

Long-Term Effects of Psychotherapy for Non-Chronic Depressive Disorder: A Systematic Review of Studies in Comparison with Pharmacotherapy

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Keywords

Depression · Psychotherapy · Long-term effects · Antidepressant

Summary

The short-term effects of psychotherapy and pharmacotherapy – as monotherapy or in combination – in the treatment of depression have been documented in various studies. Strikingly, there are only a few studies proving the long-term efficacy 1 year or more after acute treatment. Therefore, a systematic review was conducted searching the databases Pubmed and PsychINFO. 13 randomized controlled trials (RCTs) could be retrieved (psychotherapy vs. pharmacotherapy in combination or as monotherapy). The follow-up period varied between 12 and 75 months ($M = 27.06$), cognitive behavioral therapy being the most frequently used psychotherapeutic strategy. The results indicate an advantage of psychotherapy alone or the combination of psychotherapy and pharmacotherapy when compared with pharmacotherapy alone. The advantage persisted even if the pharmacotherapy was maintained during the follow-up period. However, comparing studies is difficult due to methodological issues (e.g., selection of data relating to patients with or without therapy success after acute therapy; further treatments during follow-up). In order to make more valid statements about the long-term efficacy of psychotherapy and pharmacotherapy in the treatment of depression, more RCTs with longer follow-up periods are needed.

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Schlüsselwörter

Depression · Psychotherapie · Langzeitwirkungen · Antidepressiva

Zusammenfassung

Die kurzfristige Wirksamkeit von Psycho- und Pharmakotherapie bei Depressionen, ob als Monotherapie oder in Kombination, ist durch viele Studien gut belegt. Weitaus weniger Belege gibt es jedoch für die langfristige Wirksamkeit ab 1 Jahr nach Akuttherapie dieser Behandlungsformen. Durch eine systematische Suche in den Datenbanken Pubmed und PsychINFO konnten 13 randomisierte kontrollierte Studien (RCTs; Psychotherapie vs. Pharmakotherapie in Kombination oder als Monotherapie) identifiziert werden, bei denen Follow-up-Ergebnisse vorliegen; der entsprechende Follow-up-Zeitraum lag dabei zwischen 12 und 75 Monaten ($M = 27,06$). Meist kam als psychotherapeutisches Verfahren die kognitive Verhaltenstherapie zum Einsatz. Die Studienlage spricht für eine Überlegenheit der Psychotherapie oder der Kombination aus Psychotherapie und Pharmakotherapie im Vergleich zur Pharmakotherapie mit oder ohne Erhaltungsphase nach der Akutbehandlung bezüglich langfristiger Effekte über die Beendigung der Therapie hinaus. Die Studien sind aufgrund vielfältiger methodischer Faktoren nur begrenzt vergleichbar (z.B. hinsichtlich der Datenselektion zu Patienten mit und ohne Therapieerfolg nach Akuttherapie oder weiterer Behandlungen im Follow-up-Zeitraum). Um besser abgesicherte Aussagen zur langfristigen Wirksamkeit von Psycho- und Pharmakotherapie in der Behandlung der Depression treffen zu können, bedarf es weiterer RCTs mit längeren Follow-up-Zeiträumen.

Introduction

Due to their lifetime prevalence of 16.2% [Kessler et al., 2003] and the resulting severe negative socioeconomic repercussions [Marschall et al., 2016], depressive disorders are of major societal importance. Depressive disorders are characterized by their propensity of relapse and by chronicity for a third of the patients [Murphy and Byrne, 2012]. Empirically, singular depressive episodes constitute an exception: in a population-based study by Eaton et al. [2008], 15% of the patients experienced no single year free of depressive episodes over the course of 23 years and roughly half of the patients experienced at least 1 further episode. Therefore, above and beyond short-term efficacy after acute treatment, when viewed with regard to long-term effects as well as the minimization of recurrence, the long-term efficacy of therapies constitutes a decisive therapeutic challenge. In the current medical guidelines [APA, 2010; DGPPN et al., 2015; NICE, 2016], grading the evidence plays a vital role for the process of evaluating the current scientific knowledge. However, the current guideline recommendations hardly consider the issue of long-term or sustainable effects of therapies. Accordingly, therapies whose efficacy of acute treatment (psychotherapy/pharmacotherapy) is well-documented by means of several randomized controlled trials (RCTs) of a duration of 6 or 12 weeks are especially recommended. However, this may be critical, as we have to call into question whether a therapy with a well-documented short-term efficacy is to be recommended, even though long-term – potentially detrimental – effects that may arise are unknown. For example, there is some evidence that antidepressants may have an adverse effect on the course and the risk of recurrence of depression [Andrews et al., 2012; Babyak et al., 2000; Shrestha et al., 2014].

