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Trajectories of Acute Antidepressant Efficacy: How Long to Wait for Response?

A Systematic Review and Meta-Analysis of Long-Term, Placebo-Controlled Acute Treatment Trials

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ABSTRACT

Background: In patients who are not responding to antidepressant pharmacotherapy, information regarding the future probability of response with the same treatment is scarce. Specifically, it is unclear at what point in time the probability to respond or remit ceases to increase, because few studies report data on response or remission at repeated time points beyond 4 or 8 weeks of treatment. Consequently, treatment recommendations in clinical practice guidelines differ widely.

Data Sources: We systematically searched MEDLINE, Embase, PsycINFO, and CENTRAL databases through March 2014 using generic terms for depressive or affective disorders, individual drug names, and placebo (Prospero Registration: CRD42014010105).

Study Selection: We identified double-blind, randomized studies with continuous outcome reporting from 4 weeks up to at least 12 weeks that compared antidepressant monotherapy to placebo in adult patients suffering from acute depressive disorder.

Data Extraction: Data extraction and synthesis followed Cochrane Collaboration guidelines. Primary outcome was response; secondary outcomes were remission and changes in rating scale scores in previously unresponsive patients, respectively.

Results: Of 6,043 articles screened, we selected 9 studies including 3,466 patients. Altogether, 21.6% (18.6%, 24.9%) of previously nonresponsive patients achieved response with ongoing antidepressant treatment between weeks 5 and 8, and 9.9% (7.5%, 12.7%), between weeks 9 and 12. Probability of response when taking placebo was 13.0% (9.9%, 16.5%) between weeks 5 and 8 and 2.4% (1.2%, 4.6%) between weeks 9 and 12. Differences in the probability of response between antidepressant and placebo translated into a number needed to treat of 11 after 4 weeks and 17 after 8 weeks. Heterogeneity was low to moderate, and results remained stable across subgroup and sensitivity analyses.

Conclusions: In patients unresponsive to antidepressant pharmacotherapy, improvements in psychopathology can be expected with ongoing antidepressant treatment for up to 3 months. After 8 weeks of treatment, improvement with ongoing monotherapy is relatively small.

J Clin Psychiatry 2018;79(3):17r11470

To cite: Henssler J, Kurschus M, Franklin J, et al. Trajectories of acute antidepressant efficacy: how long to wait for response? a systematic review and meta-analysis of long-term, placebo-controlled acute treatment trials. *J Clin Psychiatry*. 2018;79(3):17r11470.

To share: https://doi.org/10.4088/JCP.17r11470

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Major depressive disorder (MDD) is one of the most burdensome diseases, not only in mental health but also in the whole field of medicine, with 12-month prevalence rates of depressive episodes ranging from 1% to 10%.[1] The development of antidepressants has been a cornerstone in the treatment of the disorder, but rates of nonresponse to antidepressant monotherapy remain unsatisfactorily high, ranging from 40% to 60%.[2–5]

Duration of acute antidepressant treatment is still subject to debate, and recommendations of international practice guidelines differ widely: For example, while the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*[6] recommends continuation of antidepressant treatment for 4 to 8 weeks prior to reconsideration of pharmacologic treatment and continuation up to 12 weeks to observe full improvement, especially in "real world" patients, the German National Clinical Practice Guideline[7] suggests reconsideration of ineffective treatment after 3 to 4 weeks (6 weeks in older patients). The Canadian Network for Mood and Anxiety Treatments, however, recommends considering treatment changes sooner, after 2 weeks of treatment, if patients did not experience at least 20% symptom reduction.[8]

One reason for the inconsistencies among guidelines is the dearth of data on the probability of response and remission after 4 to 6 weeks of unsuccessful antidepressant treatment. Observational studies in "real world" settings indicate substantial improvement in symptomatology even after 6 to 12 weeks of antidepressant treatment in incomplete responders.[5,9]

In an earlier meta-analysis, we summarized the results of placebo-controlled antidepressant studies with durations of 8 weeks and beyond and found evidence that antidepressants exhibit sustained superiority over placebo up to 24 weeks.[10] It remains unclear, however, how many unresponsive patients can expect improvement

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Clinical Points

- In patients not responding to antidepressant pharmacotherapy, information regarding the future probability of response on the same treatment after 4 and 8 weeks is sparse.
- Benefits with regard to depressive symptoms can be expected for up to 12 weeks, even in previous nonresponders.
- Between 8 and 12 weeks of treatment, however, the incremental benefit with ongoing monotherapy is small.

after several weeks of treatment because in most studies data on response and remission are not reported at repeated time points. Most studies report response or remission figures with respect to only 1 date, but for clinical decision making and for counseling patients, it is imperative to know at what point in time the probability to respond or remit ceases to increase during a trial with an antidepressant. To our knowledge, no systematic review and meta-analysis of studies with reporting of response or remission repeated measurements and over an extended period of time exists to date.

