

Review Article

Antidepressants in children and adolescents with major depressive disorder and the influence of placebo response: A meta-analysis

Anna Feeney^{*}, Rebecca S. Hock, Maurizio Fava, Jesús M. Hernández Ortiz, Nadia Iovieno, George I. Papakostas

Clinical Trials Network and Institute, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States

ARTICLE INFO

Keywords:

Antidepressant
Major depressive disorder
Clinical trials
Placebo
Pediatric depression

ABSTRACT

Background: There are few available antidepressants for pediatric Major Depressive Disorder (MDD). The objective of this systematic review and meta-analysis was to review industry-funded studies of antidepressants in children and adolescents with MDD, and to better understand the contribution of study design and placebo response to the findings of these studies.

Methods: Randomized, double-blind, placebo-controlled clinical trials that compared antidepressant with placebo for the acute treatment of MDD in children and/or adolescents were selected. Estimates of the standardized mean difference (SMD) in change in Children's Depression Rating Scale-Revised scores were pooled, after examining for heterogeneity. A random-effects meta-analysis was completed.

Results: Thirty-four antidepressant-placebo comparisons, involving 6161 subjects, were included. The SMD among all studies was 0.12 (CI 0.08, 0.17; $p < 0.001$), a very small effect size, lower than that seen in studies of adults with MDD. When the meta-analysis was limited to studies with a low mean placebo response, the SMD increased to 0.19 and further increased to 0.22 when studies with at least a 50% chance of receiving placebo were included.

Limitations: Many studies focused on older children and younger adolescents. Our findings may not reflect antidepressant efficacy in older adolescents.

Conclusions: The modest SMD identified in this analysis may reflect study design factors and the application of antidepressants developed for adults to pediatric patients. Given the urgent clinical need for more pediatric MDD treatments, the influence of placebo response and the need for drug development tailored to this population should be considered in pediatric MDD trial design.

1. Introduction

Major Depressive Disorder (MDD) affects many children and adolescents worldwide, however, there are far fewer evidence-based treatments available relative to adults. In 2018, 14.4% of adolescents aged 12 to 17 years in the United States (US) were estimated to have had a past year Major Depressive Episode (MDE), a proportion that has been rising over the past two decades (Lipari and Park-Lee, 2019). Adolescent depression increases the odds of adult depression (Johnson et al., 2018), underscoring the importance of early recognition and treatment of pediatric presentations. Despite dozens of antidepressants and medical devices approved for the treatment of MDD in adults, only two antidepressants have been approved for children and adolescents in the US:

fluoxetine has been approved for use in children with MDD, and both fluoxetine and escitalopram for use in adolescents (Food and Drug Administration, 2021a). The use of antidepressants in children and adolescents has been further complicated by the reported risk of increased suicidal thoughts and behaviors on initiation of treatment (average risk of 4% with drug vs. 2% with placebo), with no completed suicides (Food and Drug Administration, 2021b), leading to safety warnings accompanying these treatments (European Medicines Agency, 2021). Internationally, most treatment guidelines for children and adolescents recommend psychotherapy for mild depressive episodes and a combination of psychotherapy and an antidepressant for moderate to severe episodes (Malhi et al., 2015; Birmaher et al., 2007; National Institute for Health and Care Excellence, 2021).

^{*} Corresponding author at: Clinical Trials Network and Institute, Massachusetts General Hospital, One Bowdoin Square, 9th Floor, Boston, MA 02114, United States.

E-mail address: feeneyac@tcd.ie (A. Feeney).

<https://doi.org/10.1016/j.jad.2022.02.074>

Received 16 October 2021; Received in revised form 29 December 2021; Accepted 27 February 2022

Available online 3 March 2022

0165-0327/© 2022 Elsevier B.V. All rights reserved.

Two recent meta-analyses support the use of fluoxetine (Cipriani et al., 2016; Ignaszewski and Waslick, 2018) and escitalopram (Ignaszewski and Waslick, 2018) for the treatment of MDD in children and adolescents. However, a 2014 Cochrane review concluded that there was limited evidence upon which to draw conclusions about the relative efficacy of antidepressants, psychotherapy or a combination of these among children and adolescents with depressive disorders (Cox et al., 2014) and a more recent Cochrane review observed that most antidepressants for this patient group are associated with a “small and unimportant” reduction in depressive symptoms (Hetrick et al., 2021). Many antidepressant clinical trials fail in pediatric populations. Obstacles to the development of MDD treatments include the placebo response and measurement error in studies of MDD (Iovieno et al., 2021; Papakostas et al., 2015; Salloum et al., 2020). Our group's previous work has identified that in studies of adult MDD, a greater likelihood of receiving placebo predicts a greater antidepressant-placebo separation at study endpoint (Papakostas and Fava, 2009); lower probability of receiving placebo is associated with increased placebo response rates and lower likelihood of drug-placebo separation. One explanation for this finding may be that when patients are aware that they are more likely to receive an active drug than placebo, there is a greater expectation of response and they are thus more likely to have a placebo response. A high placebo response rate in pediatric MDD studies is widely reported (Cohen et al., 2008; Ignaszewski and Waslick, 2018; Locher et al., 2017; Meister et al., 2020), with a higher placebo response seen in studies with a larger number of study sites (Li et al., 2019; Meister et al., 2020) and those using clinician rating rather than self-rating (Meister et al., 2020). The placebo response to antidepressants in children and adolescents appears to be greater in MDD than in anxiety disorders (Cohen et al., 2008), and it exceeds that observed in studies of adult MDD (Meister et al., 2020).

Against this background, we sought to review industry-funded studies of antidepressants in children and adolescents with MDD, and to better understand the contribution of study design and placebo response to the findings of these studies. Specifically, we sought to draw upon our group's earlier work that examined the probability of placebo (Papakostas and Fava, 2009) as well as the degree of improvement in the placebo group (Iovieno et al., 2021; Iovieno and Papakostas, 2012) as predictors of antidepressant-placebo effect size.