In light of the above, exploring possible long-term positive effects of psychotherapy which – beside antidepressants – has also proven to be beneficial [Cognitive Behavioral Therapy (CBT): Cuijpers et al., 2013a; Interpersonal Psychotherapy (IPT): Cuijpers et al., 2011b; Psychodynamic Psychotherapy: Driessen et al., 2015] is of particular interest to clinical researchers. Psychotherapy and drug treatment are still equally comparable in terms of acute efficacy, the combination of the 2 being more efficacious than the respective monotherapeutic approach for all degrees of severity of depression [Cuijpers et al., 2011a; Cuijpers et al., 2014b; Weitz et al., 2015]. Roughly two thirds of patients no longer meet the criteria of a clinical depression upon completion of psychotherapeutic treatment [Cuijpers et al., 2014a]. A substantial part of these positive effects, however, can be explained by placebo effects – this is the case for antidepressants as well as for psychotherapy [Khan et al., 2012; Kirsch, 2016]. Furthermore, studies have not yet revealed how long the carry-over effects of treatment last upon completion.

It is universally recognized that pharmacotherapy should be continued after acute treatment (maintenance therapy) so as to reduce the risk of recurrence. The current guidelines recommend at least 6 months of further treatment after remission [APA, 2010; DGPPN et al., 2015; NICE, 2016]. On the other hand, ac-

ording to the guidelines for psychotherapy, psychotherapeutic treatment is to be ended after a specified allocation of hours. Maintenance therapy would not be compatible with the self-understanding of psychotherapy, which strives to impart skills and strategies to patients to overcome their disorders and to cope differently with trigger factors in the future. Thus, patients are supposed to learn sustainable strategies beyond their therapy sessions and not grow more dependent on therapeutic treatment. Consequently, this concept of psychotherapy for both CBT as well as Psychodynamic Psychotherapies assumes a long-term effect preventing recurrence. Every practitioner knows, however, that this cannot always be achieved. As a result, psychotherapy researchers have been discussing booster sessions, i.e. sessions to refresh the topics learned in the scope of psychotherapy [Vittengl et al., 2007] long ago.

Long-Term Effects of Treatment of Acute Episodic Unipolar Depression in Past Meta-Analyses

A meta-analysis from 18 years ago by Gloaguen et al. [1998] exploring the efficacy of CBT for depression showed that only 8 of the 48 included RCTs had follow-up data for 1–2 years. Five out of 8 studies showed that psychotherapy was superior to pharmacotherapy in the long term. At follow up, only 29.5% of the patients treated with Cognitive Therapy relapsed compared to 60% of those treated with antidepressants. Vittengl et al. [2007] conducted a meta-analysis of 28 studies including 1,880 patients showing that after discontinuation of acute-phase Cognitive Therapy 29% of the patients relapsed within 1 year and 54% within 2 years. Only data from patients with therapeutic success after acute treatment was included. Compared to pharmacotherapy, however, Cognitive Therapy decreased the risk of recurrence by 22–23%. Moreover, the authors reported that the rate of relapse rose with an increasing time period between follow-up measurement and acute treatment. Steinert et al. [2014] could not confirm the latter. In 6 of the studies included in their meta-analysis, psychotherapy was compared to non-psychotherapeutic treatments (pharmacotherapy, Clinical Management, Treatment as Usual). The studies included patients with and without therapeutic success after acute treatment as well as patients with residual depressive symptoms. For a 2-year time period, psychotherapy resulted in significantly less relapses: patients with psychotherapy showed a relapse rate of 53% vs. 71% for patients treated with non-psychotherapeutic treatment. Additionally, the authors concluded that both a monotherapeutic and a combined treatment decrease the risk of relapse within a time period of roughly 4.4 years. Karyotaki et al. [2016] obtained similar results in their meta-analysis with 23 RCTs (N = 2,184 patients). Here, combined treatment (psychotherapy and pharmacotherapy) was compared to the respective monotherapeutic approaches in the form of acute treatment as well as maintenance therapy. Studies with and without therapeutic success after acute treatment were included. Combined therapy and psychotherapy alone resulted in a superior enduring effect compared to antidepressants alone. A meta-analysis by Cuijpers et al. [2013a] comparing follow-up data after CBT

and maintenance therapy with antidepressants for 6–18 months displayed a non-significant trend in favor of CBT. Comparing the sustainability of psychotherapy with the study arms which first administered antidepressants and then stopped them revealed that CBT was significantly superior to the other treatments. A further meta-analysis by Cuijpers et al. [2014b] with 32 studies compared the effects of combined pharmacotherapy and psychotherapy with pharmacotherapy alone in adults with a diagnosed depressive disorder. The authors concluded that combined treatment appears to be more effective than treatment with antidepressant medication; and this effect remained significantly superior up to 2 years after treatment.