Accordingly, we conducted a systematic review and meta-analysis of double-blind, randomized controlled trials (RCTs) of antidepressants with continuous reporting of response and remission. We aimed at estimating the probability of additional responses to antidepressant treatment (in comparison to placebo) after 4 weeks of treatment and up to 24 weeks in previously unresponsive patients.

METHODS

This systematic literature review, meta-analysis, and meta-regression has been registered on PROSPERO International Prospective Register of Systematic Reviews (Prospero Registration: CRD42014010105).

The methods of this study followed guidelines by the Cochrane Collaboration for the conduct of systematic reviews.[11]

Literature Search

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) until March 20, 2014, for double-blind, randomized, placebo-controlled studies comparing antidepressant monotherapy to placebo in adult patients suffering from acute depressive disorder. No language or date restrictions applied. CENTRAL comprises, among other sources, articles indexed in MEDLINE, PsycINFO, and Embase databases as screened by the Cochrane Depression, Anxiety, and Neurosis Group. It is often used in systematic reviews.[12,13] Additionally, we conducted top-up searches in MEDLINE, PsycINFO, and Embase from January 1, 2013, to March 20, 2014.

We used trial filters for placebo-controlled studies and generic terms for depressive disorders as well as affective disorders combined with generic terms for individual drugs. In brief, the following search terms were used: (*depress** OR *dysthymi** OR *adjustment disorder** OR *mood disorder** OR *affective disorder* OR *affective symptoms*) AND ([individual drug names, combined with OR]) AND (*placebo** OR *dummy**).

We also searched reference lists of all articles included and of relevant review articles.

Eligibility Criteria

To be eligible for inclusion, trials had to meet the following criteria: participants aged ≥ 18 years; acute episode of a depressive disorder diagnosed according to standard operationalized criteria, such as Research Diagnostic Criteria, *DSM-III* to *DSM-IV-TR*, Chinese Classification of Mental Disorders, and *ICD-10*; the existence of a placebo-control group (for the whole duration of the trial); and assessment of severity of depression via standardized and established rating scales (eg, Hamilton Depression Rating Scale [HDRS], Montgomery-Asberg Depression Rating Scale [MADRS], Clinical Global Impressions scale). Concurrent psychiatric disorders or medical comorbidities were not exclusion criteria, as long as they were not the primary condition of interest. Studies specifically focusing on bipolar depression or dysthymia were excluded. In particular, trials on continuation or maintenance therapy were not eligible for inclusion, as these are based on different patient populations (ie, responders/remitters to previous treatment only).

Trials of first-step treatment and trials among patients with resistance to previous antidepressant treatment(s) were both considered relevant.

In a first step, we extracted all interventions using antidepressant monotherapy with a minimum duration of 8 weeks prior to final assessment. The resulting studies constituted the sample of studies for another research project, investigating sustainability of antidepressant effect over placebo for treatment periods up to 6 months.[10]

To be eligible for inclusion in the present analysis, trials had to provide consistent outcome (response or remission) reporting every 4 weeks from 4 to at least 12 weeks (ie, at baseline; after 4, 8–9, and 10–12 weeks; and optionally after 16, 20, and 24 weeks, as were the predefined time points and intervals), making it possible to calculate the *additional* response of the so far nonresponsive subjects.

Data Collection

Literature search, study screening and selection, data extraction, and risk of bias assessment were all carried out independently by 2 reviewers (J.H. and M.K.) and followed recommendations by the Cochrane Collaboration's *Handbook* and Cochrane's risk of bias tool.[11]

Outcome Criteria

Primary outcome. The primary outcome criterion was response of previously unresponsive patients at different time points, with response defined as a decrease on depression rating scales (eg, at least 50% on the HDRS or the MADRS). We adopted trial authors' definitions.

