



Factors Related to Placebo Response in Randomized, Double-Blind Clinical Trials of Antidepressants in Children and Adolescents: A Meta-regression Analysis

Risa Okubo¹ · Kazuhiro Matsui¹ · Mamoru Narukawa¹

Accepted: 18 April 2023 / Published online: 24 May 2023
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2023

Abstract

Background and Objective Many randomized clinical trials (RCTs) for antidepressants in children and adolescents have failed to demonstrate efficacy due to a high placebo response. The aim of this study was to identify the potential factors affecting placebo response using meta-regression analysis of RCTs for antidepressants in children and adolescents using the Children's Depressive Rating Scale-Revised (CDRS-R) as the outcome.

Methods PubMed and ClinicalTrials.gov were searched for randomized, double-blind, placebo-controlled trials of antidepressants for the acute treatment of major depressive disorder in children and adolescents. The outcome used in the present study was the mean change of the CDRS-R total score from baseline to the last assessment for the primary efficacy in the placebo arm. Potential factors related to the placebo response, such as study design, operational, and patient factors, were explored using meta-regression.

Results The analyses included 23 trials. On multivariable meta-regression, setting up a placebo lead-in period was significantly associated with a smaller placebo response in the CDRS-R.

Conclusion Setting up a placebo lead-in period should be considered in future clinical trials of antidepressants in adolescents and children.

Key Points

Randomized clinical trials for antidepressants in children and adolescents often show a high placebo response.

Meta-regression analysis showed trials using placebo lead-in period were associated with smaller placebo responses when comparing the Children's Depressive Rating Scale-Revised score before and after the trial.

Placebo lead-in periods should be included in future trials with the aim to increase the trial's success.

1 Introduction

Major depressive disorder (MDD) is one of the most common mental disorders in children and adolescents with an estimated lifetime prevalence at the end of adolescence of 11–12% [1, 2]. When present during childhood or adolescence, MDD impairs academic performance and peer relationships and increases the risk of recurrent depression in adulthood [3]. About half of all adult mental health disorders begin during the teenage years [4]. In addition, MDD represents a significant risk factor for suicidal ideation, suicide attempts, and suicides [5]. Therefore, there is a high unmet need for safe and efficacious treatment for children and adolescents [6].

In adolescents and children, the most recent clinical guidelines recommend psychological intervention as a first-line treatment for mild depression, and psychological intervention and antidepressant therapy, alone or in combination, are recommended for moderate-to-severe depression [7–9].

Currently, only two antidepressants have regulatory approval

✉ Risa Okubo
dl21402@st.kitasato-u.ac.jp

¹ Department of Clinical Medicine (Pharmaceutical Medicine), Graduate School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

for pediatric patient populations in the USA: fluoxetine (8–17 years of age) and escitalopram (12–17 years of age).

To date, many antidepressants approved for adults have been developed for MDD in children and adolescents, but most clinical trials failed to verify their efficacy. These trials could be classified into two types: (1) a negative trial, where the treatment did not demonstrate efficacy, and (2) a failed trial with methodological problems. The latter is problematic, and methodological improvements are needed.

According to previous reports concerning trials for antidepressants in adults with MDD, increased placebo response was associated with a failure in demonstrating efficacy [10, 11]. High placebo response was seen in the trials with more treatment arms, fixed dosing strategies, higher completion rates, longer treatment periods, more study sites, and fewer patients enrolled from academic sites [11–14].

Likewise, pediatric studies evaluating the efficacy of antidepressants have generally been faced with the challenge of a high degree of placebo response, with several studies failing to demonstrate a separation between active treatment and placebo [15–21]. Previous reviews and meta-analyses showed that active drug response rate ranged from 55% to 60% in many trials, while the placebo response rate sometimes approached 60% [22]. In children and adolescents with MDD, increased placebo response was associated with negative outcomes of the clinical trials for antidepressants [23]. Given the large placebo effects, it is warranted to augment our understanding of factors related to the increase or decrease of the placebo response.

Several meta-analyses and systematic reviews on placebo response in clinical trials of MDDs in pediatric populations have been published recently. They reported that the number of study sites, industry funding, and baseline severity of illness were identified as factors related to the high placebo response rate in children and adolescents [22–25]. These studies set the response rate as the outcome, which includes response rates in various rating scales such as clinical global impression-improvement (CGI-I), the Children's Depressive Rating Scale-Revised (CDRS-R), and the Montgomery–Åsberg Depression Rating Scale (MADRS). To date, there is no meta-analysis based on the outcome of a single efficacy variable such as the CDRS-R score.

