample to the subset of other studies that used the kind of care-as-usual or nonspecific controls that tended to be used in the high-quality studies.

Another reason why the effects of psychotherapies have been overestimated is publication bias. Publication bias is the tendency for authors to submit, or journals to accept, manuscripts for publication based on the direction or strength of the study's findings (Dickersin, 1990). We identified U.S. National Institutes of Health grants funding randomized clinical trials on psychological treatments and we determined whether those grants led to publications (Driessen, Hollon, Bockting, Cuijpers, & Turner, 2015). A total of 13 (24%) of the 55 funded grants did not result in publications. We also requested the data of the unpublished studies from the researchers. We found that among the comparisons of therapy to control conditions, adding unpublished studies to published studies reduced the psychotherapy effect size by 25%, from g = 0.52 (95% CI [0.37, 0.68]) to g = 0.39 (95% CI [0.08, 0.70]).

This direct evidence of publication bias is in line with more indirect evidence we have found in our meta-analyses (Cuijpers, Smit, Bohlmeijer, Hollon, & Andersson, 2010). The indirect evidence for publication bias can be based on the symmetry of the funnel plot. A funnel plot gives a measure of study size (the standard error) on the vertical axis as a function of effect size on the horizontal axis. Large studies appear at the top of the graph and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph. As there is more sampling variation in effect size estimates in the smaller studies, they will be dispersed across a larger range of values than large studies. Studies can be expected to be distributed symmetrically about the pooled effect size when publication bias is absent. In the presence of bias, it can be expected that the lower part of the plot will show a higher concentration of studies on one side of the mean than on the other. It is possible to calculate the effect size after adjustment for this asymmetry of the funnel plot (Duval & Tweedie, 2000). We found in a meta-analysis of 175 comparisons between a therapy and control group that the overall effect size was g = 0.67 (95% CI [0.60, 0.75]), but after adjustment for publication bias this was reduced to g = 0.42 (95% CI [0.33, 0.51]; number of missing studies was 51).

This analysis shows that the effects of psychotherapy for depression have probably been considerably overestimated. The true effects are smaller than has been assumed on the basis of earlier meta-analyses.

Directions for Future Research

In the series of meta-analyses described in this article, it became clear that psychological interventions are effective in the treatment of depression. Based on four decades of research on these interventions we also learned much about the characteristics of the participants of these interventions, as well as about the types, formats, and contents of these interventions. However, we also saw that the effects of psychotherapies have been overestimated because of the low quality of many trials and because of publication bias. So, how should the field move forward in the next decades?

It is clear that there is a strong need for further reduction of the disease burden of depression. As we saw in the introduction of this article, the disease burden of depression is very high. It is high in terms of personal suffering among patients and their families, as well as from a societal and economic perspective. And although current treatments are considered to be effective, there is also much room for improvement (Cuijpers, 2015). Modelling studies have shown that all available evidence-based treatments together can reduce the disease burden of depression by only about 33% (Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004). More than 40% of the patients only partially respond to treatment if at all, and less than one third of the patients are completely recovered after treatment (Hollon et al., 2002). Furthermore, relapse rates are estimated to be 50% after 2 years and up to 85% within 15 years after recovery from an initial episode (Mueller et al., 1999).

So, from a public health perspective it is very important to improve treatment outcomes for depression and to further reduce the disease burden. How can that be realised? One important direction for the future is not to waste funding and resources on research that is not needed and will not contribute to a further reduction of the disease burden of depression. The 500 trials on psychotherapy for depression that have been conducted in the past decades have made it clear that although many new therapies have been developed for depression, none of them is more effective than the others. Despite claims of being superior to existing therapies, no new therapy for depression has been found to be better than the existing ones. This finding of no superiority of one therapy over others cannot be considered as evidence that there are indeed no differences. However, it is very unlikely that a new therapy would suddenly appear and turn out to be more effective than existing ones. If a reduction of the disease burden is the goal of future research it would be unwise to spend available resources on that. We have seen this too often in the past and end up with just another therapy that is equally effective but does not add anything to a further reduction of the disease burden.