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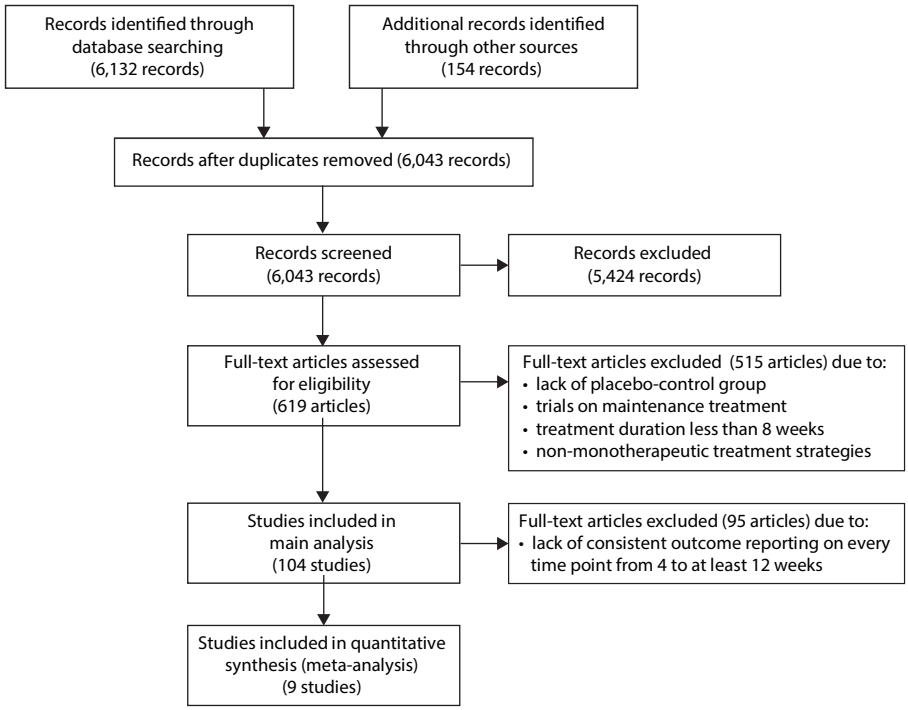
Figure 1. Flowchart of Trials Considered, Eliminated, and Included in Study (adapted from PRISMA)



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement.org).

Secondary outcome. The secondary outcome criteria were (1) remission, defined as scores below thresholds on a depression scale (we adopted trial authors' definitions) and (2) rating scale scores; if more than 1 rating scale was used, we selected HDRS (then MADRS, then other).

To identify an incremental gain in efficacy, we focused on studies reporting outcomes consistently every 4 weeks from 4 to at least 12 weeks (ie, after 4, 8–9, and 10–12 weeks). The meta-analysis was conducted for predefined time points or intervals (4, 8–9, 10–12, 16, 20, 24 weeks). We determined the intervals as soon as it was clear how many studies would be included for each time point but without knowing any efficacy results. If a trial provided more than 1 value within an interval, the latest value was included.

Taking into account rates of response and remission at consecutive time points, the possibility of transition from nonresponse to response under treatment continuation was calculated separately for antidepressants and placebo. We aimed at estimating additional probabilities of psychopathology improvements over time in order to see whether there is a treatment duration beyond which continuation is associated with only marginal utility.

For rating scale score outcomes, some of the included studies did not consistently report standard deviation (SD) or other measures of dispersion for every time point. We therefore imputed missing SDs by use of correlation coefficients for measures of dispersion of other time points in the studies. Due to the risk of bias introduced through imputation, we considered analyses of rating scale scores—normally statistically superior—as a secondary outcome in this study.

Publication bias was assessed by funnel plots for the primary outcome.

We repeated analyses of the primary outcome by removing all studies one by one from the analyses, to avoid undue reliance on single studies.

Using Cochrane's risk of bias tool,[11] studies included in our primary outcome analyses were assessed as holding "low" or "unknown/high" risk of bias. Additional sensitivity analyses of our primary outcome took into account low–risk of bias studies only.

To avoid double counting of patients,[11] we combined intervention groups if studies presented more than 1 comparison (eg, more than 1 antidepressant monotherapy group). Outcome data of multiple groups were pooled, and corresponding SDs were calculated.

Heterogeneity among studies was assessed by both I^2 and τ^2 statistics, as the former is known to become inflated with increasing sample size.[14] Irrespective of heterogeneity assessment, all effect estimates were calculated using random-effects models because the studies selected differed with regard to several methodological aspects, such as diagnostic criteria and measurement scales used.

Statistical significance was set at an α of .05 for the primary outcome. For all secondary outcomes and all other analyses, *P* values are presented in a nonconfirmatory sense.