The CDRS-R is a validated, semistructured, 17-item, clinician-rated instrument designed to measure the severity of symptoms commonly associated with depression in children and adolescents. Most randomized clinical trials (RCTs) recently conducted in children and adolescents use CDRS-R as a primary endpoint, and the difference in the change from baseline in the CDRS-R score between the test drug group and the placebo group is the main outcome of the trial.

Given the above, we believe that identifying the potential factors related to the increased placebo response in CDRS-R

will improve the success rate of placebo-controlled RCTs for antidepressants in children and adolescents. In this study, we aimed to identify the factors influencing the placebo response in CDRS-R in placebo-controlled RCTs for antidepressants in children and adolescents through meta-regression analysis.

2 Methods

2.1 Search Strategy

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standard. PubMed was searched using keywords “major depressive disorder or depression” and “adolescents or children or pediatric or youth” and generic names of antidepressants for randomized, double-blind, controlled clinical trials. The retrieval deadline was 20 March 2023. We additionally searched the references of the extracted articles and ClinicalTrials.gov. The detailed search strategies are described in the Supplementary Appendix.

2.2 Inclusion and Exclusion Criteria

We included the following trials: (1) randomized, double-blind, placebo-controlled trials in which an antidepressant, which had been approved for adults, was used in monotherapy as the acute-phase treatment, (2) trials for which participants were children or adolescents (< 18 years of age) who met the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for MDD, and (3) trials reporting the values of mean change of the CDRS-R score from baseline to the last assessment for the primary efficacy in the placebo arm. We excluded trials with combination treatment, treatment-resistant depression, prevention of relapse of MDD, and trials with non-oral administration.

2.3 Outcome Measures and Data Extraction

The outcome in the present study was the mean change of CDRS-R total score from baseline to the last assessment for the primary efficacy in the placebo arm. We extracted data or values from the selected articles and also referred to the review report for new drug approval by the Pharmaceuticals and Medical Devices Agency and ClinicalTrials.gov when data or values were not available in the article. Three trials did not include the information on standard errors of the mean change of the CDRS-R total score, and they were imputed using the leaving-one-out method [26]. In addition, we selected potential factors related to the placebo response including those reported to have influenced placebo response

rates in children and adolescents and categorized them into the following groups:

Study design factors: Dosing regimen, placebo lead-in, treatment duration, percentage receiving active treatments, number of arms, drug type, and inclusion age. The dosing regimen was categorized as trials either with a fixed dose throughout the treatment period or with a flexible dose. Placebo lead-in was categorized as trials with or without a single-blind placebo lead-in period. Drug type was categorized as trials for selective serotonin reuptake inhibitors (SSRIs) drugs or non-SSRIs drugs. Inclusion age was categorized as trials with children and adolescents or adolescents only.

Operational factors: Number of study sites, number of countries, funding source. The funding source was categorized as industry-sponsored trials or not.

Patient factors: Baseline CDRS-R average score.

The quality of the included trials was assessed using the Jadad score [27]. Two authors (R. O. and M. N.) independently assessed the selected studies and extracted data. Any disagreements were resolved by discussion between the two authors. The Jadad score of the included trials was 4 or higher.

2.4 Data Analysis

Univariable meta-regression analyses for the potential factors related to placebo response in CDRS-R were performed using a random-effects model. A significant association was

defined as $p < 0.2$ in the univariable analysis. Of the factors identified by the univariable analysis, factors with strong correlations with other factors by Pearson correlation coefficient or factors with a large imbalance in the number of data within a category were excluded. Then multivariable meta-regression analysis was performed. A significant association was defined as $p < 0.05$ in the multivariable analysis. All the analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 Results

3.1 Studies Included in the Analysis

In total, 1298 abstracts were identified through the database search, ClinicalTrials.gov, and the references from other meta-analysis, and 34 potentially eligible full-text articles were retrieved from them. Finally, 23 trials were included in our meta-regression analysis (Fig. 1). The characteristics of the 23 identified placebo-controlled RCTs are presented in Table 1.