In summary, the results from past meta-analyses reveal that even patients who respond to acute psychotherapeutic treatment will, in half the cases, suffer a relapse within 2 years and evidently require intense relapse prevention. Moreover, the results of previous reviews and meta-analyses have limited significance related to the long-term effects of psychotherapy due to methodical issues and other differences harbored in the observed studies. The studies frequently did not distinguish between acute and residual depressive symptoms or only included patients who had experienced therapeutic success in the analysis. Inadequate documentation of follow-up, in particular, is of concern in these studies. Consequently, when comparing treatments, the authors did not distinguish whether or not patients continued therapy after acute treatment. In order to draw a fair comparison and evaluation of types of treatment in terms of sustainability, each treatment condition has to fulfill the criterion of discontinuing the treatment. Otherwise, the subject of analysis would be the sustained effect, rather than the «carry-over effect». The present systematic review thus intends to thoroughly investigate past long-term studies exploring the treatment of episodic unipolar depression in order to learn more about long-term efficacy in terms of a «carry-over effect» of psychotherapeutic acute therapy compared to acute drug treatment with and without maintenance therapy and compared to combination therapy (drug treatment and psychotherapy). While the subject of «chronic depression» was not included in the present article, the authors would like to point to the paucity of long-term studies on chronic depression.

Methods

Search Strategy

The databases Pubmed and PsychINFO were searched in February 2016 for English- and German-speaking articles with the following keywords: ('long-term' [title] OR 'follow-up' [title] OR 'enduring effect' [title] OR 'lasting effect' [title] OR 'persist*' [title] OR relapse [title] OR stability [title] OR stable [title] OR recurrence [title] OR relapse [title]) AND (depressi* [title] OR 'affective disorder' [title] OR 'depressive episode' [title] OR 'major depression' [title]) AND (efficac* OR effect* OR outcome OR results) AND (treatment OR therapy OR CBT OR 'cognitive behavioral therapy' OR IPT OR 'interpersonal therapy' OR CBASP OR psychoanal*

OR psychodynamic* OR psychotherapy*) AND (antidepress* OR SSRI OR 'Selective serotonin reuptake inhibitors' OR SNRI 'Serotonin-norepinephrine reuptake inhibitors' OR 'MAO inhibitors' OR 'Monoamine oxidase inhibitors' OR NARI OR 'noradrenaline reuptake inhibitors' OR 'tricyclic antidepressants' OR TCA OR 'Tetracyclic antidepressants' OR TeCA OR pharmacothera*). The searches identified any journal articles published between 1980 and 2016. The bibliographies of all articles included for data extraction as well as other systematic reviews and meta-analyses were hand-searched for further eligible articles.

Inclusion and Exclusion Criteria

Articles were included in the review if they satisfied the following inclusion criteria: 1) RCTs, 2) the principal diagnosis at beginning of acute treatment being a unipolar depressive episode, 3) a direct comparison between psychotherapy and antidepressants after acute treatment and after follow-up period, 4) a follow-up length of at least 12 months, and 5) adult age of ≥ 18 years. Articles were excluded if they met the following criteria: 1) uncontrolled studies, 2) studies that involved psychotherapeutic maintenance treatment during the follow-up period (which thus did not meet the inclusion criterion of a follow-up length of at least 12 months), 3) studies with a focus on reducing depressive residual symptoms, and finally 4) studies on depression in old age. Studies with maintenance therapy that lasted short enough for a ≥ 12 -month follow-up period to follow (without treatment) were included.

Results

The search strategy for the comprehensive systematic review retrieved and screened 432 articles. Overall, 13 studies comprising 946 patients met all inclusion criteria and were included in the review. (fig. 1, Online Supplemental Table; www.karger.com/?DOI=446674).

Follow-Up Length

The follow-up period of the involved studies ranged between 12 and 75 months ($M = 27.06$ months). The most commonly reported follow-up length ranged between 12 and 24 months. This was the case for 11 studies, whereas only 4 studies had a follow-up period of 24 months and longer. On average, the data related to patients with a moderate depressive episode (measured with the 17-item Hamilton Depression Scale; HAMD-17), respectively patients at the border of a severe depressive episode (measured with the Beck Depression Inventory; BDI).

Psychotherapeutic Procedures during Acute Treatment

Predominantly, Cognitive Therapies were analyzed. For half of the studies, Cognitive Therapy was the subject of review [Dobson et al., 2008; Blackburn et al., 1986; Evans et al., 1992; Simons et al., 1986; Beck et al., 1985; Kovacs et al., 1981], Shea et al. [1992] as well as De Jong-Meyer et al. [1996] examined CBT, and, finally,