2. Material and methods

2.1. Data sources and search strategy

Studies were first identified using a search of PubMed on January 8, 2021. Searches were conducted by cross-referencing the terms “placebo” and “adolescent” and “antidepressant” and “major depressive”. The PubMed search was repeated using the following terms: “placebo” and “children” and “antidepressant” and “major depressive”. A further search using the Cochrane Library, Embase, PsycINFO and CINAHL yielded no additional manuscripts for inclusion. No language or year of publication restrictions were used. This was supplemented by searching www.clinicaltrials.gov, followed by www.clinicaltrialsregister.eu for relevant studies.

2.2. Study selection

We selected randomized, double-blind, placebo-controlled clinical trials comparing antidepressants and placebo for the acute treatment of MDD in children and/or adolescents. We then selected studies that also met the following inclusion criteria:

- 1) Studies that used the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985)
- 2) Studies that exclusively focused on patients with MDD.

Reports were excluded if they:

- 1) Were not funded by industry
- 2) Exclusively focused on MDD subjects enriched for a particular axis-I or -III disorder
- 3) Did not involve selective serotonin reuptake inhibitors (SSRIs) or newer agents approved in the U.S. or E.U. for the treatment of MDD in adults
- 4) Did not describe original data (i.e., contained data published elsewhere)
- 5) Did not focus on the acute phase of treatment (i.e., continuation, maintenance, relapse prevention).

2.3. Data extraction

Data were extracted with the use of a pre-coded form. The following data were extracted from trials included in the study: mean baseline CDRS-R severity, percent adolescents in total sample, mean age, probability of receiving placebo, study duration, medications and dosages, the number of patients randomized to each treatment arm, CDRS-R mean change in scores from baseline to endpoint and their corresponding standard deviation or standard errors. Data were screened and extracted by two of the authors (GIP and NI). Any discrepancies were resolved in a joint meeting when compiling the final dataset. In the case of missing data, these were obtained by directly contacting the sponsor.

2.4. Quantitative data synthesis

Random-effects meta-analysis and meta-regression were utilized with the change in CDRS-R symptom score over time as the dependent variable. For studies which examined different doses of the same drug, each dose was compared separately to placebo. All analyses utilized the meta package of meta-analytic tools as implemented in Stata 15 (College Station, TX). Meta-regressions were completed to examine the relationship between specific covariates of interest and the effect size, including baseline severity, mean age and percentage of adolescent patients.

3. Results

A total of 989 abstracts were identified with the use of PubMed. Of these, 958 were excluded because they did not describe eligible studies (open-label studies, reviews, meta-analyses, post-hoc analyses, studies of healthy subjects, studies of other disorders or unrelated abstracts). Nine abstracts were excluded because they studied antidepressants as adjuncts to psychotherapy (Cornelius et al., 2010, 2009; Davey et al., 2019; Dinan, 2000; Goodyer et al., 2008; Iftene et al., 2015; Mandoki et al., 1997; Melvin et al., 2006; Riggs et al., 2007); three because they did not use the CDRS-R (Berard et al., 2006; Keller et al., 2001; Von Knorring et al., 2006); two because they did not focus on FDA or EMA-approved agents (Berk et al., 2020; Gabbay et al., 2018); one because it focused on subjects with alcohol or cannabis use disorder and depression (Findling et al., 2009); and one because it was not funded by industry (March, 2004). The remaining 15 manuscripts described eligible trials (Durgam et al., 2018) (Findling et al., 2020) (Atkinson et al., 2014) (Emslie et al., 2014) (Atkinson et al., 2018) (Weihs et al., 2018) (Emslie et al., 2007) (Emslie et al., 1997) (Emslie et al., 2002) (Wagner et al., 2003) (Emslie et al., 2006) (Wagner et al., 2004) (Emslie et al., 2009) (Wagner et al., 2006) (DelBello et al., 2014). Three additional unpublished studies, NCT02709746, NCT02431806, and NCT00812812 were identified with the use of www.clinicaltrials.gov (<https://clinicaltrials.gov/ct2/show/NCT02709746>; <https://clinicaltrials.gov/ct2/show/NCT02431806>; <https://clinicaltrials.gov/ct2/show/NCT00812812>). Finally, one unpublished study, 2015-002181-23, was identified with the use of www.clinicaltrialsregister.eu (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-002181-23/results>). These 15 published studies and four unpublished trials yielded 34 drug-placebo comparisons for inclusion in the meta-analysis. A PRISMA flow

diagram of this information is shown in Fig. 1.

These trials and some of their characteristics are outlined in Table 1. All identified manuscripts were in English. All studies used the CDRS-R as an outcome measure. Mean CDRS-R score changes, and their standard deviations (SD), from baseline to endpoint were available for all treatment arms. In summary, the pooled dataset involved 6161 subjects randomized to antidepressants ($n = 3844$) or placebo ($n = 2317$).

Subjects ranged in age from seven to 17 years, with a mean age of 13.15 years (SD 1.07), a mean proportion of adolescents in the sample of 67.55% (SD 21.12) and a mean baseline severity (CDRS-R score) of 58.73 (SD 2.80).

The standardized mean difference (SMD) among all studies was 0.12 (Confidence Interval (CI) 0.08, 0.17; $p < 0.001$), with a heterogeneity estimate (Tau-squared) of 0.0027 (heterogeneity $p = 0.250$) (Fig. 2). The

