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PERSONALIZED TREATMENT OF ADULT DEPRESSION: MEDICATION, PSYCHOTHERAPY, OR BOTH? A SYSTEMATIC REVIEW

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Background: *Personalized medicine aims to identify which characteristics of an individual predict the outcome of a specific treatment, in order to get a better match between the individual and the treatment received. We conducted a systematic review and meta-analysis of randomized trials comparing two treatments directly in a group of patients with a specific characteristic.* **Methods:** *We searched relevant studies from bibliographical databases and included trials comparing (1) medication with psychotherapy, (2) medication with combined treatment, and (3) psychotherapy with combined treatment, in specific target groups (a) with a predefined sociodemographic characteristic, (b) a specific type of depression, (c) a comorbid mental or somatic disorder, or (d) from a specific setting (outpatients, primary care).* **Results:** *We included 52 studies with 4,734 depressed patients. In these studies, 20 characteristics of the target groups were examined. The results showed that medication is probably the best treatment for dysthymia, and combined treatments are more effective in depressed outpatients, as well as in depressed older adults. However, in order to examine the 20 characteristics in the three categories of comparisons, 254 studies would be needed for having sufficient statistical power to show an effect size of g = 0.5. Currently, only 20.1% of these studies have been conducted.* **Conclusions:** *Although a considerable number of studies have compared medication, psychotherapy, and combined treatments, and some preliminary results are useful for deciding which treatment is best for which patient, the development of personalized treatment of depression has only just begun. Depression and Anxiety 00:1–10, 2012.*

Key words: *antidepressants; clinical trials; depression; dysthymic disorder; treatment*

INTRODUCTION

It is well established that antidepressive medication, as well as psychotherapies have significant effects on adult depressive disorders,[1–4] that both are about equally effective,[5–7] and that combined treatments are slightly more effective than either psychotherapy alone,[8–10] or

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medication alone.[11,12] However, it is also clear that many patients do not respond to these treatments,[13,14] and it is largely unknown which individual patient will respond to which medication or psychotherapy.[15,16]

Personalized medicine aims at identifying which characteristics of an individual predict the outcome of a specific treatment in order to get a better match between the individual and treatment received.[17] These characteristics may include sociodemographic characteristics and clinical characteristics of the depressive disorder, as well as biological markers, such as neuroimaging or genetic variation.[17] The development of personalized treatments is considered by many to be one of the major challenges for health care research in the next decades.[18–20]

One good design to examine whether one treatment is better than another treatment for a patient with a specific characteristic would be a randomized controlled trial comparing these two treatments directly in a group of patients with that characteristic.[17] For example, if we want to examine whether a new antidepressant is more effective than existing antidepressants in older patients, a randomized trial directly comparing the new antidepressant with an existing antidepressant in a group of older patients would be the optimal design. A design that does not include a direct comparison between two treatments, but only, for example, a comparison between an active treatment and a control condition, does not answer the question whether one treatment is better than another for this specific group of patients. This type of research is therefore not helpful in developing personalized treatments.[17]

Another design that may be helpful in developing personalized treatments is a direct comparison between two treatments in an unselected group of patients with a depressive disorder, with analyses examining whether one treatment was more effective than the other in predefined subgroups of patients. In our example that would mean that we would compare two treatments in a large group of depressed patients, and examine whether older adults benefit more from one treatment than from the other, compared with younger adults. In such trials, however, it is important to define in advance which characteristics will be examined, in order to avoid capitalization on chance and a focus on post hoc analyses. Until now, hardly any of such trials with predefined moderators have been conducted,[15,16] and we will therefore not review these studies here.

In the past few decades, several dozens of randomized trials have directly compared antidepressive medication, psychotherapy, and combined treatments with each other. Many of these comparative studies have been conducted in specific subgroups of patients, such as dysthymic patients and patients with postpartum depression, but also in older adults, and in patients with general medical disorders. These studies can be used to examine whether one treatment is better than another in these specific target groups, and can contribute to the development of personalized treatments for adult depression.

We decided to conduct a systematic review of these studies. Such a review can give a general indication of where we are in the development of personalized treatments of adult depression. Because we expected that many studies would not have sufficient statistical power to find significant differences between treatments in a specific subgroup of patients, we also calculated how many studies are needed to find clinically relevant comparative effects in such subgroups, and how many more should be conducted in order to be sure that we have not missed any relevant differences.