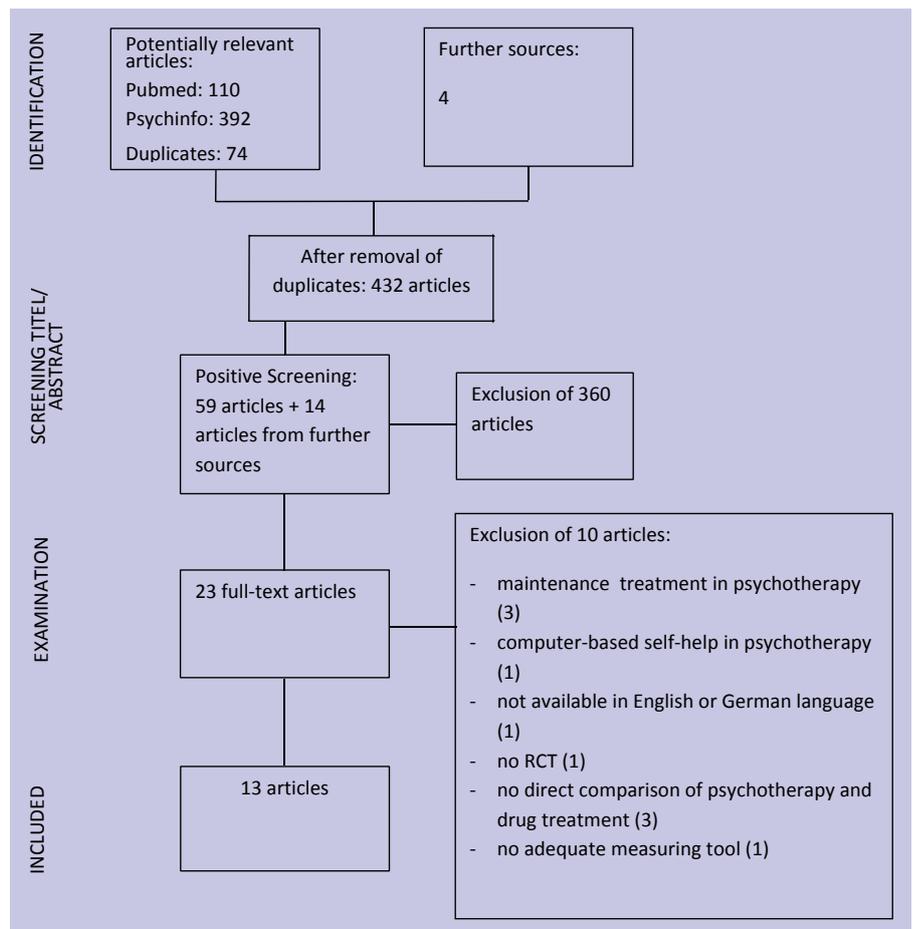


Fig. 1. Chart of included studies.

Dobson et al. [2008] explored behavioral activation. Further therapeutic approaches were problem solving [Mynors-Wallis et al., 2000], IPT [Schramm et al., 2007; Shea et al., 1992; Weissman et al., 1981; Zobel et al., 2011] and psychodynamic approaches [Koppers et al., 2011; Maina et al., 2009]. The amount of therapy sessions ranged between 6–30, and the length of therapy ranged between 5–24 weeks.

Antidepressants during Acute Treatment

The most frequently used antidepressant was Amitriptyline, a tricyclic antidepressant. Medications administered in the study are summed up in the table (Online Supplemental Table; www.karger.com/?DOI=446674), even those in case of intolerances.

Treatment Setting

Acute treatment was performed at outpatient departments with 2 exceptions [De Jong-Meyer et al., 1996; Schramm et al., 2007; Zobel et al., 2011].

Distinction between Patients with and without Therapeutic Success after Acute Treatment

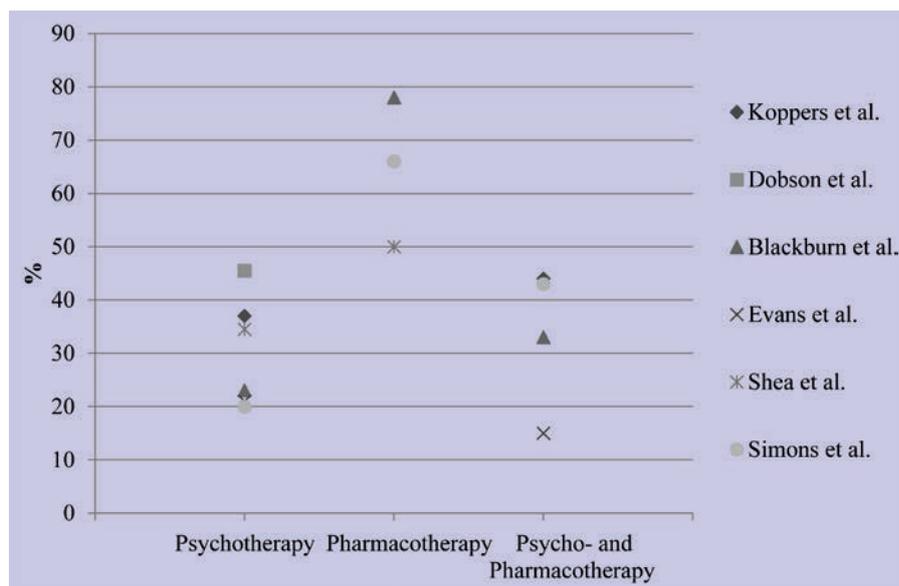
The studies included differed for the follow-up period in terms of inclusion criteria. Thus, in 4 studies, only patients with therapeutic success after acute therapy were included [Blackburn et al.,

1986; Dobson et al., 2008; Evans et al., 1992; Maina et al., 2009]. De Jong-Meyer et al. [1996], Weissman et al. [1981], Zobel et al. [2011], Shea et al. [1992], and Simons et al. [1986] had no predefined exclusion criteria for the follow-up; however, the latter 2 focused on patients with therapeutic success in their data presentation. In 4 further studies, only completers of acute treatment were admitted to the follow-up [Beck et al., 1985; Koppers et al., 2011; Kovacs et al., 1981; Mynors-Wallis et al., 2000]. Schramm et al. [2007] distinguished between Intention-to-Treat (ITT) and completer analyses for each time period.