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Table 1. Characteristics of Trials

Author	Year	N (ITT)	Diagnosis	Age +65 y	Exclusion of Bipolar Patients	Follow-Up (Weeks)	Active Drug/Comparator	Baseline Score Severity (±SD/SE)	Risk of Bias
Cunningham[15]	1997	278	MDD (*DSM-III-R*)	Yes	Yes	12		HDRS	Low
							Venlafaxine XR, n = 92	24.5	
							Venlafaxine IR, n = 87	24.0	
							Placebo, n = 99	24.9	
Dunlop et al[16]	2011	427	MDD (*DSM-IV*)	Yes	Yes	12		HDRS	Unknown/ high
							Desvenlafaxine, n = 285	22.0 ± 4.2	
							Placebo, n = 142	21.8 ± 4.5	
Khan et al[17]	1998	353	MDD (*DSM-III-R*)	No	Not specified	12		HDRS	Unknown/ high
							Venlafaxine 75 mg, n = 85	24.3	
							Venlafaxine 150 mg, n = 90	24.5	
							Venlafaxine 200 mg, n = 83	24.8	
							Placebo, n = 95	25.1	
Malt et al[24]	1999	372	MDD (*DSM-III-R*), mild to moderate	Yes	Yes	24		MADRS	Low
							Mianserin, n = 121	26.8 ± 4.5	
							Sertraline, n = 122	26.8 ± 4.4	
							Placebo, n = 129	26.5 ± 4.0	
Montgomery et al[19]	2013	553	MDD (*DSM-IV*)	Yes	Yes	10		MADRS	Low
							Levomilnacipran, n = 276	30.9 ± 4.1	
							Placebo, n = 277	30.5 ± 3.7	
Rapaport et al[20]	2009	515	MDD (*DSM-IV*)	60+ only	Yes	10		HDRS	Low
							Paroxetine 12.5 mg, n = 163	22.6 ± 3.6	
							Paroxetine 25 mg, n = 173	23.1 ± 3.9	
							Placebo, n = 179	22.7 ± 4.0	
Robinson et al[21]	2014	299	Recurrent MDD (*DSM-IV*)	65+ only	Yes	12		HDRS Maier subscale	Unknown/ high
							Duloxetine, n = 204	10.1 ± 3.4	
							Placebo, n = 95	9.96 ± 3.1	
Silverstone and Ravindran[22]	1999	359	MDD (*DSM-IV*)	Yes	Yes	12		HDRS	Low
							Venlafaxine, n = 122	27.6 ± 5.1	
							Fluoxetine, n = 199	27.0 ± 4.6	
							Placebo, n = 118	27.1 ± 4.5	
Stahl[23]	2000	316	MDD (*DSM-IV*)	No	Yes	24		HDRS	Low
							Citalopram, n = 103	26.5	
							Sertraline, n = 106	26.6	
							Placebo, n = 107	26.4	

Abbreviations: ER = extended release, HDRS = Hamilton Depression Rating Scale, IR = immediate release, ITT = intention-to-treat population, MDD = major depressive disorder, SD = standard deviation, SE = standard error.

95% confidence limits (CL) of values are presented in squared brackets.

Analyses were conducted according to the Cochrane Collaboration's *Handbook*[11] and using Review Manager (RevMan 5.2.5, The Cochrane Collaboration), Comprehensive Meta-Analysis (Version 2) (Biostat), OpenMetaAnalyst (Center for Evidence Synthesis in Health–Brown University), and Microsoft Excel (Version 12.3.6) (Microsoft Corporation). If data in original articles were presented only in figures, values were extracted using Plot Digitizer 2.6.4 MacOSX (Slashdot Media). Proportions and exact binominal confidence intervals were calculated via an online calculator (http://statpages.info/confint.html; accessed September 20, 2016).

RESULTS

Of 6,043 different articles retrieved through our literature search, 104 studies, published between 1971 and 2014, reported results for at least 8 weeks of treatment duration.[10] Among these studies, 9 met our inclusion criteria (Figure 1).

In total, study populations consisted of 3,466 patients, 2,227 receiving antidepressant monotherapy and 1,239 receiving placebo. All studies were randomized and double-blind. Trial sample sizes ranged from 278 to 553 participants, all of whom had a diagnosis of MDD according to *DSM-III-R* or *DSM-IV*. In active treatment arms, patients received citalopram, desvenlafaxine, duloxetine, fluoxetine, levomilnacipran, mianserin, paroxetine, sertraline, or venlafaxine (Table 1). Invariably, study authors employed the HDRS (HDRS-17, HDRS-21, and Maier subscale).

Efficacy

Primary outcome (response).