METHOD

IDENTIFICATION AND SELECTION OF STUDIES

A database of 1,237 papers on the psychological treatment of depression was used. This database has been described in detail elsewhere,[21] and used in a series of earlier published meta-analyses (www.evidencebasedpsychotherapies.org), including several meta-analyses comparing psychotherapy, antidepressive medication, and combined treatments.[6,7,10,12] The database is continuously updated and was developed through a comprehensive literature search (from 1966 to January 2011) in which 12,368 abstracts in Pubmed (3,077 abstracts), PsycInfo (2,860), Embase (3,811), and the Cochrane Central Register of Controlled Trials (2,885) were examined. These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). For this database, the primary studies from 42 meta-analyses of psychological treatment for depression were also checked to ensure that no published studies had been missed (http://www.evidencebasedpsychotherapies.org). For the current study, the full texts of these 1,237 papers were examined. The reference lists of earlier review and meta-analyses comparing medication, psychotherapy, and combined treatments were also examined,[5–12] as well as the references of the included primary studies.

We included randomized trials on short-term or acute treatment in which the effects of antidepressant medication were directly compared with the effects of psychotherapy or with a combined treatment, as well as randomized trials in which psychotherapy was compared with a combined treatment. We only included studies in which participants had an established depressive disorder according to a diagnostic interview. From these trials we selected those in which one of the comparisons (pharmacotherapy versus psychotherapy, pharmacotherapy versus combined, psychotherapy versus combined) was examined in a specific target group with (a) a predefined sociodemographic characteristic (such as older adults or minority groups), (b) with a specific type of depression (such as dysthymia, chronic depression, or postnatal depression), (c) depression and a comorbid (mental or somatic) disorder, or (d) a target group from a specific setting (outpatients, primary care). Target groups from outpatient and primary care settings were considered to represent specific categories of depressed patients with distinctive characteristics. Studies in which patients were recruited from the community were not included because this does not represent a specific or definable patient group. We excluded studies on inpatients and on children and adolescents below 18 years of age.

QUALITY ASSESSMENT

We assessed the quality of the studies according to four basic criteria suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*[22]: adequate sequence generation (the randomization scheme was generated correctly), allocation to conditions by an independent (third) party, blinding of assessors of outcomes, and

completeness of follow-up data. Data extraction was conducted by two independent researchers.

META-ANALYSES

We distinguished three types of comparisons: (1) medication versus psychotherapy, (2) medication only versus combined medication plus psychotherapy, and (3) psychotherapy only versus combined medication plus psychotherapy. Analyses were conducted separately for each of these three types of comparisons.

For each comparison we calculated the effect size indicating the difference between the two treatments at posttest, adjusted for small sample bias (Hedges' *g*).[23] Effect sizes were calculated by subtracting (at posttest) the average score of the first treatment from the average score of the second treatment, and dividing the result by the pooled standard deviations of the two groups. We only used those instruments that explicitly measured symptoms of depression, such as the Beck Depression Inventory,[24] or the Hamilton Rating Scale for Depression (HRSD).[25] If more than one depression measure was used, the mean of the effect sizes was calculated, so that each study provided only one effect.

Within each of the three categories of comparisons, we calculated effect sizes for each study in which a specific target group was examined (with a specific sociodemographic characteristic, a specific type of depression; a specific comorbid disorder; or a specific setting). If more outcomes for each such comparison were available, we used the computer program Comprehensive Meta-Analysis (version 2.2.021) to calculate pooled mean effect sizes. As we expected considerable heterogeneity, we decided to calculate mean effect sizes using a random effects model. In all analyses we calculated the I^2-statistic an indicator of heterogeneity in percentages (25% indicates low, 50% moderate, and 75% high heterogeneity).[26] We also calculated the *Q*-statistic, but only report whether this was significant or not.

POWER CALCULATIONS

Because we examined three groups of comparisons (medication versus psychotherapy, medication versus combined treatment, psychotherapy versus combined treatment), and wanted to examine separate effect sizes for specific target groups (with a specific sociodemographic characteristic, type of depression, comorbid disorder, setting), we expected that for most comparisons insufficient statistical power was available to find clinically relevant effect sizes. Therefore, we conducted a power calculation for each comparison we examined.