Specifications Regarding Treatment of Depression within the Follow-Up Period

The majority of cases had a naturalistic follow-up setting, meaning that patients were not obliged to refrain from further treatment or from resuming treatment of their depression. Five studies recorded further treatment of depression during the follow-up period. In the majority of cases (14–91%), patients received further treatment during follow-up (Online Supplemental Table; www.karger.com/?DOI=446674). Strikingly, in 3 studies [Shea et al., 1992; Beck et al., 1985; Weissman et al., 1981], patients that had received drug treatment engaged in further therapy programs more often (Online Supplemental Table; www.karger.com/?DOI=446674). Koppers et al. [2011] and Maina et al. [2009] did not

Fig. 2. Relapse rates at follow-up measurement upon treatment completion. Results by Schramm et al. [2007] were not presented in this figure due to the high amount of patients receiving further treatment after in-patient acute treatment.



specify treatment procedures for their follow-up periods, neither for drug treatment nor for psychotherapeutic procedures. Dobson et al. [2008] reported that in each psychotherapeutic treatment arm 1 patient engaged in further treatment during the first year of follow-up and was thus excluded from the study.

Maintenance Therapy

During the follow-up period, psychopharmacological maintenance therapy was performed in the first 12 months [Dobson et al., 2008] or in the first 6 months, respectively [Evans et al., 1992; Maina et al., 2009; Blackburn et al., 1986]. Only once was a form of psychotherapeutic maintenance therapy performed in addition to drug therapy within the first 6 months of follow-up [Blackburn et al., 1986]. In the latter study, psychotherapeutic booster sessions were offered in a 6-week cycle during the first 6 months.

Short-Term Efficacy of Psychotherapy and Pharmacotherapy

For the majority of studies, no significant difference was observed between the treatment forms after acute therapy [Beck et al., 1985; Blackburn et al., 1986; De Jong-Meyer et al., 1996; Evans et al., 1992; Koppers et al., 2011; Maina et al., 2009; Mynors-Wallis et al., 2000; Schramm et al., 2007; Shea et al., 1992; Simons et al., 1986]. Dobson et al. [2008], Kovacs et al. [1981], and Weissman et al. [1981] found a significant difference in terms of therapeutic success between various treatment arms after acute treatment (Online Supplemental Table; www.karger.com/?DOI=446674).

Long-Term Efficacy of Psychotherapy and Pharmacotherapy

In some studies, no significant differences between psycho- and pharmacotherapy in terms of long-term efficacy were observed. While psychotherapy was found superior to pharmacotherapy in some studies (even as maintenance therapy), there was no study that observed the opposite. The same applies for the comparison of monotherapy (psychotherapy or pharmacotherapy) and combined

treatment (psychotherapy plus pharmacotherapy). In the long run, psychotherapy was equal to combined therapy in terms of efficacy in all studies [Beck et al., 1985; Blackburn et al., 1986; Evans et al., 1992; Koppers et al., 2011; Mynors-Wallis et al., 2000; Simons et al., 1986; Weissman et al., 1981]. However, the situation is ambiguous when comparing antidepressant monotherapy with combined therapy: although there were studies in which pharmacotherapy (including 1 study with maintenance therapy) proved to be equally efficacious as combined therapy [De Jong-Meyer et al., 1996; Evans et al., 1992; Mynors-Wallis et al., 2000; Simons et al., 1986; Weissman et al., 1981], some studies showed that combined therapy was superior (1 of which also had maintenance pharmacotherapy as treatment condition) [Blackburn et al., 1986; Evans et al., 1992; Maina et al., 2009; Schramm et al., 2007; Zobel et al., 2011]. Simons et al. [1986] observed no significant difference between the treatment arms. However, in a further analysis they drew a distinction between patients who were given antidepressants (monotherapy or combined treatment with psychotherapy) and patients who were not. The group of participants enrolled in drug treatment showed significantly higher rates of relapse. The authors also compared data from patients who enrolled in psychotherapeutic treatments (monotherapy or combined treatment) with patients who did not and found significantly smaller rates of relapse for patients with psychotherapy.

The rates of relapse upon completion of treatment of all studies included in the present review ranged between 20–50% for psychotherapy, between 29–78% for pharmacotherapy and between 15–44% for combined treatment (fig. 2). Among patients who (still) achieved remission or response at follow-up, the number of patients treated only pharmacotherapeutically was smaller – ranging between 11–35% and 23–69%, respectively, compared to combined treatment (28–57% and 49–71%, respectively) or psychotherapy (56–80% and 34–44%, respectively).