3.2 Univariable Meta-regression Analysis

The results of univariable meta-regression showed that placebo lead-in period, drug type (SSRIs or non-SSRIs), and funding source (industry-sponsored or not) were

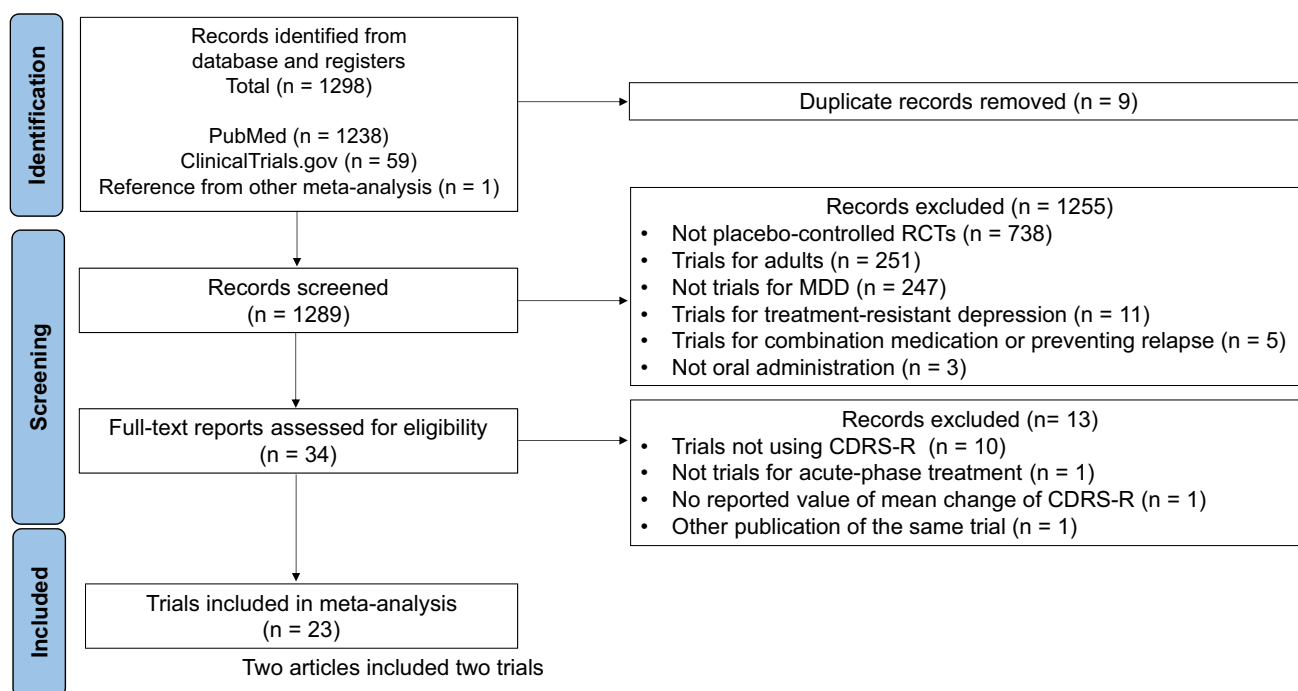


Fig. 1 Article review and selection of studies. *CDRS-R* Children's Depressive Rating Scale-Revised, *MDD* major depressive disorder

Table 1 Characteristics of identified placebo-controlled randomized clinical trials (RCTs) in children and adolescents