Primary analysis (5 studies). Meta-analyses by treatment arm revealed a probability of response of 21.63% (18.57%, 24.89%) between weeks 5 and 8 in previously unresponsive patients taking antidepressants. The corresponding figure in previously unresponsive patients taking placebo was 13.01% (9.88%, 16.53%). Between weeks 9 and 12, additional response rates were 9.93% (7.54%, 12.73%) in antidepressant arms and 2.41% (1.22%, 4.59%) under placebo.

Meta-analyses of risk differences between antidepressant and placebo arms differed slightly in the weights attached to each study but confirmed the results. Between weeks 5

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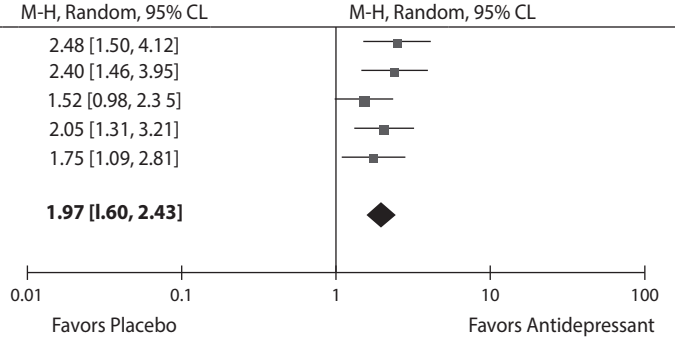
Figure 2. Forest Plot: Primary Outcome—Response (odds ratio) After 8 Weeks of Antidepressant Monotherapy Versus Placebo in Randomized Double-Blind Trials[a]

Study or Subgroup	Antidepressant Events	Antidepressant Total	Placebo Events	Placebo Total	Weight (%)	Odds Ratio M-H, Random, 95% CL
Cunningham 1997[15]	105	179	36	99	17.2	2.48 [1.50, 4.12]
Khan et al 1998[17]	138	253	31	93	17.9	2.40 [1.46, 3.95]
Malt et al 1999[24]	115	243	48	129	23.1	1.52 [0.98, 2.3 5]
Silverstone and Ravindran 1999[22]	143	241	49	118	22.0	2.05 [1.31, 3.21]
Stahl 2000[23]	113	209	43	107	19.8	1.75 [1.09, 2.81]
Total (95% CL)		**1,125**		**546**	**100.0**	**1.97 [l.60, 2.43]**
Total events	614		207			

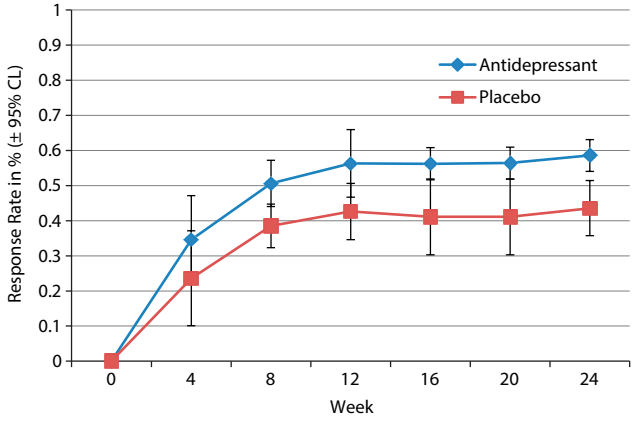
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_4 = 3.06$ ($P = .55$); $I^2 = 0\%$

Test for overall effect: $Z = 6.33$ ($P < .00001$)



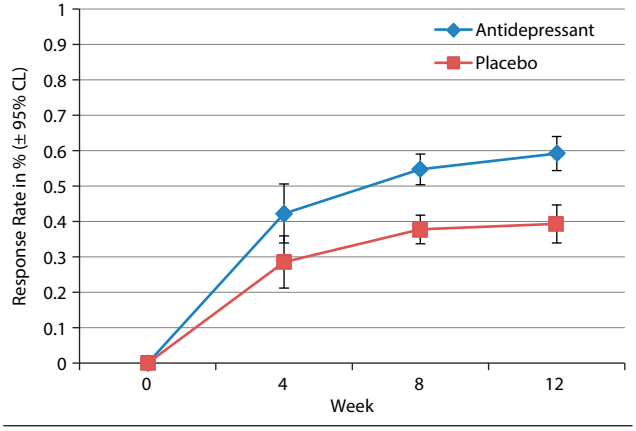
[a]Weighted according to random-effects analysis.
Abbreviations: CL = confidence limits, M-H = Mantel-Haenszel.