Comparing Short- and Long-Term Efficacy

Most studies that did not find a superiority of psychotherapy, pharmacotherapy, or combined treatment after acute therapy, revealed a significant difference in efficacy between treatment arms at follow-up, indicating that psychotherapy is more efficacious in the long run. Shea et al. [1992] as well as De Jong-Meyer et al. [1996] still found no significant differences between treatment arms after the follow-up period. In 1 study, as a procedure for acute treatment, Cognitive Therapy was inferior to drug treatment and behavioral activation in terms of efficacy. However, in the course of the study, Cognitive Therapy proved to be superior to drug treatment and equal to behavioral activation regarding efficacy [Dobson et al., 2008]. The superiority of Cognitive Therapy compared with pharmacotherapy disappeared in the study by Kovacs et al. [1981] at follow-up-measurement. In the study by Weissman et al. [1981], the superiority of combined treatment compared with both monotherapeutic treatments disappeared at follow-up resulting in all treatment arms being equally efficacious.

Discussion

Long-Term Efficacy of Pharmacotherapy and Psychotherapy in the Treatment of Depression

The present review of long-term efficacy of psychotherapy furnishes 2 preeminent conclusions: existing empirical data suggests that for moderate unipolar depressive episodes psychotherapy is superior to antidepressants in terms of sustainability. Not once was drug therapy superior to psychotherapy in either acute treatment or maintenance therapy. While psychotherapy as monotherapeutic treatment was comparably efficacious to combined treatment (psycho- and pharmacotherapy) across all studies, some studies revealed that a monotherapeutic drug treatment was less efficacious. Apparently, psychotherapy treatment adds a positive long-term effect to combined treatment, whereas pharmacotherapy does not. The choice of psychotherapy seems to be secondary, even though cognitive treatments were predominantly used. After acute treatment, there were mostly no significant differences between psychotherapy and pharmacotherapy in terms of efficacy, whereas psychotherapy as well as combined therapy appear to be superior in the long run. A smaller percentage of relapses as well as a higher amount of therapeutic successes compared to drug treatment additionally highlight the higher long-term efficacy of psychotherapy. The percent values of relapses, response rates, and remissions should be interpreted with care due to a relatively small amount of cases. A further interesting observation is that the time of relapse seems to differ between psychotherapeutic and drug treatment. Thus, Evans et al. [1992] found that relapses occurred faster after drug treatment compared to psychotherapeutic treatment (3.3 months; standard deviation (SD) = 4 months vs. 17.4 months; SD = 12 months). Furthermore, there is some evidence that patients with acute drug treatment more frequently needed subsequent treatments afterwards. However, this is possibly due to the higher relapse rates within this specific patient group.

Another primary result is that the availability of data is limited; further research is needed to answer these clinically relevant questions. No conclusions can be drawn with regards to the impact of the severity of symptoms, as the analyzed studies did not distinguish sufficiently between symptom severities.

Comparison with Previous Reviews in Terms of Long-Term Efficacy

Similarly to previous reviews, psychotherapy was associated with a reduced risk of relapse compared to pharmacotherapy. The identified rates of relapse (psychotherapy: 20–50%; pharmacotherapy: 29–78%) conform to other reported rates of relapse (for psychotherapy: Gloaguen et al. [1998] (29.5%), Steinert et al. [2014] (53%), and Vittengl et al. [2007] (29–54%); for pharmacotherapy: Gloaguen et al. [1998] (60%)).

In line with results by Karyotaki et al. [2016] and Cuijpers et al. [2014b], combined treatment of psycho- and pharmacotherapy produced better long-term results compared to drug treatment on its own. According to Karyotaki et al. [2016], Steinert et al. [2014], and Cuijpers et al. [2013b], both studies with and without patients with therapeutic success after acute therapy were included in the analysis.

Length of Follow-Up

Even though the follow-up period was specified to have a length of 1–6 years, the majority of studies had a follow-up period of approximately 1–2 years. Only 3 studies had a follow-up period of more than 4 years. Two of these studies [Koppers et al., 2011; Mynors-Wallis et al., 2000] found no difference between psychotherapy and drug treatment in the long run, however, Maina et al. [2009] and Zobel et al. [2011] observed an additive effect of psychotherapeutic treatment in the scope of combined therapy compared to monotherapeutic drug treatment. Due to the insufficient number and heterogeneity of studies, we cannot confirm the observation by Vittengl et al. [2007] that a shorter follow-up period leads to higher relapse rates.

Study Limitations

Since only English- and German-language studies were included in the present review, not all relevant articles could be included in the literature research. Furthermore, we cannot ensure that our research strategy was ideal even though we additionally searched through the references of relevant studies, reviews, and meta-analyses.