Publication year	References	Drug	No. of randomized subjects to placebo (ITT)	Treatment duration (week)	Mean CDRS-R score at baseline in placebo group	Mean change of CDRS-R score from baseline in placebo group	SE	Placebo lead-in	No. of sites	Percentage receiving active treatment	Funding source
1997	Emslie et al. [28]	Fluoxetine	48	8	57.6	-10.5	NA	Yes	1	50	Non-industry
2002	Emslie et al. [29]	Fluoxetine	110	8	55.1	-14.9	NA	Yes	15	50	Industry
2003	Wagner et al. [30]	Sertraline	88	10	NA	-22.1	1.5	No	53	50	Industry
2003	Wagner et al. [30]	Sertraline	91	10	NA	-25.6	1.6	No	53	50	Industry
2004	March et al. [31]	Fluoxetine	112	12	61.18	-19.41	NA	No	13	75	Non-industry
2006	Emslie et al. [32]	Paroxetine	101	8	62.6	-23.4	1.6	No	40	50	Industry
2006	Wagner et al. [33]	Escitalopram	132	8	56.6	-20.3	1.3	Yes	25	50	Industry
2007	Emslie et al. [34]	Venlafaxine	73	8	54.4	-16.1	1.5	Yes	14	50	Industry
2007	Emslie et al. [34]	Venlafaxine	92	8	57.3	-22.8	1.4	Yes	37	50	Industry
2009	Findling et al. [35]	Fluoxetine	16	8	53.94	-22.63	3.12	No	1	50	Industry
2009	Emslie et al. [36]	Escitalopram	157	8	56	-18.8	1.27	Yes	40	50	Industry
2014	Atkinson et al. [15]	Duloxetine	103	10	60.2	-24.3	1.11	No	65	67	Industry
2014	Emslie et al. [16]	Duloxetine	117	10	58.2	-21.6	1.27	No	60	75	Industry
2018	Wehls et al. [18]	Desvenlafaxine	112	8	57.06	-23.1	1.18	No	37	67	Industry
2018	Durgam et al. [19]	Vilazodone	170	8	57.5	-22.5	0.9	No	56	67	Industry
2018	Atkinson et al. [20]	Desvenlafaxine	119	8	57.28	-22.85	1.13	No	33	67	Industry
2020	Findling et al. [21]	Vilazodone	182	8	57.7	-20.3	1	No	55	67	Industry
2022	Saito et al. [37]	Duloxetine	74	6	63.3	-22.42	2.05	No	5	50	Industry
2022	Findling et al. [38]	Vortioxetine	137	8	60.6	-18.22	1.22	Yes	118	75	Industry

Table 1 (continued)

Publication year	References	Drug	No. of randomized subjects to placebo (ITT)	Treatment duration (week)	Mean CDRS-R score at baseline in placebo group	SE	Placebo lead-in	No. of sites	Percentage receiving active treatment	Funding source
NA	ClinicalTrials.gov [39]	Paroxetine	27	8	NA	2.54	Yes	33	50	Industry
NA	ClinicalTrials.gov [40]	Levomilnacipran	118	8	61.1	1.09	No	49	75	Industry
NA	ClinicalTrials.gov [41]	Levomilnacipran	146	8	60.8	1.01	No	51	67	Industry
NA	ClinicalTrials.gov [42]	Vortioxetine	136	8	63.4	1.35	Yes	98	75	Industry

CDRS-R Children's Depressive Rating Scale-Revised. No, number, SE standard error, NA not applicable

significantly correlated with the mean change of CDRS-R score (Table 2).

3.3 Multivariable Meta-regression Analysis

Of the three factors identified in the univariable meta-regression, we excluded one factor based on the predetermined criteria: funding source, for a large imbalance in the number of data and a strong correlation with placebo lead-in period. Multivariable meta-regression analysis was performed using two factors (placebo lead-in period and drug type) as the explanatory variables. The results of multivariable meta-regression showed that a placebo lead-in period was significantly correlated with the mean change of CDRS-R score (Table 2).

The univariable meta-regression analysis did not show a significant association of the baseline CDRS-R score with the mean change of CDRS-R score. However, as it has been reported that the greater the baseline symptom severity, the greater the magnitude of the difference between placebo and active medication for depression [43–45], multivariable meta-regression analysis was performed adding the baseline CDRS-R average score to the above two variables as a sensitivity analysis. The results of the sensitivity analysis also suggested that placebo lead-in period was significantly correlated with the mean change of CDRS-R score.

4 Discussion

Clinician-rated outcome measures are the current standard for assessing efficacy in clinical trials of antidepressants. For children and adolescents, only CDRS-R is the recommended rating scale as a primary endpoint [46, 47] and almost all studies set CDRS-R as the primary endpoint. Thus, changes in the CDRS-R from baseline to the last assessment for the primary efficacy in the placebo arm directly reflect the outcomes of clinical trials for antidepressants in children and adolescents. However, there is a lack of systematic review from this point of view. To our knowledge, this study is the first to identify the factors associated with placebo response based on CDRS-R scores.