For each comparison, we calculated how many studies are needed to have sufficient statistical power for finding an effect size of $g = 0.5$. Effect sizes of 0.5 have been defined as a threshold for clinical significance in several studies.[27,28] Hedges' *g* indicates the difference between two treatments at posttest in terms of standard deviations, adjusted for small sample bias. An effect size of $g = 0.5$ corresponds with a numbers-needed-to-be-treated (NNT) of 3.62.[29]

For each comparison, we calculated the mean number of participants in each treatment condition. Then we calculated how many studies with this number of participants would be needed to find an effect size of $g = 0.5$. The power calculations were conducted according to the procedures suggested by Bohrenstein et al.[30] In these calculations we conservatively assumed a medium level of between-study variance, $\tau 2$, a statistical power of 0.80, and a significance level, alpha, of .05.

Because we calculated the number of studies needed to show significant effect sizes of 0.5, we were also able to calculate what percent of the studies needed to find these effect sizes, have been conducted. This gives an indication how many studies still have to be conducted in order to find significant effect sizes of $g = 0.5$ for each of the examined characteristics.

RESULTS

SELECTION AND INCLUSION OF STUDIES

Having examined 12,368 abstracts (9,634 after removal of duplicates), we retrieved 1,237 full-text papers for further consideration, of which 1,185 were excluded. Fifty-two trials met inclusion criteria (Fig. 1).

CHARACTERISTICS OF INCLUDED STUDIES

Selected characteristics of the included studies appear in Appendix A, and references are given in Appendix S1 (available as supplementary data online). Depressed patients (4,734) participated in these studies (1,720 in psychotherapy; 1,925 in pharmacotherapy; and 1,089 in combined conditions). These 52 studies contained 33 direct comparisons between psychotherapy and pharmacotherapy, 29 comparisons between pharmacotherapy and combined treatment, and 14 comparisons between psychotherapy and combined treatment.

In the included studies, 20 characteristics of the target groups were examined. Six of these were examined in each of the three categories of comparisons (psychotherapy versus medication, medication versus combined, psychotherapy versus combined: dysthymia, chronic depression, older adults, stroke patients, primary care, outpatients), one characteristic was examined in two categories (postnatal depression), and the remaining 13 characteristics were examined in one of the three categories (Table 1).

QUALITY ASSESSMENT

The quality of the studies varied. Nineteen studies reported an adequate sequence generation, whereas the other 33 did not report a sequence generation method.

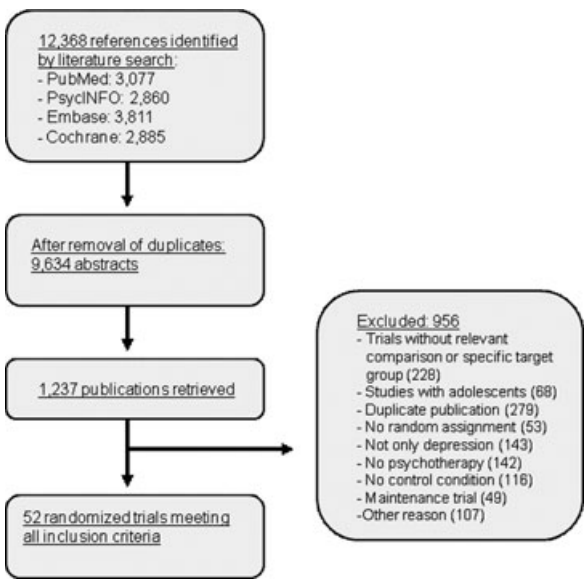

Figure 1. Flowchart of inclusion of studies.

TABLE 1. Comparative studies of psychotherapy, pharmacotherapy, and combined treatments adult depression for specific target populations