Limitations of the Included Studies

As a consequence of several factors, the results of the present review should be treated with caution. For one, it should be noted that the data quality of clinical studies decreases upon completion of treatment (increase of missing values), with the result that effect differences are less comparable. Moreover, there were too few studies that had a follow-up period of more than 2 years, in order to draw conclusions regarding long-term efficacy. Furthermore, in some cases, drug treatment had an average length of 3 months

which is much shorter than the guidelines recommend [APA, 2010; DGPPN et al., 2015; NICE, 2016]. In addition, the comparability of psychotherapies was reduced due to the heterogeneous amount of therapy sessions with a range of 6–30 sessions across the included studies. What exactly happens in the follow-up period has not been standardized thus far, although a standardized procedure would be difficult to apply in practice. As a result, it is mostly unclear whether at all and how many psycho- and pharmacotherapeutic treatment sessions took place during the follow-up period and how they might have impacted the results. A further limitation across the studies is the varying usage and definition of the terms ‘relapse’, ‘response’, ‘recovery’, ‘recurrence’, ‘sustained response’, ‘sustained remission’, and ‘sustained recovery’.

Finally, a question of high relevance remains whether findings on long-term efficacy are only valid for patients with therapeutic success after acute therapy. Four studies only included patients with therapeutic success after acute therapy in their follow-up. An argument in favor of this approach is that only by this means true relapses can be identified. On the other hand, clinicians possibly would miss those therapy effects that involve latency periods.

Implications for Future Research

Further studies with extended follow-up periods are required for consolidated evidence of the long-term efficacy of psycho- and pharmacotherapy in the treatment of depression. Also, more thorough documentations of follow-up periods (including the commencement of further therapies) would be desirable. Then again, a precise documentation of effectively acquired therapy sessions, not only of those that are prescribed in the study protocol, would be of importance. In pursuance of better comparability between study results, consistent definitions of ‘therapeutic success’ and ‘relapse’ are essential. It would be desirable, then, to regularly specify both of these. Moreover, a combination of self- and external ratings with regard to evaluating the symptoms would be required, so as to identify possible differences, since the primary focus on expert ratings (e.g., HAM-D) increases the Pygmalion effect. In addition to descriptions of symptoms, it would be interesting to gather data on the overall level of functioning and on the quality of life. Thus, Kovacs et al. [1981] showed that psychotherapy sustainably changed the way a person thinks as well as their pessimistic attitudes. Future studies should also focus on long-term efficacy of psycho- and

pharmacotherapy in the inpatient sector. After all, it is especially important to specify all data – i.e., data from patients with and without therapeutic success as well as from so-called ITT and completer patients. Success and relapse quotes of the studies included in the present review reveal that there still is scope for improvement of treatments.

Practical Implications

The final outcome of the present review is that psychotherapy of depression is superior to pharmacotherapy with regard to sustainable effects. For the future, guidelines regarding the question of sustainability of therapies should be more strictly considered. At least a recommendation should be given that patients who are undergoing drug treatment need to be informed that no sustainable effect of antidepressants could be shown and that clinical research is unsure whether there may be potential long-term detrimental effects of antidepressants. As yet, there has been no controlled-design study exploring whether antidepressants impact the risk of relapse upon completion of treatment, as compared to a placebo. Previous studies analyzing the risk of relapse after a depressive episode compared to a placebo examined the data of patients who had already taken antidepressants beforehand. Thus, it is uncertain whether the risk of relapse of the respective placebo groups was influenced by a drug treatment prior to the study. The existing uncertainties regarding long-term effects of antidepressants and the need for research established in this review advocate the use of psychotherapy for depressive disorders and support the need for a stronger participation of patients in terms of a shared decision making when it comes to the choice of treatment.

Online Supplemental Material

Online Supplemental Table Characteristics of studies included

To access the supplemental table please refer to www.karger.com/?DOI=446674.

Disclosure Statement

The authors report no conflicts of interest.

References

- Andrews P, Thomson J, Amstadter A, et al: Primum non nocere: an evolutionary analysis of whether antidepressants do more harm than good. *Front Psychol* 2012;3:117.
- APA: Practice Guideline for the Treatment of Patients With Major Depressive Disorder, ed 3. American Psychiatric Association, 2010.
- Babiyak M, Blumenthal J, Herman S, et al: Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med* 2000;62:633–638.
- Beck A, Hollon S, Young J, et al: Treatment of depression with cognitive therapy and amitriptyline. *Arch Gen Psychiatry* 1985;42:142–148.
- Blackburn I, Eunson K, Bishop S: A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. *J Affect Disord* 1986;10:67–75.
- Cuijpers P, Andersson G, Donker T, et al: Psychological treatment of depression: results of a series of meta-analyses. *Nord J Psychiatry* 2011a;65:354–364.
- Cuijpers P, Berking M, Andersson G, et al: A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Can J Psychiatry* 2013a;58:376–385.
- Cuijpers P, Geraedts A, van Oppen P, et al: Interpersonal psychotherapy for depression: a meta-analysis. *Am J Psychiatry* 2011b;168:581–592.
- Cuijpers P, Hollon S, van Straten A, et al: Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open* 2013b;3:e002542.