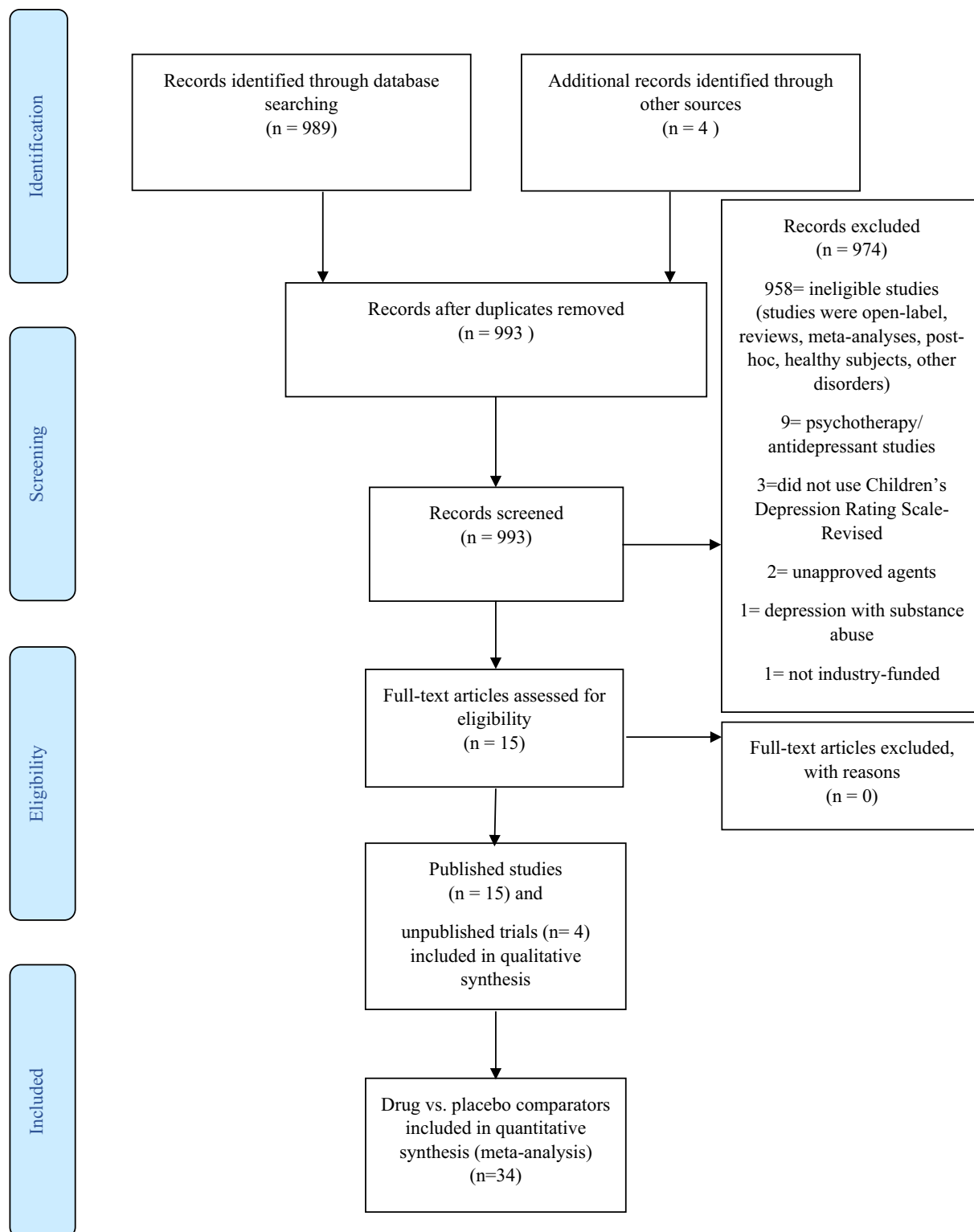


Fig. 1. PRISMA diagram of study flow.

Table 1
Trials information.

Study arm/ publication	Year	Drug	Duration (weeks)	Age range	Mean age	N drug	Mean change CDRS-R drug	N placebo	Mean change CDRS-R placebo	Prop. adolesc.	Prob. placebo	Baseline severity
NCT02709746	2020	Vortioxetine 10 mg	8	12 to 17	14.6	126	−17.09	137	−18.22	1.0	0.25	63.85
NCT02709746	2020	Vortioxetine 20 mg	8	12 to 17	14.6	139	−18.94	137	−18.22	1.0	0.25	63.85
NCT02709746	2020	Fluoxetine 20 mg	8	12 to 17	14.6	137	−21.95	137	−18.22	1.0	0.25	63.85
Durgam et al., 2018	2018	Vilazodone 15 mg	8	12 to 17	14.8	174	−22.94	170	−22.48	1.0	0.33	57.2
Durgam et al., 2018	2018	Vilazodone 30 mg	8	12 to 17	14.8	180	−24.22	170	−22.48	1.0	0.33	57.2
Findling et al., 2020	2020	Vilazodone 15–30 mg	8	7 to 17	13	186	−20.72	182	−20.32	0.69	0.4	57.8
Findling et al., 2020	2020	Fluoxetine 20 mg	8	7 to 17	13	97	−22.71	182	−20.32	0.69	0.4	57.8
NCT02431806	2020	Levomilnacipran 40 mg	8	12 to 17	14.7	115	−23.28	118	−22.9	1.0	0.25	60.95
NCT02431806	2020	Levomilnacipran 80 mg	8	12 to 17	14.7	110	−22.64	118	−22.9	1.0	0.25	60.95
NCT02431806	2020	Fluoxetine 20 mg	8	12 to 17	14.7	112	−24.37	118	−22.9	1.0	0.25	60.95
Atkinson et al., 2014	2014	Duloxetine 60–120 mg	10	7 to 17	13.16	113	−24.3	103	−24.3	0.6	0.33	59.4
Atkinson et al., 2014	2014	Fluoxetine 20 mg	10	7 to 17	13.16	113	−23.7	103	−24.3	0.6	0.33	59.4
Emslie et al., 2014	2014	Duloxetine 30 mg	10	7 to 17	13	114	−24.6	117	−21.6	0.59	0.25	58.8
Emslie et al., 2014	2014	Duloxetine 60 mg	10	7 to 17	13	105	−23.9	117	−21.6	0.59	0.25	58.8
Emslie et al., 2014	2014	Fluoxetine 20 mg	10	7 to 17	13	112	−22.6	117	−21.6	0.59	0.25	58.8
Atkinson et al., 2018	2018	DVS SR 20–25 mg	8	7 to 17	13	120	−23.7	119	−22.85	0.69	0.33	58
Atkinson et al., 2018	2018	DVS SR 25–50 mg	8	7 to 17	13	121	−24.3	119	−22.85	0.69	0.33	58
Weihls et al., 2018	2017	DVS SR 25–50 mg	8	7 to 17	12.7	99	−22.61	99	−23.07	0.61	0.33	56.8
Weihls et al., 2018	2017	Fluoxetine 20 mg	8	7 to 17	12.7	101	−24.79	99	−23.07	0.61	0.33	56.8
Emslie et al., 2007 study 1	2007	Venlafaxine XR 37.5–225 mg	8	7 to 17	12.2	80	−18.1	85	−16.1	0.45	0.5	56
Emslie et al., 2007 study 2	2007	Venlafaxine XR 37.5–225 mg	8	7 to 17	12.2	101	−24.6	92	−22.8	0.45	0.5	56
2015-002181-23	2020	Agomelatine 10 mg	12	7 to 17	13.6	102	−20.9	101	−19.7	0.8	0.25	
2015-002181-23	2020	Agomelatine 25 mg	12	7 to 17	13.6	94	−22.5	101	−19.7	0.8	0.25	
2015-002181-23	2020	Fluoxetine 20 mg	12	7 to 17	13.6	99	−21.7	101	−19.7	0.8	0.25	
DelBello et al., 2014	2014	Selegiline Patch	12	12 to 17	14.7	150	−21.4	154	−21.5	1.0	0.5	57.3
Emslie et al., 1997	1997	Fluoxetine 20 mg	8	7 to 17	12.2	48	−20.2	48	−10.5	0.5	0.5	58
Emslie et al., 2002	2002	Fluoxetine 20 mg	9	7 to 17	12.7	109	−22.1	110	−14.9	0.44	0.5	57.1
Wagner et al., 2003 study 1	2003	Sertraline 50–200 mg	10	7 to 17	12	93	−26.1	88	−21.9	0.54	0.5	64
Wagner et al., 2003 study 2	2003	Sertraline 50–200 mg	10	7 to 17	12	92	−28.3	91	−26.1	0.51	0.5	65
Emslie et al., 2006	2006	Paroxetine 10–50 mg	8	7 to 17	12	101	−22.6	102	−23.4	0.52	0.5	59
NCT00812812	2017	Paroxetine 10 mg–20 mg	8	7 to 17	14.6	29	−16.5	27	−11.9		0.5	
Wagner et al., 2004	2004	Citalopram 20–40 mg	8	7 to 17	12.1	89	−21.7	85	−16.5	0.52	0.5	58.3
Emslie et al., 2009	2009	Escitalopram 10–20 mg	8	12 to 17	14.6	154	−22.4	157	−18.4	1.0	0.5	56.8
Wagner et al., 2006	2006	Escitalopram 10–20 mg	8	7 to 17	12.3	129	−20.9	132	−20.3	0.6	0.5	55.5