The same is true for research on different treatment formats. Individual, group, and guided self-help (including Internet-based) formats are probably (about) equally effective. However, this research cannot be completely certain about whether there are no differences; if there are any they are probably small and not clinically relevant. But again, if a reduction of the disease is our primary aim, this is not what we should focus on. The same is true for trials in specific populations. The research from the past decades suggests that psychotherapies are effective in all adults. There is no reason that it is not effective in specific subgroups such as older adults, patients with general medical disorders, and college students.

But if we should not focus our research on new therapies, treatment formats, or specific populations, what should the targets of future research be? Of course there is a lot we need to know about depression outside the therapy field. For example, we need more understanding of what depression is, the biological and psychological mechanisms and etiology involved, the heterogeneity of depression, and possible subcategories. We also need better and more accurate diagnostic tools.

But in the field of psychological interventions there are several goals for future research that are important from a public health

perspective. First, preventive interventions are an important topic. Because current treatments can take away only one third of the disease burden of depression, maybe prevention can remove a part of the other two thirds? There is a considerable number of trials showing that selective and indicated interventions can prevent the onset of new cases of major depression at one to 2-year follow-up (Cuijpers, van Straten, Warmerdam, & Andersson, 2008; van Zoonen et al., 2014).

Another important way to improve outcomes and reduce the disease burden is by focusing on treatments of chronic and treatment-resistant depression, and on preventing relapse (Cuijpers, 2015). Many patients suffer from depressive disorder for a considerable time period and do not respond to treatments, or they relapse after successful recovery. If we want to reduce the disease burden of depression further, this is one of the main subjects we should focus on. Fortunately, the number of trials in chronic depression and relapse prevention is growing. Several psychological therapies specifically aimed at chronic depression have been developed and tested (Carter et al., 2013; Rohricht, Papadopoulos, & Priebe, 2013; Schramm et al., 2011; Strauss, Hayward, & Chadwick, 2012; Wiles et al., 2013). Other trials have provided further evidence that relapse can be effectively prevented with cognitive behaviour therapy (Jarrett, Minhajuddin, Gershenfeld, Friedman, & Thase, 2013), especially in patients with a higher number of previous episodes (Stangier et al., 2013).

Another important way to further reduce the disease burden of depression is to develop methods for applying psychological treatments in a simpler and more efficient way (Cuijpers, 2015). Psychotherapies have not been scaled up to the extent that they may help reduce the disease burden of mental disorders (Kazdin & Blase, 2011). Even in high-income countries less than half the people with depressive disorders receive treatment. This is much lower in low and middle income countries, but also in older adults, people with lower socioeconomic status, and people from ethnic minorities. Scaling up treatments can be realized, for example, by training lay health counselors to deliver psychological therapies (Patel et al., 2010). This is especially interesting in low- and middle-income countries that want to build an infrastructure for mental health care, while fully trained therapists are not available. In addition, guided self-help interventions (including Internet-based interventions) can be useful for scaling up treatments, as has been done in the United Kingdom in the Increasing Access to Psychological Therapies program (Gyani, Shafran, Layard, & Clark, 2013). Such treatments save therapists' time and are probably as effective as face-to-face therapies, while requiring fewer resources.

Discussion

In this article we presented an overview of a series of meta-analyses we conducted on the 500 randomized trials that have examined the effects of psychological treatments of adult depression. We saw that several of these interventions have been tested and that they are effective in the treatment of depression. Furthermore, we saw that there are no significant differences between treatments and that they have effects that last for 6 to 12 months. We also saw that these therapies are about equally effective as pharmacotherapy in the short-term, and that the combination of psychotherapy and antidepressants is significantly more effective than either of these alone. Therapies are also effective in specific target groups, such as older adults, college students, women with postpartum depression, and patients with general medical disorders. These therapies may be somewhat less effective in chronic depression, and in patients with comorbid substance use disorders. Treatments are effective when delivered in individual, group, and guided self-help format. They are less effective when delivered without any kind of human support. We also saw that the effects of psychotherapies have been overestimated because of the low quality of many trials as well as publication bias.