					Studies needed to show effect size $g = 0.5$	
	k[a]	G	95% CI	N/cond[b]	k[a]	Percentage realized
Pharmacotherapy or psychotherapy?[c]						
Type of depression						
• Dysthymia	6	−0.28	−0.53∼−0.04*	43	3	100%
• Atypical depression	1	−0.22	−0.68∼0.24	36	3	33.3%
• Chronic depression	1	−0,04	−0.23∼0.15	218	1	100%
• Postnatal depression	1	−0.48	−0.75∼−0.22***	109	1	100%
• Minor depression	2	−0.09	−0.44∼0.26	39	3	66.7%
Sociodemographic						
• Older adults	3	0.05	−0.16∼0.25	62	2	100%
• Poor minority women	1	−0,24	−0.53∼0.05	89	2	50.0%
• infertile women	1	−0.94	−1.47∼−0.41**	30	4	25.5%
• Living with a partner[e]	1	0.00	−0.44∼0.44	39	3	37.5%
Comorbid conditions						
• Multiple sclerosis	2	−0.18	−0.70∼0.34	18	6	33.3%
• Stroke patients	1	0.25	−0.30∼0.79	26	5	20.0%
Setting						
• Primary care	10	−0.01	−0.14∼0.11	48	3	100%
• Outpatients	11	0.08	−0.16∼0.32	101	2	100%
Pharmacotherapy or combined?[d]						
Type of depression						
• Dysthymia[b]	4	0.06	−0.20∼0.33	46	3	100%
• Chronic depression	1	0.54	0.35∼0.73***	221	1	100%
• Postnatal depression	1	−0.03	−0.71∼0.66	16	7	14.3%
• Treatment resistant	1	1.82	0.21∼3.43*	13	9	11.1
• High cognitive dysfunction	1	1.31	0.32∼2.29**	9	12	8.3
• Bereavement related	1	0.30	−0.42∼1.01	21	6	16.7%
Sociodemographic						
• Older adults	3	0.46	0.12∼0.80**	21	6	50.0%
Comorbid conditions						
• Coronary heart disease	1	0.06	−0.27∼0.39	71	2	50.0%
• Stroke patients	1	−0.12	−0.68∼0.45	24	5	20.0%
• OCD	1	0.36	−0.17∼0.89	27	4	25.0%
• Borderline	1	0.90	0.19∼1.61*	16	7	14.3%
• Personality disorder	1	0.34	−0.36∼1.05	16	7	14.3%
Setting						
• Primary care	2	0.75	−0.97∼2.47	24	5	40.0%
• Outpatients	15	0.54	0.35∼0.74***	28	4	100%
Psychotherapy or combined?[d]						
Type of depression						
• Dysthymia[b]	2	0.41	−0.17∼0.98	62	2	100%
• Chronic depression	1	0.54	0.35∼0.73***	221	1	100%
Sociodemographic						
• Older adults	1	0.08	−0.40∼0.55	34	4	25.0%
Comorbid conditions						
• Stroke patients	1	−0.29	−0.84∼0.26	25	5	20.0%
Setting						
• Primary care	2	0.31	−0.01∼0.63	40	3	66.7%
• Outpatients	9	0.40	0.13∼0.67**	44	3	100%

[a] k indicates the number of studies.
[b] N/cond indicates the mean number of patients per research condition.
[c] A positive effect size indicates a superior effect of the psychological treatment.
[d] A positive effect size indicates that combined treatment is more effective.
[e] This study examined couple therapy and therefore required the presence of a partner.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

TABLE 2. Meta-analyses of specific subsets of studies on treatments for adult depression with at least three comparisons and sufficient statistical power

	k	*g*	95% CI	*Z*	I^2
Pharmacotherapy or psychotherapy?					
• Dysthymia	6	−0.28	−0.53∼−0.04	−2.29*	32.96
• Older adults	3	0.05	−0.16∼0.25	0.46	0
• Primary care	10	−0.01	−0.14∼0.11	−0.23	0
• Outpatients: all studies	11	0.08	−0.16∼0.32	0.65	68.24***
o Two outliers excluded	9	−0.09	−0.23∼0.04	−1.32	11.24
Pharmacotherapy or combined?					
• Dysthymia[b]	4	0.06	−0.20∼0.33	0.48	15.70
• Older adults	3	0.46	0.12∼0.80	2.66**	0
• Outpatients	15	0.54	0.35∼0.74	5.51***	34.36
o Two outliers removed	13	0.47	0.32∼0.62	6.05***	2.36
Psychotherapy or combined?					
• Outpatients	9	0.44	0.19∼0.69	3.40**	45.36
o One outlier removed	8	0.37	0.18∼0.55	3.89***	9.11

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Seventeen studies reported allocation to conditions by an independent (third) party. Forty studies reported using blinded outcome assessors, 12 did not report blinding of assessors or used self-report outcome measures. In 32 studies, intent-to-treat analyses (completeness of follow-up data) were conducted. Eleven studies (21%) met all quality criteria.

PSYCHOTHERAPY OR PHARMACOTHERAPY?