CDRS-R = Children's Depression Rating Scale-Revised.

Prop. adolesc. = proportion of study sample that were adolescents.

Prob. placebo = the probability of receiving placebo rather than active drug in each study.

Baseline severity = CDRS-R score at baseline.

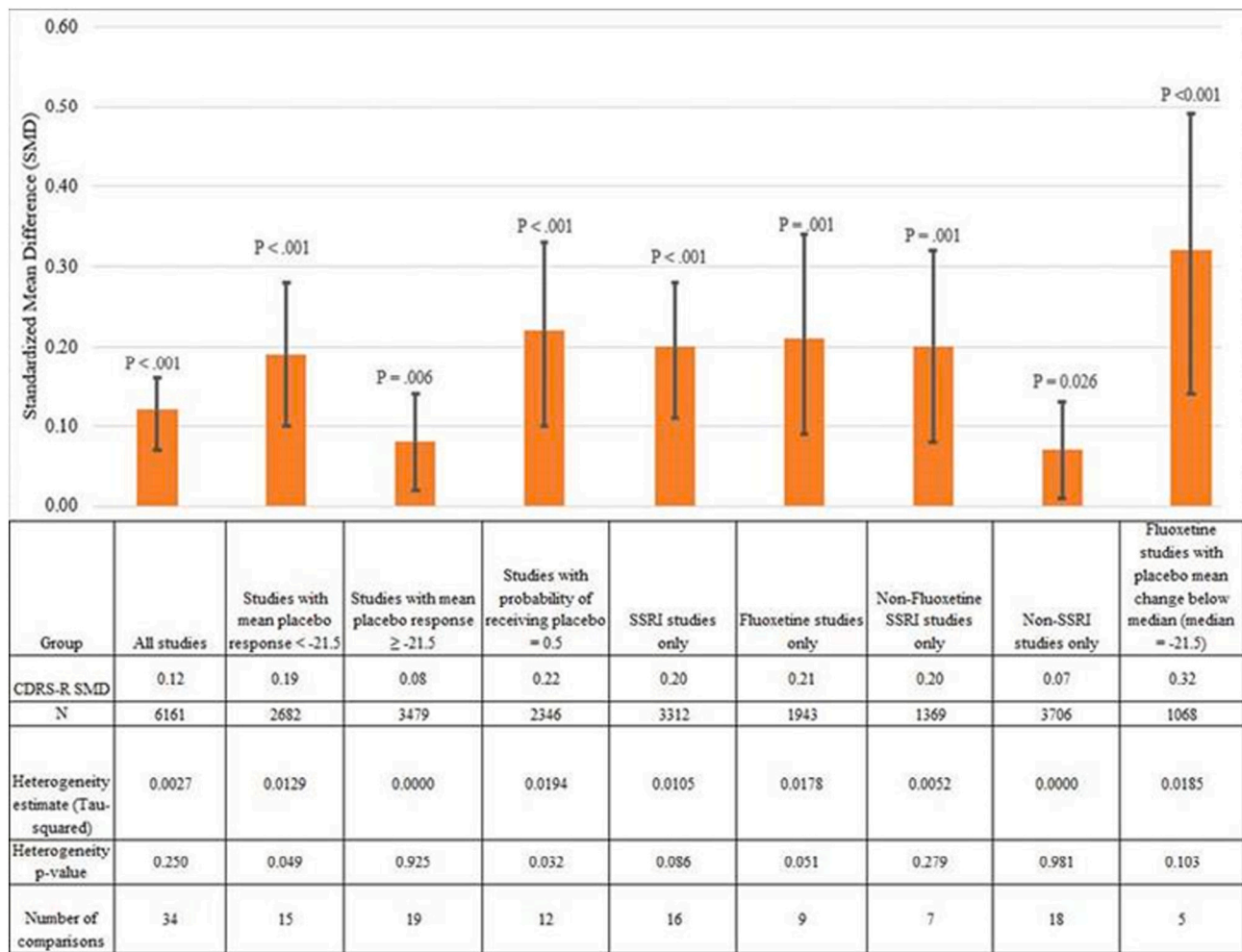
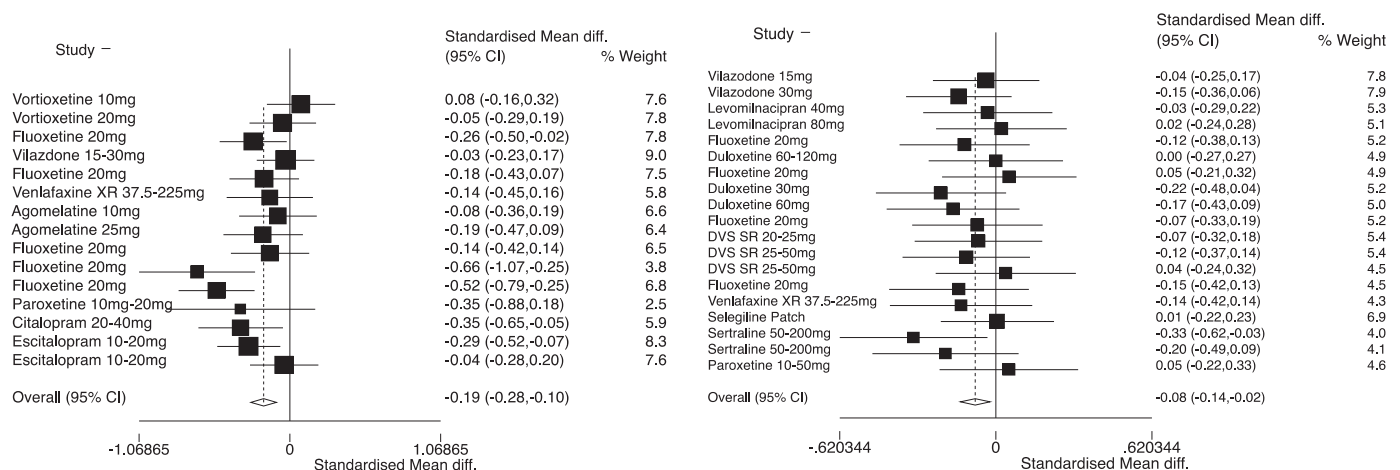