Figure 3. Trajectory of Response Over Time in Only Malt et al[24] and Stahl[23] Studies[a]



[a]Weighted according to random-effects analysis.
Abbreviation: CL = confidence limits.

Figure 4. Trajectory of Response Over Time in Randomized Double-Blind Trials of Antidepressant Monotherapy Versus Placebo[a]



[a]Weighted according to random-effects analysis.
Abbreviation: CL = confidence limits.

and 8, the difference amounted to 9% (2%, 16%) (number needed to treat [NNT]: 11) and, between weeks 9 and 12, to 6% (−1%, 13%) (NNT: 17) among previously unresponsive patients.

Response rates in active treatment arms were statistically significantly superior to placebo arms after 8 (OR = 1.97 [1.60, 2.43]) (forest plot—Figure 2) and 12 (OR = 2.25 [1.58, 3.19]) weeks. Removing all studies one by one, odds ratios ranged from 1.88 (1.49, 2.37) to 2.13 (1.68, 2.71) after 8 weeks and from 2.02 (1.42, 2.89) to 2.63 (2.07, 3.35) after 12 weeks with repeated calculations. Outcomes did not differ when analyses were restricted to studies with a low risk of bias: OR = 1.89 (1.50, 2.38) after 8 and 2.21 (1.42, 3.44) after 12 weeks of treatment.

Detailed analyses. Two studies, including 688 patients, provided complete data over 24 weeks[23,24] and were used to analyze the trajectory of long-term response. After 4, 8, 12, 16, 20, and 24 weeks, respectively, pooled weighted response rates in active treatment arms were 35% (22%, 47%), 51% (44%, 57%), 56% (47%, 66%), 56% (52%, 61%), 56% (52%, 61%), and 59% (54%, 63%). Corresponding response rates in placebo arms amounted to 24% (10%, 37%), 39% (32%, 45%), 43% (35%, 51%), 41% (30%, 52%), 41% (30%, 52%), and 44% (36%, 51%) (Figure 3).

Five studies[15,17,22–24] including 1,671 patients reported response rates on every time point (ie, every 4 weeks) from 4 to 12 weeks. After 4, 8, and 12 weeks, respectively, response rates in active treatment arms were 42% (34%, 51%), 55% (50%, 59%), and 59% (54%, 64%). The figures in placebo arms were 29% (21%, 36%), 38% (34%, 42%), and 39% (34%, 45%) after 4, 8, and 12 weeks, respectively (Figure 4).

Secondary outcomes.

Remission. The probability of remission among previously unremitted patients in meta-analyses by treatment arm was 17.29% (13.55%, 21.36%) between weeks 5 and 8 and 13.53% (10.13%, 17.95%) between weeks 9 and 12 when treated with antidepressants, and 15.70% (11.12%, 21.33%) and 8.20% (4.76%, 13.21%) when treated with placebo, respectively.

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Meta-analyses of risk differences between antidepressant and placebo arms differed slightly in the weights attached to each study but confirmed the results: The difference amounted to 0% (−17%, 17%) between weeks 5 and 8 and to 5% (−11%, 21%) between weeks 9 and 12.

In detail, 2 studies[21,22] including 658 patients reported remission rates on every time point from 4 to 12 weeks. The trajectory of remission was meta-analytically calculated using remission rates in active treatment arms. Remission rates after 4, 8, and 12 weeks, respectively, were 20% (13%, 26%), 34% (29%, 38%), and 43% (35%, 50%). In placebo arms, the corresponding figures were 9% (5%, 13%), 23% (12%, 35%), and 30% (16%, 43%) after 4, 8, and 12 weeks, respectively.

Rating scale scores. Seven studies including 2,735 patients reported rating scale scores on every time point from 4 to 12 weeks. Rating scale scores were statistically significantly lower in active treatment arms compared to placebo (as measured in percent of baseline scores). Differences were −7% (−9%, −5%), −9% (−10%, −8%), and −11% (−13%, −9%) after 4, 8, and 12 weeks, respectively. Specifically, rates in active treatment were 59% (56%, 61%), 51% (49%, 54%), and 49% (45%, 52%) after 4, 8, and 12 weeks, respectively, and 66% (64%, 69%), 61% (58%, 65%), and 60% (57%, 63%) in placebo arms.