We found that setting up a placebo lead-in period was significantly correlated with a smaller placebo response in CDRS-R on multivariable meta-regression. In typical RCTs using a placebo lead-in period, all subjects are given a placebo prior to randomization. Then, those who demonstrated large improvement within this period are excluded, and the remaining subjects are randomized to the treatment or placebo arm. Setting up a placebo lead-in period is expected to attenuate the placebo response.

In adults, single-blind placebo lead-in periods are common in RCTs of antidepressants. However, using this design

Table 2 Meta-regression of potential factors affecting placebo response in the trials of antidepressants in children and adolescents

Variable	No. of trials	Estimate	SE	<i>p</i> value
Univariable meta-regression				
Study design factors				
Dosing regimen (fixed or flexible dose)	23	− 0.988	1.442	0.493
Placebo lead-in period	23	5.026	0.992	< 0.001
Treatment duration	23	− 0.319	0.614	0.603
Percentage of receiving active treatments	23	− 0.069	0.066	0.296
Number of arms	23	− 0.644	0.889	0.469
Drug type (SSRIs of non-SSRIs)	23	2.273	1.39	0.102
Inclusion age (children and adolescents or adolescents only)	23	− 1.068	1.754	0.543
Operational factors				
Number of study sites	23	− 0.025	0.026	0.325
Number of countries	23	0.031	0.139	0.824
Funding source (industry-sponsored or not)	23	− 5.354	2.391	0.025
Patient factors				
Baseline CDRS-R average score	20	− 0.302	0.255	0.237
Multivariable meta-regression				
Study design factors				
Placebo lead-in period	23	4.750	0.995	< 0.001
Drug type (SSRIs of non-SSRIs)	23	1.125	0.992	0.257

CDRS-R Children's Depressive Rating Scale-Revised, SSRI selective serotonin reuptake inhibitors, No. number, SE standard errors

has been criticized as being no more effective than no placebo lead-in at all in adult studies. In the recent systematic review and meta-analysis, RCTs with a single-blind placebo lead-in period reported a smaller placebo response than those without. On the other hand, the drug response was also smaller in RCTs that used a single-blind placebo lead-in period than in those that did not, suggesting that the RCTs using this method do not increase trial sensitivity. They noted that single-blind placebo lead-in design yielded less robust symptomatic changes regardless of treatment assignment owing to the mitigation of additive placebo and nonspecific effects [48]. In contrast, double-blind placebo lead-in design can identify early response and reduce the ultimate placebo response at the study endpoint.

The success of blinding during a single-blind placebo lead-in period and whether participants are truly masked is not known. It is known that site-based clinicians are not blinded to the enrollment criteria in single-blind placebo lead-in design and therefore are not unbiased assessors. In contrast, in a double-blind placebo lead-in period, neither the potential study participants nor the site clinicians know about the existence of the placebo lead-in period. However, to date, few studies have used a double-blind placebo lead-in period in adults.

In children and adolescents, three RCTs with positive outcomes for the currently approved antidepressants, escitalopram and fluoxetine, all used a single-blind placebo lead-in

period. Also, a study of vortioxetine using a single-blind placebo lead-in period in adolescents showed that the fluoxetine group, an active reference, was significantly different from placebo. A previous study showed that children and adolescents with MDD exhibited higher placebo response rates compared with adult patients (46% versus 31%) [49], and it was also pointed out that psychological and physiological characteristics of children and adolescents were quite different from those of adults, e.g., difference in the signal transduction pathway (pharmacodynamics) and pharmacokinetics including the half-life of the drug [50]. Therefore, the findings from adults might not be applicable to children and adolescents. In the trials of children and adolescents analyzed in our study, 9 of 23 trials used placebo lead-in periods, among which 8 trials used single-blind placebo lead-in periods (for the remaining one trial, information on the blinding method was unavailable). The double-blind placebo lead-in period may be taken into account when designing future pediatric trials, as it is expected to reduce bias as in adult trials.

In the present study, we evaluated the response in the placebo-arm alone and did not investigate the relationship between drug response and the use of a placebo lead-in period. Further research is needed to clarify the effect of the placebo lead-in period on the degree of drug response.