Fig. 2. Meta-analyses: all studies and sub-groups.

mean change in CDRS-R score with antidepressant treatment was -22.45 (SD 2.42) and the mean change with placebo was -19.99 (SD 4.07). The median change in CDRS-R score with placebo was -21.5 . Several subgroup meta-analyses were completed and are described in Fig. 2. When the meta-analysis was limited to studies with a mean placebo response below the median for all studies (-21.5), the SMD was 0.19 (CI 0.10, 0.28; $p < 0.001$) and when limited to studies with a mean

placebo response above the median SMD was 0.08 (CI 0.02, 0.14; $p = 0.006$) (Fig. 3). The SMD was 0.22 (CI 0.11, 0.34; $p < 0.001$) among studies with a probability of receiving placebo of 0.5 (Fig. 4), 0.20 (CI 0.12, 0.29; $p < 0.001$) among SSRI studies, 0.21 (CI 0.08, 0.33; $p = 0.001$) among Fluoxetine studies, 0.20 (CI 0.08, 0.32; $p = 0.001$) among non-Fluoxetine SSRI studies, 0.07 (CI 0.01, 0.13; $p = 0.026$) among non-SSRI studies, and 0.32 (CI 0.15, 0.50; $p < 0.001$) among Fluoxetine

Fig. 3. Meta-analyses including only studies with a placebo mean change < -21.5 (left) or ≥ -21.5 (right).

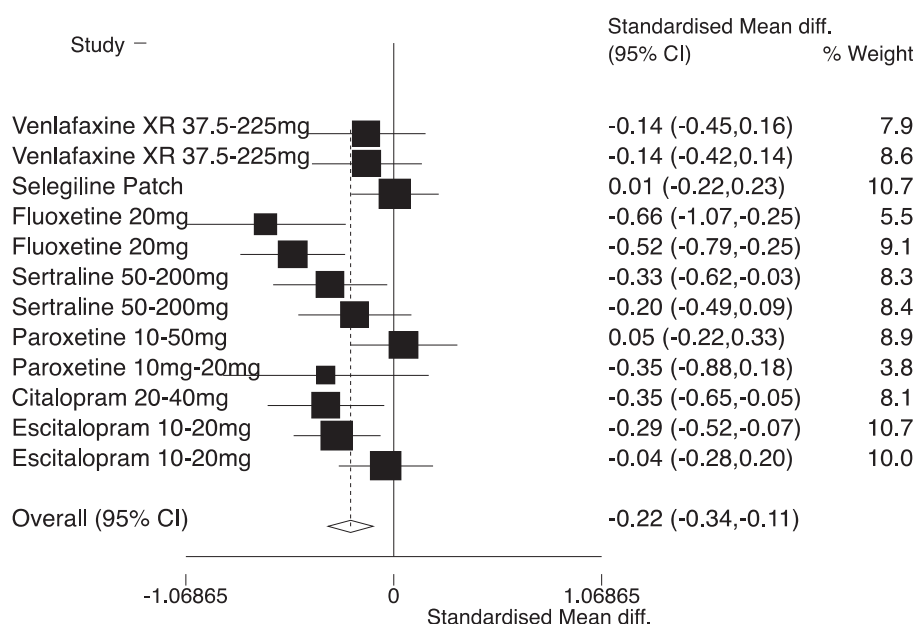


Fig. 4. Meta-analysis including only studies with a probability of receiving placebo of 0.5.

studies with mean placebo change below the median (Fig. 2). None of the meta-regressions examining covariates of interest yielded significant findings: baseline severity ($z = 0.02, p = 0.986$); mean age ($z = 0.15, p = 0.884$); and percentage of adolescent patients ($z = 0.17, p = 0.869$).