We identified 13 patient characteristics that were examined in comparative outcome studies of medication and psychotherapy (Table 1). We found that medication was significantly more effective than psychotherapy in patients with dysthymia ($g = -0.28$; 95% CI: −0.53∼0.04), in patients with postnatal depression, and depressed infertile women. However, the results in postnatal depression and infertile women were each based on only one study.

We found no significant difference between the effects of medication and psychotherapy in primary care patients and outpatients, chronic depression and older adults, while there was sufficient statistical power. For all other characteristics we found no significant difference between medication and psychotherapy, but the studies of these characteristic also had insufficient statistical power to find significant effects.

Overall, the power calculations indicated that we would need 38 studies to show that the 13 characteristics had a differential effect size of $g = 0.5$. Only 21 studies (55.3%) have been conducted.

For the groups of studies with at least three comparisons, we conducted additional analyses (Table 2). We found no indication for significant heterogeneity in studies on dysthymia, older adults, and primary care. We did find significant heterogeneity in studies in outpatients. After exclusion of two possible outliers (with effect sizes outside the 95% confidence interval of the mean effect size), heterogeneity was reduced to a very low

TABLE 3. Preliminary advice on personalized treatment for adult depression

	Summary of outcomes[a]	Differential effect size	*k*[b]	First choice of treatment
Dysthymia	PHA > PSY	−0.28*	6	PHA
	PHA = COMB	0.06	4	
	PSY = COMB	0.41	2	
Older adults	PHA = PSY	0.05	3	COMB
	COMB > PHA	0.46**	3	
Primary care	PHA = PSY	−0.01	10	PSY or PHA
Outpatients	PHA = PSY	0.08	11	COMB
	COMB > PHA	0.54***	15	
	COMB > PSY	0.44*	9	

PHA, pharmacotherapy; PSY, psychotherapy; COMB, combined treatment.

[a]">" indicates that the first treatment is more effective than the second treatment; " = " indicates that no significant difference was found between the two treatments, while sufficient statistical power was available.

[b]*k*, number of studies.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

level and was no longer significant. One of the outliers was conducted in a non-Western country,[31] whereas the other one was a very small, older, and low-quality study.[32]

PHARMACOTHERAPY OR COMBINED TREATMENT?

We identified 14 patients characteristics that were examined in comparative outcome studies of medication and combined treatment. We found that combined treatment was significantly more effective than medication alone in outpatients ($g = 0.54$; 95% CI: 0.35∼0.74), in older patients, and in chronically depressed patients, treatment resistant depression, in depressed patients with impaired cognitive function, and patients with a comorbid borderline personality disorder. However, the results in older adults, chronic depression, cognitive impairment, and comorbid personality disorder were each based on only one study. Furthermore, the studies in high cognitive dysfunction and comorbid personality disorder did not have sufficient power to find significant effects.

No significant difference was found between medication and combined treatment in dysthymic patients, although the four studies examining this comparison had sufficient power. For all other characteristics we found no significant difference between medication and psychotherapy, and the studies for each characteristic had insufficient statistical power.

The power calculations indicated that we would need 78 studies to show that the 14 characteristics had a differential effect size of $g = 0.5$. However, only 22 studies (28.2%) have been conducted.

For the groups of studies with at least three comparisons, we again examined the level and if needed possible sources of heterogeneity. The three studies in older adults indicated that combined treatment was more effective than pharmacotherapy alone, although this did not reach the level of clinical significance of $g = 0.5$. As can be seen in Table 2, heterogeneity was not significant in all three groups of studies. Although heterogeneity was low in studies in dysthymia and older adults, it was low to moderate in studies among outpatients. After removal of two comparisons from one small, old, and low-quality study,[32] with extremely high effect sizes in favor of combined treatment, the mean effect size was somewhat smaller ($g = 0.47$), but heterogeneity was reduced to almost zero ($I^2 = 2.36\%$).

PSYCHOTHERAPY OR COMBINED TREATMENT?

We found six patients characteristics that were examined in comparative outcome studies of psychotherapy and combined treatment. Combined treatment was significantly more effective than psychotherapy alone in outpatients ($g = 0.48$; 95% CI: 0.34∼0.63), and in chronic depression, although this last outcome was based on only one study. Both outcomes had sufficient power. None of the other examined characteristics was associated with a larger effect size for either treatment, nor did these studies have sufficient statistical power.