Heterogeneity

Between-study heterogeneity in our primary outcome meta-analyses was low to moderate (τ^2; I^2): week 8: (0.00; 0%) and week 12: (0.10; 64%) (5 studies; see forest plot). Among secondary outcome analyses, heterogeneity was (τ^2; I^2): (0.12; 62%) after 8 and (0.41; 86%) after 12 weeks for remission (2 studies only) and (0.00; 17%) after 8 and (0.00; 55%) after 12 weeks for rating scale scores (7 studies), respectively. Leave-one-out analyses did not indicate that single studies greatly influenced the calculation (see above).

Publication Bias

At 8 and 12 weeks of treatment, funnel plots of primary outcome analyses did not indicate publication bias (data not shown, figures available from the authors on request). Following recommendations of the Cochrane Collaboration's *Handbook*, no additional tests for funnel plot asymmetry were conducted due to the limited number of studies.

DISCUSSION

Our findings indicate substantial changes in psychopathology up to 8 and up to 12 weeks of acute antidepressant treatment in patients previously unresponsive. According to our calculations, incomplete responders will have a 22% chance of achieving response between weeks 5 and 8, and nonremitters will have a 17% chance of achieving remission. Between weeks 9 to 12, among nonresponders and nonremitters, the probability of achieving response and remission with active treatment amounts to 10% and 14%, respectively. Risk difference to placebo of probabilities to respond among nonresponders amounted to 9% from 5 to 8 weeks and 6% from 9 to 12 weeks. This translates into numbers needed to treat of 11 (week 5 to 8) and 17 (week 9 to 12).

On the basis of limited data, it appears that after 12 weeks (and up to 24 weeks) no further increase in response rates can be expected (see sensitivity analysis of studies by Malt et al[24] and Stahl,[23] Figure 3).

With substantial changes in remission rates as well as response rates, our findings indicate that changes in psychopathology after 4 weeks occur not only in patients who have already responded to treatment (and achieving remission with ongoing treatment duration) but also in those who have not yet responded. On the basis of analyses of changes in rating scale scores at group level, we would not be able to differentiate which of the patients are experiencing improvements in symptomatology.

Our findings may be helpful for clinical practice. To determine when to change an ineffective treatment strategy, clinicians need evidence on probabilities of changes in symptomatology with ongoing treatment. Apart from looking for the time point when no further change can be expected at all, however, it may particularly be necessary to weigh a patient's probability to respond up to postponement of possibly more effective treatment alternatives.

While an approximately 10% chance of responding to another 4 weeks of treatment (and 6% risk difference to placebo) after 8 weeks of nonresponse may not justify ongoing unchanged treatment, a 22% (9% risk difference to placebo) chance of achieving response after 4 weeks may be a reasonable basis for decision making—particularly in light of adverse effects that may come with second-step treatment strategies.

Further, recent meta-analytic evidence on switching from one antidepressant to another after nonresponse indicates that this strategy may even be less favorable than continuing an ineffective monotherapy.[25] Other second-step treatment alternatives, however, have been shown to be effective after nonresponse to antidepressant monotherapy, eg, augmentation (especially with lithium[26] or second-generation antipsychotics[27]), combining 2 antidepressants,[28] high-dose antidepressant therapy,[29] and electroconvulsive therapy (ECT).[30] In Sequenced Treatment Alternatives to Relieve Depression (STAR*D), the largest study comparing treatment alternatives after nonremittal to date, however, overall remission rates with additional 14 weeks of second-step treatments (ie, switching, augmentation) were at best moderate, ranging from 25% to 39% (among nonremitters after initial 14 weeks of citalopram monotherapy).[31]

Pending better predictors for response to different treatment strategies, the decision to change ineffective antidepressant monotherapy, and if so at what point in time, may often be an individual decision—based in part on patients' preferences and anticipated adverse effects of treatment alternatives. Certain patient characteristics may inform attempts at tailoring antidepressant treatment to the needs of individual patients. For example, increased age

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and medical comorbidities may justify prolonged treatment durations as these factors may delay response in depressed patients.[31,32] Accordingly, clinician-patient communication will be crucial in shared decision making. On the basis of our results, we believe it is justified to inform the patients that achieving response or remission can be expected—with declining probability—for up to 3 months of monotherapy. Afterward changes seem less likely, but it must be borne in mind that data on treatment response after 12 weeks are sparse. Notwithstanding that there may be good reasons to change treatment earlier, we propose that 3 months is the maximum duration of efficacy assessment in antidepressant monotherapy.