4. Discussion

In this systematic review and meta-analysis of industry-funded antidepressant trials in pediatric subjects, 34 drug-placebo comparisons were pooled, involving 6161 participants. The SMD in CDRS-R change across all studies was 0.12, a very small effect size, without significant statistical heterogeneity. This modest SMD may reflect several factors including study design (i.e. probability of receiving placebo), study informativeness (greater placebo response corresponding to less informative studies), misdiagnosis, lower outcome measure sensitivity to detect a signal, and the application of drugs developed for adults to pediatric populations (under the assumption that these are efficacious in the latter population). The very small effect sized found in this study is in keeping with the findings of a recent network meta-analysis of 26 randomized trials of antidepressants in children and adolescents with depression (Hetrick et al., 2021). The authors of that meta-analysis concluded that most antidepressants examined may be associated with a “small and unimportant” reduction in depressive symptoms, as measured by change in CDRS-R scores, compared to placebo. The largest identified reduction in CDRS-R score was 3.5 points for Sertraline compared to placebo; for Fluoxetine, this reduction was 2.8 points.

To put our findings in perspective, the SMD identified in this study of pediatric subjects is markedly lower (almost one third) than an SMD of 0.30 found in a recent meta-analysis of antidepressants in adults with MDD (CI 0.26, 0.34; $p < 0.0001$) (Cipriani et al., 2018). Similarly, with atypical anti-psychotic augmentation in adults with MDD, SMDs are higher and range from -0.27 to -0.43 (Zhou et al., 2015b). When compared with psychotherapy interventions for pediatric depression, again the SMD found in this analysis is low. SMDs of -0.41 (Oud et al., 2019) and -0.47 to -0.96 (Zhou et al., 2015a) are reported for CBT and Interpersonal Therapy studies in depressed children and adolescents. However, a meta-analysis of psychotherapy for pre-adolescent children only did not show significance (SMD -0.34 , CI -0.961 , 0.278 ; $p = 0.280$) (Forti-Buratti et al., 2016) and placebo response is also considerable in youth psychotherapy studies (Weisz et al., 2017).

Given that study design can influence placebo response rate in

studies of adults with MDD (Iovieno and Papakostas, 2012; Papakostas et al., 2015; Papakostas and Fava, 2009) and pediatric MDD studies with a lower placebo response show greater drug-placebo separation (Li et al., 2019), we investigated the impact of mean placebo improvement on effect size. When studies with lower placebo improvement (mean placebo change below the median) were analyzed, the SMD increased to 0.19 (with significant heterogeneity, likely reflecting study design factors) and increased further when only fluoxetine studies with lower placebo improvement were analyzed (SMD 0.32). When studies with higher placebo improvement were considered (mean placebo change equal to or above the median), the SMD dropped to 0.08 (without significant heterogeneity, which may reflect studies that are uniformly uninformative regardless of the agent chosen). When only studies where there was at least a 50% chance of receiving placebo were included in the meta-analysis the SMD was 0.22, higher than the main meta-analysis, suggesting that such a study design may enhance signal detection. All SSRI subgroup meta-analyses had larger effect sizes than that seen in the main meta-analysis (0.20 to 0.32), supporting their current centrality in pediatric MDD treatment. In contrast, the totality of the data does not support the use of non-SSRIs in pediatric populations with MDD.

Misdiagnosis may be a contributing factor to the higher placebo response rates reported in these studies. While we see a marked increase in the adoption of independent adjudication and validation of adults with MDD participating in clinical trials, with subsequent decrease in placebo response rates (Freeman et al., 2017), these independent assessments are not typically adopted in pediatric MDD trials. This may have led to the enrollment of patients with depressive symptoms that are actually not due to MDD, and therefore more likely to have spontaneous improvements or fluctuations.

Another possible contributing factor to the higher placebo response rates in these studies may be the lower outcome measure sensitivity to detect a signal. Adult studies typically use scales such as the Hamilton Rating Scale for Depression and the Montgomery-Asberg Depression Rating Scale, measures with well-known psychometric and clinimetric properties, as well as adequate sensitivity to detect therapeutic signals (Carrozzino et al., 2020; Kjærgaard et al., 2014), while the pediatric MDD studies typically utilize the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985). It is quite possible that the CDRS-R may not be as sensitive to detect therapeutic signal as the scales used in adults.

Our findings also strongly suggest the need for tailored antidepressant drug development for children and adolescents, rather than the current model of trialing adult-approved drugs in children with the CDRS-R as the primary outcome measure and without independent adjudication or validation of enrolled subjects. MDD, a disorder whose clinical presentation is different in pediatric and adult populations (Rice et al., 2019a), may also require distinct treatment strategies for these two groups. This is most clearly seen in the case of non-SSRI agents. Factors to consider may include the greater genetic overlay of early-onset pediatric depression with bipolar affective disorder, schizophrenia and ADHD compared to late adolescent onset (Power et al., 2017; Rice et al., 2019b; Verduijn et al., 2017), with a greater risk of misclassification and misdiagnosis, particularly when the studies are conducted without independent adjudication; the influence of changing drug metabolism throughout development (Ramsey et al., 2019) and the prominence of certain somatic symptoms (particularly headache and fatigue) in adolescent depression (Ramsey et al., 2019).

Finally, in considering clinical trial design, to maximize the possibility of seeing a drug-placebo difference where such a difference exists, several factors should be considered including the proportion of subjects receiving placebo and the influence of placebo response on trial outcome. There is good evidence that higher placebo response rates lead to smaller effect sizes (Iovieno and Papakostas, 2012). The benefit of adding an active treatment arm involving an approved antidepressant (fluoxetine or escitalopram) should be carefully weighted with the risk an uninformative study due to high placebo response rate when fewer patients are assigned to placebo.