Overall, the power calculations indicated that we would need 18 studies to show that the six characteristics had a differential effect size of $g = 0.5$. However, only 10 studies (55.6%) have been conducted.

The only group of studies with three comparisons was aimed at depressed outpatients. The effect size indicating the difference between psychotherapy and combined treatment was 0.40 (95% CI: 0.13∼0.67). Heterogeneity was moderately high and significant ($P < .05$), but after removal of one outlier,[33] heterogeneity became small and non-significant.

OVERALL RESULTS

If we would want to examine the 20 characteristics in each of the three categories of comparisons (resulting in 60 comparisons), we would need 254 studies with a comparable N as the studies that have been conducted until now, in order to have sufficient statistical power for an effect size of $g = 0.5$. At this moment, only 51 of these studies have been conducted (20.1%; this number is lower than the actual number of available studies because some characteristics have been examined in more studies than would be needed from the point of view of statistical power).

Based on the results of this review, it would be possible to make a preliminary recommendation for four of the characteristics (Table 3). In patients with dysthymia, medication is significantly more effective than psychotherapy, whereas combined treatment is not significantly more effective than either medication or psychotherapy alone. Therefore, medication seems to be the best first-line treatment in these patients, at least in the short term. In older adults, no significant difference between medication and psychotherapy was found, but combined treatment is significantly better than medication alone. Combined treatment seems to be the best treatment option in this group. In outpatients, combined treatment is significantly more effective than either psychotherapy alone or medication alone, and seems to be the best treatment for this group. However, the only effect size that was larger than $g = 0.5$ (indicating clinical significance) was the effect size indicating that combined treatment is more effective than pharmacotherapy alone in outpatients. In primary care patients, only medication and psychotherapy have been compared directly with each other and no significant difference between the two was found. Insufficient research on combined treatments is available, so no further advice can be given for this group of patients.

DISCUSSION

We reviewed studies in which psychotherapy, medication, and combined treatment were directly compared in depressed populations with specific characteristics,

because these studies are one of the best sources of knowledge for personalized treatments. We identified 52 of such studies, examining 20 specific patient characteristics. Although this may seem a considerable number of studies, we found that many more studies are needed. If we want to have sufficient statistical power to find clinically relevant differential effect sizes of 0.5,[27] we would need 254 studies (with about 23,000 patients) of which only 51 have been conducted (20.1%).

This is only what is needed to develop personalized decisions about three types of treatment. If we would want to differentiate between the many available antidepressant medications and psychotherapies, and all possible combinations (in combined treatments), we will probably need many thousands of studies, only a fraction of which have now been conducted, and millions of participating patients. This problem is multiplied if we focus on other characteristics that have not yet been examined in trials until now, such as biomarkers. And if we really want to develop personalized treatments of depression, we should not only look at individual characteristics of patients and treatments, but also on combinations of characteristics, such as older adults with atypical depression and a specific biomarker. Furthermore, we may want to look at other outcomes, such as side effects of medications, long-term outcomes, patient preferences, and prediction of treatment dropout. And we could also choose for a more precise effect size of $g = 0.3$ or even 0.2. This would require an almost endless number of randomized trials and even more patients who are willing to participate in such trials. There is no doubt that the path toward personalized treatments is a long one, requiring considerable resources.

On the other hand, the number of studies can be reduced considerably if we also use other research designs instead of randomized trials comparing different treatments in specific target populations. As indicated earlier, another design that may be helpful in developing personalized treatments is a direct comparison between two treatments in an unselected group of patients with a depressive disorder, with analyses examining whether one treatment was more effective than the other in specific predefined subgroups of patients.[17] Several of such studies have, for example, examined the severity of depression in comparative outcome studies of medication and psychotherapy,[34,35] as has been discussed in a recent thoughtful discussion of personalized treatments for depression.[17] However, such designs do not solve the problem of statistical power, because in such a trial still sufficient patients should be included with the specific characteristic we want to examine. And as indicated earlier, in order to avoid capitalization on chance, we need to define in advance what the patient characteristics are that we want to examine. Otherwise we will only be able to conduct post hoc analyses, and these would require replication in a new trial. Until now, hardly any of such trials with predefined moderators have been conducted.[16]

Currently, new methodological approaches are developed to examine moderators of outcome, such as Bayesian approaches and decision tree analyses.[36] Although such studies do not solve the problem of statistical power and capitalization on chance, they may prove to be a considerable help in developing relevant hypotheses for personalized treatments. A recent report of the Institute of Medicine on comparative outcome research, comparisons of the effectiveness of pharmacologic treatment and behavioral interventions in managing major depressive disorders are described as one of the priorities for further research.[37] This will certainly lead to more sophisticated and economical methodologies for developing personalized treatments.