There is need for further study of differences in long-term effects among different antidepressive agents. Evidence from our study is limited because trials selected for the present analysis are restricted to second-generation antidepressants (ie, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], and other). In another analysis, we found preliminary evidence that tricyclic agents may be superior to SSRIs in studies of 8 weeks' duration and beyond,[10] which is in line with other findings.[33]

Future research should focus on efficacy of treatment alternatives at different time points in order to answer the question of when changing treatment will be more effective than ongoing monotherapy. Additionally, future study designs need to take into account the identification of patient-specific variables correlating with efficacy over time. It is highly desirable to identify those patients who are most likely to respond after initial nonresponse. This, however, is beyond the scope of this analysis. The most promising approach to elucidate predictors seems to be meta-analysis of individual patients.

Limitations

First, while results are consistent over different outcome parameter analyses, data on treatment periods exceeding 12 weeks are particularly sparse. Only 2 studies reported outcomes on every time point from 4 up to 24 weeks. These studies, however, were of high methodological quality, and sample sizes still represented considerable numbers of patients. More evidence from methodologically rigid trials on treatment periods exceeding 12 weeks—a not uncommon treatment duration in clinical practice—is warranted.

To a lesser extent, this applies to studies of shorter duration as well. With only 5 studies reporting on response and remission between weeks 5 and 12, summary confidence intervals are still wide: For example, response rate differences between weeks 9 and 12 did not reach statistical significance (as did remission rate differences both between weeks 5 and 8 and between 9 and 12). However, given the a priori evidence on the moderate but robust efficacy of antidepressants (eg, Henssler et al[10]) and given the statistically significant results in our secondary analyses, we believe that the results of our meta-analyses reflect true effects rather than spurious results.

Second, changes in rates of dichotomous variables based on threshold scores (eg, remission and response) may be the result of small changes in rating scale scores only and thus may be difficult to interpret. On statistical grounds, analyses of continuous variables are preferred. In clinical practice, however, dichotomous variables are essential for decision making as well as for recommendations in practice guidelines. Reassuringly, our second-line analyses of continuous data supported our findings considering rates of remission and response.

Third, interpretation of meta-analyses can be complicated by heterogeneity of included studies. I^2 statistics indicated substantial heterogeneity of effects particularly in analyses of continuous data. I^2 values, however, are known to increase with accumulating size of patient samples.[14] It is therefore important to note that, in this study, continuous data were secondary outcomes from the start, owing to risk of bias introduced by the need to impute standard deviations in this subgroup of studies. In addition, this study consisted of various sensitivity analyses, random effects models were applied, and additional moderator analyses addressed the role of possible confounders.

Meta-analyses will, to some extent, inherit limitations of included trials. We have taken into account the risk of bias, and analyses of trials with low risk of bias only confirmed our findings. Some possible sources of bias, however, may remain unknown due to incomplete reporting. The use of active placebos[34] and the assessment of the quality of reporting of blinding measures and blinding measures assessment, for example, have been shown to be insufficient in psychiatric research.[35]

Fourth, although, with 9 studies and 3,466 patients included, results of our analyses may inform clinical decision making, our literature search revealed an overall dearth of studies on long-term outcomes of acute-phase treatment with antidepressants. Particularly, there is a need for well-designed studies with consistent outcome reporting at every time point in order to identify probabilities of changes in symptomatology over time.

CONCLUSIONS

To our knowledge, this is the first research synthesis focusing on incremental changes in efficacy of antidepressant monotherapy over long—but clinically common—treatment periods. Our findings can help clinicians in deciding when to change ineffective treatment and may be helpful in shared decision making. Up to 3 months, benefits in psychopathology can be expected even in previous nonresponders. After 8 weeks of treatment, however, the prospect of improvement with ongoing monotherapy is small.

Submitted: January 19, 2017; accepted August 25, 2017.

Published online: April 3, 2018.

Author contributions: **Drs Henssler** and **Baethge** had the idea for the study and its design. **Dr Bschor** contributed to the design and gave important input. **Ms Kurschus** and **Dr Henssler** conducted the literature search and screened the articles (with the help of **Dr Baethge**). **Dr Baethge**, **Ms Kurschus**, and **Dr Henssler** reviewed all full-texts for inclusion. **Ms Kurschus** and **Dr Henssler**

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collected the data independently. All authors analyzed the data, **Dr Henssler** drafted the paper, and all authors revised the paper and approved the final version.

Potential conflicts of interest: The authors report no conflicts of interest.

Funding/support: **Ms Kurschus** was supported by the Koeln Fortune Program/Faculty of Medicine, University of Cologne.

Role of the sponsor: The funding agency had no influence on the idea, the design, the execution, data analysis, or the publication of this work.

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