In addition, previous studies have reported that the number of study sites was significantly correlated with the placebo response rate, which was not consistent with

our findings. It was considered that the main cause was the difference in study outcomes (placebo response rate or change of CDRS-R scores). Industry-funded trials were also reported to be a factor related to the placebo response rate. In our study, industry-funded trials were significantly correlated with a larger placebo response in CDRS-R on univariable meta-regression. However, since there were only 2 non-industry funded trials in the included 23 trials, we did not include this factor in the multivariable meta-regression. It was reported that baseline severity of Hamilton Rating Scale of Depression was associated with effect size [43–45], and we conducted a sensitivity analysis adding the baseline CDRS-R as an explanatory variable. Baseline severity of CDRS-R was not a significant factor for smaller placebo response, which was consistent with the previous study [25].

Factors such as rater training and rating experiences, which seems to be related to the quality of CDRS-R assessments, might be related to the increased placebo response. In industry-funded trials, to recruit a large number of participants within a very short time frame, investigators who are inexperienced or who do not have expertise may participate in the trial. Little additional training in rating is provided for such investigators [51]. We did not investigate this aspect since rater training and requirements for investigators were not always reported.

Several limitations should be considered when interpreting our results. First, all included clinical trials were published in English, which may contribute to publication bias. Second, our study data were limited to trials for which the mean change from baseline to the last assessment for the primary efficacy in the CDRS-R total score was available.

5 Conclusion

Placebo lead-in period was significantly associated with a smaller placebo response in the CDRS-R. In future clinical trials of antidepressants in adolescents and children, setting up a placebo lead-in period should be considered with the aim to increase the trial's success.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40261-023-01273-8>.

Declarations

Funding The preparation of this manuscript was not supported by any external funding.

Conflicts of interest All authors declare that they have no conflict of interests. Risa Okubo is an employee of Janssen Pharmaceutical K.K.

Availability of data and material All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions RO and MN were involved in study design and data interpretation. KM was involved in the data analysis. RO drafted the original manuscript. MN and KM revised the manuscript drafts. All authors have approved the submitted version of the manuscript and agreed to be accountable for any part of the work.

References

1. Avenevoli S, Swendsen J, He J-P, Burstein M, Merikangas KR. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. *J Am Acad Child Adolesc Psychiatry*. 2015;54(1):37–44.e2. <https://doi.org/10.1016/j.jaac.2014.10.010>.
2. Merikangas KR, He J-P, Burstein M, et al. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980–9. <https://doi.org/10.1016/j.jaac.2010.05.017>.
3. Davies J, Sullivan S, Zammit S. Adverse life outcomes associated with adolescent psychotic experiences and depressive symptoms. *Soc Psychiatry Psychiatr Epidemiol*. 2018;53(5):497–507. <https://doi.org/10.1007/s00127-018-1496-z>.
4. Johns PB. Adult mental health disorders and their age at onset. *Br J Psychiatry Suppl*. 2013;54:s5–10. <https://doi.org/10.1192/bjp.bp.112.119164>.
5. Foley DL, Goldston DB, Costello EJ, Angold A. Proximal psychiatric risk factors for suicidality in youth: the Great Smoky Mountains Study. *Arch Gen Psychiatry*. 2006;63(9):1017–24. <https://doi.org/10.1001/archpsyc.63.9.1017>.
6. Cipriani A, Zhou X, Giovane CD, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet*. 2016;388(10047):881–90. [https://doi.org/10.1016/S0140-6736\(16\)30385-3](https://doi.org/10.1016/S0140-6736(16)30385-3).
7. Walter HJ, Abright AR, Bukstein OG, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with major and persistent depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2022;S0890–8567(22):01852–4. <https://doi.org/10.1016/j.jaac.2022.10.001>.
8. Depression in children and young people: identification and management. NICE guideline [NG134]. 2019.
9. Cheung AH, Zuckerbrot RA, Jensen PS, Laraque D, Stein REK, GLAD-PC STEERING GROUP. Guidelines for adolescent depression in primary care (GLAD-PC): Part II. Treatment and ongoing management. *Pediatrics*. 2018;141(3):e20174082. <https://doi.org/10.1542/peds.2017-4082>.
10. Papakostas GI, Østergaard SD, Iovieno N. The nature of placebo response in clinical studies of major depressive disorder. *J Clin Psychiatry*. 2015;76(4):456–66. <https://doi.org/10.4088/JCP.14r09297>.
11. Furukawa TA, Cipriani A, Atkinson LZ, et al. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. *Lancet Psychiatry*. 2016;3(11):1059–66. [https://doi.org/10.1016/S2215-0366\(16\)30307-8](https://doi.org/10.1016/S2215-0366(16)30307-8).