- Cuijpers P, Karyotaki E, Weitz E, et al: The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. *J Affect Disord* 2014a;159:118–126.
- Cuijpers P, Sijbrandij M, Koole SL, et al: Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry* 2014b;13:56–67.
- De Jong-Meyer R, Hautzinger M, Rudolf G, et al: Die Überprüfung der Wirksamkeit einer Kombination von Antidepressiva- und Verhaltenstherapie bei endogenen depressiven Patienten: Varianzanalytische Ergebnisse zu den Haupt- und Nebenkriterien des Therapieerfolges. *Z Klin Psychol* 1996;25:93–109.
- DGPPN, BÄK, KBV, et al: S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression – Langfassung, ed 2, Version 2. 2015.
- Dobson K, Hollon S, Dimidjian S, et al: Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. *J Consult Clin Psychol* 2008;76:468–477.
- Driessen E, Hegelmaier L, Abbas A, et al: The efficacy of short-term psychodynamic psychotherapy for depression: A meta-analysis update. *Clin Psychol Rev* 2015; 42:1–15.
- Eaton WW, Shao H, Nestadt G, et al: Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry* 2008;65:513–520.
- Evans M, Hollon S, DeRubeis R, et al: Differential relapse following cognitive therapy and pharmacotherapy for depression. *Arch Gen Psychiatry* 1992;49:802–808.
- Gloaguen V, Cottraux J, Cucherat M, et al: A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord* 1998;49:59–72.
- Karyotaki E, Smit Y, Holdt Henningsen K, et al: Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects. *J Affect Disord* 2016;194:144–152.
- Kessler R, Berglund P, Demler O, et al: The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289:3095–3105.
- Khan A, Fauceit J, Lichtenberg P, et al: A systematic review of comparative efficacy of treatments and controls for depression. *PLoS ONE* 2012;7:e41778.
- Kirsch I: Der Placeboeffekt in der antidepressiven Behandlung. *Verhaltenstherapie* 2016;26:55–61.
- Koppers D, Peen J, Niekerken S, et al: Prevalence and risk factors for recurrence of depression five years after short term psychodynamic therapy. *J Affect Disord* 2011;134:468–472.
- Kovacs M, Rush A, Beck A, et al: Depressed outpatients treated with cognitive therapy or pharmacotherapy. A one-year follow-up. *Arch Gen Psychiatry* 1981;38:33–39.
- Maina G, Rosso G, Bogetto F: Brief dynamic therapy combined with pharmacotherapy in the treatment of major depressive disorder: long-term results. *J Affect Disord* 2009;114:200–207.
- Marschall J, Hildebrandt S, Sydow H, et al: Gesundheitsreport 2016: Analyse der Arbeitsunfähigkeitsdaten. Beiträge zur Gesundheitsökonomie und Versorgungsforschung, Band 13. Heidelberg, medhochzwei Verlag, 2016.
- Murphy J, Byrne G: Prevalence and correlates of the proposed DSM-5 diagnosis of Chronic Depressive Disorder. *J Affect Disord* 2012;139:172–180.
- Mynors-Wallis L, Gath D, Day A, et al: Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. *BMJ* 2000;320:26–30.
- NICE: Depression in adults: recognition and management. NICE guidelines (CG90). National Institute for Health and Clinical Excellence, 2016.
- Schramm E, van Calker D, Dykierck P, et al: An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. *Am J Psychiatry* 2007;164:768–777.
- Shea M, Elkin I, Imber S, et al: Course of depressive symptoms over follow-up. Findings from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *Arch Gen Psychiatry* 1992;49:782–787.
- Shrestha S, Nelson E, Liow J, et al: Fluoxetine administered to juvenile monkeys: effects on the serotonin transporter and behavior. *Am J Psychiatry* 2014;171:323–331.
- Simons A, Murphy G, Levine J, et al: Cognitive therapy and pharmacotherapy for depression. Sustained improvement over one year. *Arch Gen Psychiatry* 1986;43:43–48.
- Steinert C, Hofmann M, Kruse J, et al: Relapse rates after psychotherapy for depression – stable long-term effects? A meta-analysis. *J Affect Disord* 2014;168:107–118.
- Vittengl J, Clark L, Dunn T, et al: Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. *J Consult Clin Psychol* 2007;75:475–488.
- Weissman M, Klerman G, Prusoff B, et al: Depressed outpatients. Results one year after treatment with drugs and/or interpersonal psychotherapy. *Arch Gen Psychiatry* 1981;38:51–55.
- Weitz E, Hollon S, Twisk J, et al: Baseline Depression Severity as Moderator of Depression Outcomes Between Cognitive Behavioral Therapy vs Pharmacotherapy: An Individual Patient Data Meta-analysis. *JAMA Psychiatry* 2015;72:1102–1109.
- Zobel I, Kech S, van Calker D, et al: Long-term effect of combined interpersonal psychotherapy and pharmacotherapy in a randomized trial of depressed patients. *Acta Psychiatr Scand* 2011;123:276–282.