As directions for future research we suggested not to develop new psychotherapies for depression because up to now all new therapies appeared to be indeed effective in the treatment of depression, but not more so than existing therapies. We also suggested not to test treatment formats and therapies in specific populations, because the evidence indicates that all formats with human involvement are effective in all specific target groups. Additionally, we recommended that a focus on a reduction of the disease burden of depression should be the starting point for new research. Promising areas include research on preventing the onset of depressive disorders, treatments of chronic and treatment-resistant depression, relapse prevention, and scaling up treatments for example by using more guided self-help interventions and training lay counselors in delivering interventions in low-resource settings.

Although this is a comprehensive overview of all the meta-analyses we have conducted in the past years, it contains some limitations. First, we only presented the meta-analyses that were conducted by us based on our database. There are, however, many other meta-analyses and these do not necessarily reach the same conclusions. Second, we merely summarised the results of these meta-analyses, but did not discuss all the results in terms of heterogeneity, moderator analyses, and analyses of publication bias from each of these meta-analyses.

Despite these limitations, we can conclude that psychotherapies are essential tools in the treatment of adult depression. Randomized trials have shown that these treatments are effective, and by focusing on key issues, such as chronic and treatment-resistant depression, on relapse, and on scaling up, psychotherapies contribute more and more to the reduction of the disease burden of depression.

Résumé

Au cours des 4 dernières décennies, environ 500 essais randomisés ont examiné les effets des traitements psychologiques de la dépression chez l'adulte. Cet article fait le sommaire des résultats d'une série de méta-analyses de ces essais. Plusieurs types de psychothérapie ont été examinés, y compris la thérapie cognitivo-comportementale, la thérapie d'activation comportementale, la psychothérapie interpersonnelle, la thérapie de résolution de problèmes, la thérapie de soutien non directive et la psychothérapie psychodynamique à court terme. Toutes les thérapies sont efficaces et il n'y a pas de différences significatives entre les traitements. Les psychothérapies sont à peu près aussi efficaces que la pharmacothérapie, et les traitements combinés sont plus efficaces que toute méthode utilisée seule. De plus, les thérapies sont efficaces parmi des groupes cibles précis, tels les aînés, les étudiants

à l'université ou les patients ayant des troubles de santé, mais quelque peu moins efficaces pour traiter la dépression chronique ou des troubles concomitants de toxicomanie. Les traitements sont efficaces lorsqu'ils sont offerts sur une base individuelle, en groupe ou selon un format d'aide personnelle autoguidée. L'efficacité des psychothérapies a été surestimée en raison de la faible qualité de nombreux essais et d'un biais de publication. Les recherches futures ne devraient pas viser à élaborer de nouvelles psychothérapies pour traiter la dépression ou encore de nouvelles formules de traitement ou de thérapies destinées à des populations précises, car les preuves révèlent que tous les types et formats impliquant une participation humaine sont efficaces parmi tous les groupes ciblés. Les recherches futures devraient plutôt se consacrer à diminuer davantage le fardeau de la maladie qu'est la dépression. Plus précisément, elles devraient se pencher sur les possibilités de prévenir les troubles dépressifs, sur les traitements de la dépression chronique et de la dépression réfractaire au traitement, la prévention des rechutes, l'intensification des traitements au moyen, par exemple, des interventions d'aide personnelle autoguidée.

Mots-clés : dépression, méta-analyse, psychothérapie, traitement psychologique, thérapie cognitivo-comportementale.

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Received September 19, 2016
Revision received November 18, 2016
Accepted November 20, 2016 ■