The trials that have been conducted until now may be only the beginning for personalized treatment of depression, but the results are already important from a clinical point of view. Medications seem to be the best treatment for dysthymia and combined treatments are clearly more effective in depressed outpatients, as well as in depressed older adults. These findings have to be considered with caution, because they are still about broad categories of treatment and not about specific medications or psychotherapies. However, this does seem to give a general direction for these target groups, which can be worked out in further research.

The results of this systematic review should be considered in light of its limitations. Several of these have been described already. The studies examined in this review are not the only type of studies that results in relevant information about specific treatments for specific target populations. However, the trials we reviewed do result in the best available evidence. And although the number of studies was relatively large, many more are needed before we actually are capable of personalizing treatments for adult depression. A problem with the current set of studies was that the quality was not optimal, and only a selected number of potentially relevant moderators were examined. We also only focused on short-term outcomes, whereas longer term outcomes may be more relevant from a clinical point of view.

Personalized treatment of depression is one of the most important challenges for mental health researchers in the next decades. A large body of research has resulted in useful preliminary data, but much more research is needed before we can actually give personalized advice to patients. There is no doubt, however, that the development of personalized treatment for depression has begun.

Conflict of interest. The authors declare that they have no competing interests.

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APPENDIX A. Selected characteristics of studies comparing psychotherapy with medication, psychotherapy with combined treatment, or medication with combined treatment in adults with depressive disorders

Studies	Patient characteristic	Psychotherapy	*N*	N_{sess}	*I/G*	Medication	*N*	Combined
Barrett (2001)	Dysthymia/minor depression	PST	37	6	Ind	Paroxetine	35	–
Beck (1985)	Outpatients	CBT	14	20	Ind	–		Amitriptyline + CBT
Bedi (2000)	Primary care	Counseling	39	6	Ind	AD protocol	44	–
Bellino (2006)	Borderline patients	–		24	Ind	Fluoxetine	16	IPT + fluoxetine
Blackburn (1997)	Outpatients	CBT	24	16	Ind	AD of choice	23	–
Blom (2007)	Outpatients	–		12	Ind	Nefazodone	30	IPT + nefazodone
Browne (2002)	Dysthymia w/wo MDD	IPT	83	10	Ind	–		IPT + sertraline
Burnand (2002)	Outpatients	–		10	Ind	Clomipramine	38	Psychodynamic + clomip.
De Jonghe (2001)	Outpatients	–		16	Ind	Protocol	84	Psychodynamic + protocol
De Mello (2001)	Outpatients	–		16	Ind	Moclobemide	13	IPT + moclobemide
Dekker (2008)	Outpatients	Psychodynamic	58	16	Ind	Venlafaxine	42	–
Dozois (2009)	Outpatients	–		15	Ind	Protocol	21	CBT + protocol
Dunner (1996)	Dysthymia	CBT	10	16	Ind	Fluoxetine	12	–
Faramarzi (2008)	Infertile women; outpatients	CBT	29	10	Grp	Fluoxetine	30	–
Finkenzeller (2009)	Stroke patients	IPT	27	12	Grp	Sertraline	24	IPT + sertraline
Frank (2010)	Outpatients	IPT	160	12	Ind	Escitalopram	158	–
Hautzinger (1996)	Outpatients	CBT	33	24	Ind	–		CBT + Amitriptyline
Hellerstein (2001)	Dysthymia; outpatients	–		16	Grp	Fluoxetine	20	Group ther + fluoxetine
Hollon (1992)	Outpatients	CBT	25	20	Ind	Imipramine	57	CBT + imipramine
Jarrett (1999)	Atypical depression	CBT	36	20	Ind	Phenelzine	36	–
Keller (2000)	Chronic depression; outpatients	CBASP	216	18	Ind	Nefazodone	220	CBASP + nefazodone
Leff (2000)	Living with a partner	Couple therapy	37	16	Ind	Desipramine [a]	40	–
Lesperance (2007)	Coronary artery disease	–		12	Ind	Citalopram	75	IPT + citalopram
Lynch (2007)	Personality disorder; elderly	–		28	Grp	Protocol	12	DBT + protocol
Lynch (2003)	Elderly	–		56	*I* + *G*	Protocol	9	DBT + protocol
Macaskil (1996)	High cognitive dysf.; outpatients	–		30	Ind	Lofepramine	9	RET + lofepramine
Maina (2010)	OCD patients	–		13	Ind	Fluvox. or sertral.	29	Dynamic + pharmacother.
Maldonado (1982)	Outpatients	CBT	8	10	Ind	TCA (ns)	8	–
Maldonado (1984)	Outpatients	–	8	10	Ind	TCA (ns)	8	CBT + TCA SST + TCA
Markowitz (2005)	Dysthymia	IPT Supportive	23 26	17 17	Ind Ind	Sertraline	24	IPT + sertraline
Martin (2001)	Primary care	IPT	13	16	Ind	Venlafaxine	15	–
Miranda (2003)	Impoverished minority women	CBT	90	8	*I* + *G*	Paroxetine [a]	88	–
Misri (2004)	Postpartum depression			12	Ind	Paroxetine	14	CBT + paroxetine
Mohr (2001)	MS patients	CBT Supportive	20 19	16 16	*I* *G*	Sertraline	15	–
Murphy (1984)	Outpatients	CBT	24	20	Ind	Nortriptyline	24	CBT + nortriptyline
Mynors-Wallis (1995)	Primary care	PST	29	6	Ind	Amitriptyline	27	–
Mynors-Wallis (2000)	Primary care	PST—GP PST—nurse	39 41	6 6	Ind Ind	Fluvox. or parox.	36	PST-GP + pharmacother.
Ravindran (1999)	Dysthymia	–		12	Grp	Sertraline	22	CBT + sertraline
Reynolds (1999)	Bereavement-related depression	–		16	Ind	Nortriptyline	25	IPT + nortriptyline
Rush (1977)	Outpatients	CBT	19	20	Ind	Imipramine	22	–
Rush (1981)	Outpatients	CBT	8	20	Ind	–		CBT + PHA protocol