12. Sinyor M, Levitt AJ, Cheung AH, et al. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. *J Clin Psychiatry*. 2010;71(3):270–9. <https://doi.org/10.4088/JCP.08r04516blu>.
13. Enck P, Klosterhalfen S, Weimer K, Horing B, Zipfel S. The placebo response in clinical trials: more questions than answers. *Philos Trans R Soc Lond B Biol Sci*. 2011;366(1572):1889–95. <https://doi.org/10.1098/rstb.2010.0384>.
14. Dunlop BW, Thase ME, Wun C-C, et al. A meta-analysis of factors impacting detection of antidepressant efficacy in clinical trials: the importance of academic sites. *Neuropsychopharmacology*. 2012;37(13):2830–6. <https://doi.org/10.1038/npp.2012.153>.
15. Atkinson SD, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014;24(4):180–9. <https://doi.org/10.1089/cap.2013.0146>.
16. Emslie GJ, Prakash A, Zhang Q, Pangallo BA, Bangs ME, March JS. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014;24(4):170–9. <https://doi.org/10.1089/cap.2013.0096>.
17. DelBello MP, Hochadel TJ, Portland KB, et al. A double-blind, placebo-controlled study of selegiline transdermal system in depressed adolescents. *J Child Adolesc Psychopharmacol*. 2014;24(6):311–7. <https://doi.org/10.1089/cap.2013.0138>.
18. Weihs KL, Murphy W, Abbas R, Chiles D, et al. Desvenlafaxine versus placebo in a fluoxetine-referenced study of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):36–46. <https://doi.org/10.1089/cap.2017.0100>.
19. Durgam S, Chen C, Migliore R, Prakash C, Edwards J, Findling RL. A phase 3, double-blind, randomized, placebo-controlled study of vilazodone in adolescents with major depressive disorder. *Paediatr Drugs*. 2018;20(4):353–63. <https://doi.org/10.1007/s40272-018-0290-4>.
20. Atkinson S, Lubaczewski S, Ramaker S, et al. Desvenlafaxine versus placebo in the treatment of children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2018;28(1):55–65. <https://doi.org/10.1089/cap.2017.0099>.
21. Findling RL, McCusker E, Strawn JR. A randomized, double-blind, placebo-controlled trial of vilazodone in children and adolescents with major depressive disorder with twenty-six-week open-label follow-up. *J Child Adolesc Psychopharmacol*. 2020;30(6):355–65. <https://doi.org/10.1089/cap.2019.0176>.
22. Mossman SA, Mills JA, Walkup JT, Strawn JR. The impact of failed antidepressant trials on outcomes in children and adolescents with anxiety and depression: a systematic review and meta-analysis. *J Child Adolesc Psychopharmacol*. 2021;31(4):259–67. <https://doi.org/10.1089/cap.2020.0195>.
23. Li Y, Huang J, He Y, et al. The impact of placebo response rates on clinical trial outcome: a systematic review and meta-analysis of antidepressants in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2019;29(9):712–20. <https://doi.org/10.1089/cap.2019.0022>.
24. Meister R, Abbas M, Antel J, et al. Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: a systematic review and meta-regression analysis. *Eur Child Adolesc Psychiatry*. 2018;29(3):253–73. <https://doi.org/10.1007/s00787-018-1244-7>.
25. Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *Am J Psychiatry*. 2009;166(1):42–9. <https://doi.org/10.1176/appi.ajp.2008.08020247>.
26. Furukawa T, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analysis can provide accurate results. *J Clin Epidemiol*. 2006;59(1):7–10. <https://doi.org/10.1016/j.jclinepi.2005.06.006>.
27. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12. [https://doi.org/10.1016/0197-2456\(95\)00134-4](https://doi.org/10.1016/0197-2456(95)00134-4).
28. Emslie GJ, Rush AJ, Weinberg WA, et al. A Double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54(11):1031–7. <https://doi.org/10.1001/archpsyc.1997.01830230069010>.
29. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1205–15. <https://doi.org/10.1097/00004583-200210000-00010>.
30. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA*. 2003;290(8):1033–41. <https://doi.org/10.1001/jama.290.8.1033>.
31. March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807–20. <https://doi.org/10.1001/jama.292.7.807>.
32. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45(6):709–19. <https://doi.org/10.1097/01.chi.0000214189.73240.63>.
33. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):280–8. <https://doi.org/10.1097/01.chi.0000192250.38400.9e>.
34. Emslie GJ, Findling RL, Yeung PP, Kunz NR, Li Y. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2007;46(4):479–88. <https://doi.org/10.1097/chi.0b013e31802f5f03>.
35. Findling RL, Pagano ME, McNamara NK, et al. The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child Adolesc Psychiatry Ment Health*. 2009. <https://doi.org/10.1186/1753-2000-3-11>.
36. Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry*. 2009;3(1):11. <https://doi.org/10.1097/CHI.0b013e3181a2b304>.
37. Saito T, Ishida M, Nishiyori A, Ochiai T, Katagiri H, Matsumoto H. Efficacy and safety of duloxetine in children and adolescents with major depressive disorder in Japan: a randomized double-blind placebo-controlled clinical trial followed by an open-label long-term extension trial. *J Child Adolesc Psychopharmacol*. 2022;2(3):132–42. <https://doi.org/10.1089/cap.2021.0104>.
38. Findling RL, DelBello MP, Zuddas A, et al. Vortioxetine for major depressive disorder in adolescents: 12-week randomized, placebo-controlled, fluoxetine-referenced, fixed-dose study. *J Child Adolesc Psychopharmacol*. 2022;61(9):1106–1118.e2. <https://doi.org/10.1016/j.jaac.2022.01.004>.