The strength of our present work includes the relatively large number of studies pooled, the uniformity of the outcome measure (CDRS-R) across studies, and that estimates of treatment effect (mean, standard deviation) were available for all studies deemed eligible for inclusion. Limitations of our work include the fact that some trials (three out of 22 or 13.6%) could not be included because they did not involve the use of the CDRS-R. In addition, it should be noted that the mean age of the pooled sample was rather uniform (13.15 years, SD 1.07) bringing into question whether these findings would apply to patients much younger or older than 13–14. Looking at mean and standard deviations from individual studies, it appears that many focused on older children and younger adolescents.

In conclusion, currently approved antidepressants for children and adolescents with MDD have small effect sizes and many antidepressant trials in this population fail. Antidepressant drug development for children and adolescents needs to be tailored, rather than simply applying adult-approved treatments to children. The influence of placebo response should be considered in pediatric MDD clinical trial design and implementation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

All authors substantially contributed to the conception of the work, had full access to all the data in the study and had final responsibility for the decision to submit for publication. Individual study data was gathered and verified by GIP, AF and RSH. NI and AF did the data analysis. Tables and figures were prepared by AF, RSH, NI and JMHO. The manuscript was drafted and revised by AF, RSH, MF, NI, JMHO and GIP.

Declaration of competing interest

Anna Feeney, Rebecca S. Hock, Nadia Iovieno and Jesús M. Hernández Ortiz report no financial relationships with commercial interests.

Disclosures (lifetime): Maurizio Fava, MD

All disclosures can also be viewed online by navigating to: <https://mghcme.org/faculty> >Maurizio Fava, MD>View Bio>View Disclosures Here.

Research Support: Abbott Laboratories; Acadia Pharmaceuticals; Alkermes, Inc.; American Cyanamid; Aspect Medical Systems; AstraZeneca; Avanir Pharmaceuticals; AXSOME Therapeutics; BioClinica, Inc.; Biohaven; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; CeNeRx BioPharma; Centrexion Therapeutics Corporation; Cephalon; Cerecor; Clarus Funds; Clexio Biosciences; Clintara, LLC; Covance; Covidien; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; FORUM Pharmaceuticals; Ganeden Biotech, Inc.; Gentelon, LLC; GlaxoSmithKline; Harvard Clinical Research Institute; Hoffman-LaRoche; Icon Clinical Research; Indivior; i3 Innovus/Ingenix; Janssen R&D, LLC; Jed Foundation; Johnson & Johnson Pharmaceutical Research & Development; Lichtwer Pharma GmbH; Lorex Pharmaceuticals; Lundbeck Inc.; Marinus Pharmaceuticals; MedAvante; Methylation Sciences Inc; National Alliance for Research on Schizophrenia & Depression (NARSAD); National Center for Complementary and Alternative Medicine (NCCAM); National Coordinating Center for Integrated Medicine (NiiCM); National Institute of Drug Abuse (NIDA); National Institutes of Health; National Institute of Mental Health (NIMH); Neuralstem, Inc.; NeuroRx; Novartis AG; Novaremed; Organon Pharmaceuticals; Otsuka Pharmaceutical Development, Inc.; PamLab, LLC.; Pfizer Inc.; Pharmacia-Upjohn; Pharmaceutical Research Associates, Inc.; Pharmavite® LLC; PharmoRx Therapeutics; Photothera; Praxis Precision Medicines; Premiere Research International; Protagenic Therapeutics, Inc.; Reckitt Benckiser; Relmada Therapeutics Inc.; Roche Pharmaceuticals; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Sanofi-Aventis US LLC; Shenox Pharmaceuticals, LLC; Shire; Solvay Pharmaceuticals, Inc.; Stanley Medical Research Institute (SMRI); Synthelabo; Taisho Pharmaceuticals; Takeda Pharmaceuticals; Tal Medical; VistaGen; WinSanTor, Inc.; Wyeth-Ayerst Laboratories.

Advisory Board/Consultant: Abbott Laboratories; Acadia; Aditum Bio Management Company, LLC; Affectis Pharmaceuticals AG; Alfa-sigma USA, Inc.; Alkermes, Inc.; Altimate Health Corporation; Amarin Pharma Inc.; Amorsa Therapeutics, Inc.; Ancora Bio, Inc.; Angelini S.p. A; Aptinyx Inc.; Arbor Pharmaceuticals, LLC; Aspect Medical Systems; Astella Pharma Global Development, Inc.; AstraZeneca; Auspex Pharmaceuticals; Avanir Pharmaceuticals; AXSOME Therapeutics; Bayer AG; Best Practice Project Management, Inc.; Biogen; BioMarin Pharmaceuticals, Inc.; BioXcel Therapeutics; Biovail Corporation; Boehringer Ingelheim; Boston Pharmaceuticals; BrainCells Inc; Bristol-Myers Squibb; Cambridge Science Corporation; CeNeRx BioPharma; Cephalon, Inc.; Cerecor; Clexio Biosciences; Click Therapeutics, Inc.; CNS Response, Inc.; Compellis Pharmaceuticals; Cybin Corporation; Cypress Pharmaceutical, Inc.; Diagnostics Life Sciences (P) Ltd.; Dainippon Sumitomo Pharma Co. Inc.; Dr. Katz, Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; ElMindA; EnVivo Pharmaceuticals, Inc.; Enzymotec LTD; ePharmaSolutions; EPIX Pharmaceuticals, Inc.; Esthismos Research, Inc.; Euthymics Bioscience, Inc.; Evecxia Therapeutics, Inc.; ExpertConnect, LLC; FAAH Research Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; Forum Pharmaceuticals; Gate Neurosciences, Inc.; GenetikaPlus Ltd.; GenOmind, LLC; GlaxoSmithKline; Grunenthal GmbH; Happify; H. Lundbeck A/S; Indivior; i3 Innovus/Ingenix; Intracellular; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc.; JDS Therapeutics, LLC; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; Marinus Pharmaceuticals; MedAvante, Inc.; Merck & Co., Inc.; Mind Medicine Inc.; MSI Methylation Sciences, Inc.; Naurex, Inc.; Navitor Pharmaceuticals, Inc.; Nestle Health Sciences; Neuralstem, Inc.; Neurocrine Biosciences, Inc.; Neuronetics, Inc.; NextWave Pharmaceuticals; Niraxx Light Therapeutics, Inc; Northwestern University; Novartis AG; Nutrition 21; Opiant Pharmaceuticals; Orexigen Therapeutics, Inc.;