Studies	Patient characteristic	Psychotherapy	*N*	N_{sess}	*I/G*	Medication	*N*	Combined
Schulberg (1996)	Primary care	IPT	93	16	Ind	Nortriptyline	91	–
Scott (1992)	Primary care	CBT	29	16	Ind	Amitriptyline	26	–
		Counseling	29	16	Ind			
Shamsaei (2008)	Outpatients	CBT	40	8	Ind	Citalopram	40	CBT + citalopram
Sharp (2010)	Postnatal depression	Counseling	112	6	Ind	Protocol	106	–
Sirey (2005)	Elderly; outpatients	–		5	Ind	PHA (ns)	42	TIP + PHA (ns)
Sloane (1985)	Elderly	IPT	19	6	Ind	Nortiptyline	10	–
Stravinsky (1994)	Elderly; outpatients	CBT	9	15	Grp	–		CBT + imipramine
Thompson (2001)	Elderly	CBT	31	18	Ind	Desipramine	33	CBT + desipramine
Weissman (1979)	Outpatients	IPT	25	16	Ind	Amitriptyline	24	IPT + Amitriptyline
Wiles (2008)	Treatment resistant; outpatients	–		16	Ind	PHA (ns)	11	CBT + PHA (ns)
Williams (2000)	Primary care/dysthymia/elderly	PST	138	6	Ind	Paroxetine	137	–

CBASP, cognitive behavioral analysis system of psychotherapy; CBT, cognitive behavior therapy; clomip, clomipramine; DBT, dialectic behavior therapy; dysf., dysfuntion; Fluvox, fluvoxetine; GP, general practitioner; Group ther, group therapy; GRP, group format; *I/G*, individual or group format; *I + P*, combined individual and group format; Ind, individual format; IPT, interpersonal psychotherapy; Ns, not specified; Nsess, number of sessions; Parox, paroxetine; PHA, pharmacotherapy; PST, problem-solving therapy; RET, rational emotive therapy; Setral, sertraline; SST, social skills training; TCA, tricyclic antidepressant; TIP, Treatment Initiation Program.

[a]If there was no response, a second-line antidepressant was substituted.