39. Paxil Japanese Post Marketing Paediatric Study in Depression (Double-blind, Placebo Controlled Study). <https://clinicaltrials.gov/ct2/show/NCT00812812>. Accessed 20 Mar 2023.
40. Safety and Efficacy of Levomilnacipran ER in Adolescent Participants With Major Depressive Disorder. <https://clinicaltrials.gov/ct2/show/study/NCT02431806>. Accessed 20 Mar 2023.
41. Efficacy, Safety, and Tolerability of Levomilnacipran ER in Pediatric Patients (7-17 Years) With Major Depressive Disorder. <https://clinicaltrials.gov/ct2/show/NCT03569475>. Accessed 20 Mar 2023.
42. Active Reference (Fluoxetine) Fixed-dose Study of Vortioxetine in Paediatric Participants Aged 7 to 11 Years With Major Depressive Disorder (MDD). <https://clinicaltrials.gov/ct2/show/NCT02709655>. Accessed 20 Mar 2023.
43. Khan A, Leventhal RM, Khan SR. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J Clin Psychopharmacol*. 2002;22(1):40–5. <https://doi.org/10.1097/00004714-200202000-00007>.
44. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med*. 2008;5(2):e45. <https://doi.org/10.1371/journal.pmed.0050045>.
45. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303(1):47–53. <https://doi.org/10.1001/jama.2009.1943>.
46. US Food and Drug Administration (FDA). Major depressive disorder: developing drugs for treatment guidance for industry draft guidance. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/major-depressive-disorder-developing-drugs-treatment>. Accessed 20 Mar 2023.
47. Japan Ministry of Health, Labour and Welfare. Guidelines for clinical evaluation for antidepressants (in Japanese). 2010. <https://www.pmda.go.jp/files/000208191.pdf>. Accessed 20 Mar 2023.
48. Scott AJ, Sharpe L, Quinn V, Colagiuri B. Association of single-blind placebo run-in periods with the placebo response in randomized clinical trials of antidepressants: a systematic review and meta-analysis. *JAMA Psychiat*. 2022;79(1):42–9. <https://doi.org/10.1001/jamapsychiatry.2021.3204>.
49. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–7. <https://doi.org/10.1001/jama.287.14.1840>.
50. Bylund DB, Reed AL. Childhood and adolescent depression: why do children and adults respond differently to antidepressant drugs? *Neurochem Int*. 2007;51(5):246–53. <https://doi.org/10.1016/j.neuint.2007.06.025>.
51. Walkup JT. Antidepressant efficacy for depression in children and adolescents: industry- and NIMH-funded studies. *Am J Psychiatry*. 2017;174(5):430–7. <https://doi.org/10.1176/appi.ajp.2017.16091059>.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.