Organon Pharmaceuticals; Osmotica; Otsuka Pharmaceuticals; Ovid Therapeutics, Inc.; PamLab, LLC.; Perception Neuroscience; Pfizer Inc.; PharmaStar; PharmaTher Inc.; Pharmavite® LLC.; PharmsRx Therapeutics; Polaris Partners; Praxis Precision Medicines; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc.; Protagenic Therapeutics, Inc.; PPD; PThera, LLC.; Purdue Pharma; Puretech Ventures; Pure Tech LYT, Inc.; PsychoGenics; Psylin Neurosciences, Inc.; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC); Relmada Therapeutics, Inc.; Rexahn Pharmaceuticals, Inc.; Ridge Diagnostics, Inc.; Roche; Sanofi-Aventis US LLC.; Sensorium Therapeutics; Sentier Therapeutics; Sepacor Inc.; Servier Laboratories; Schering-Plough Corporation; Shenox Pharmaceuticals, LLC; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Sonde Health; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.; Synthelabo; Taisho Pharmaceuticals; Takeda Pharmaceutical Company Limited; Tal Medical, Inc.; Tetraxenex; Teva Pharmaceuticals; TransForm Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; University of Michigan, Department of Psychiatry; Usona Institute, Inc.; Vanda Pharmaceuticals, Inc.; Versant Venture Management, LLC; VistaGen; Xenon Pharmaceuticals Inc.

Speaking/Publishing: Adamed, Co; Advanced Meeting Partners; American Psychiatric Association; American Society of Clinical Psychopharmacology; AstraZeneca; Belvoir Media Group; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Cephalon, Inc.; CME Institute/Physicians Postgraduate Press, Inc.; Eli Lilly and Company; Forest Pharmaceuticals, Inc.; GlaxoSmithKline; Global Medical Education, Inc.; Imedex, LLC; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier; Novartis AG; Organon Pharmaceuticals; Pfizer Inc.; PharmaStar; United BioSource, Corp.; Wyeth-Ayerst Laboratories.

Stock/Other Financial Options:

Equity Holdings: Compellis; Psy Therapeutics; Sensorium Therapeutics.

Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691).

Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Lippincott, Williams & Wilkins; Wolters Kluwer; World Scientific Publishing Co. Pte. Ltd.

Dr Papakostas: Dr. Papakostas has served as a consultant for Abbott Laboratories, Acadia Pharmaceuticals, Inc.*, Alkermes, Inc., Alphasigma USA*, Inc., AstraZeneca PLC, Avanir Pharmaceuticals, Axsome Therapeutics*, Boston Pharmaceuticals, Inc.*, Brainsway Ltd., Bristol-Myers Squibb Company, Cala Health*, Cephalon Inc., Dey Pharma, L.P., Eleusis health solutions ltd*, Eli Lilly Co., Genentech, Inc.*, Genomind, Inc.*, GlaxoSmithKline, Evotec AG, H. Lundbeck A/S, Inflabloc Pharmaceuticals, Janssen Global Services LLC*, Jazz Pharmaceuticals, Johnson & Johnson Companies*, Methylation Sciences Inc., Mylan Inc. *, Novartis Pharma AG, One Carbon Therapeutics, Inc.*, Osmotica Pharmaceutical Corp.*, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc., Pierre Fabre Laboratories, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sage Therapeutics*, Shire Pharmaceuticals, Sunovion Pharmaceuticals, Taisho Pharmaceutical Co, Ltd.*, Takeda Pharmaceutical Company LTD, Theracos, Inc., and Wyeth, Inc.

Dr. Papakostas has received honoraria (for lectures or consultancy) from Abbott Laboratories, Acadia Pharmaceuticals Inc., Alkermes Inc., Alphasigma USA Inc., Asopharma America Central Y Caribe, AstraZeneca PLC, Avanir Pharmaceuticals, Bristol-Myers Squibb Company, Brainsway Ltd., Cephalon Inc., Dey Pharma, L.P., Eli Lilly Co., Evotec AG, Forest Pharmaceuticals, GlaxoSmithKline, Inflabloc Pharmaceuticals,

Grunbionics Pty LTD, Hypera S.A., Jazz Pharmaceuticals, H. Lundbeck A/S, Medichem Pharmaceuticals, Inc., Meiji Seika Pharma Co. Ltd., Novartis Pharma AG, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer, Pharma Trade SAS, Pierre Fabre Laboratories, Ridge Diagnostics, Shire Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Pharmaceutical Company LTD, Theracos, Inc., Titan Pharmaceuticals, and Wyeth Inc.

Dr. Papakostas has received research support (paid to hospital) from AstraZeneca PLC, Bristol-Myers Squibb Company, Cala Health, Forest Pharmaceuticals, the National Institute of Mental Health, Mylan Inc., Neuralstem, Inc.*, PAMLAB LLC, PCORI, Pfizer Inc., Johnson & Johnson Companies, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sunovion Pharmaceuticals, Tal Medical, and Theracos, Inc.

Dr. Papakostas has served (not currently) on the speaker's bureau for BristolMyersSquibb Co and Pfizer, Inc.

* Asterisk denotes consulting activity undertaken on behalf of Massachusetts General Hospital.

Acknowledgements

None.

References

- Active Reference (Fluoxetine) Fixed-dose Study of Vortioxetine in Paediatric Patients Aged 12 to 17 Years With Major Depressive Disorder (MDD) - Full Text View - ClinicalTrials.gov [WWW Document]. n.d. URL: <https://clinicaltrials.gov/ct2/show/NCT02709746> (accessed 2.18.21).
- Atkinson, S., Lubaczewski, S., Ramaker, S., England, R.D., Wajsbrot, D.B., Abbas, R., Findling, R.L., 2018. Desvenlafaxine versus placebo in the treatment of children and adolescents with major depressive disorder. *J. Child Adolesc. Psychopharmacol.* 28, 55–65. <https://doi.org/10.1089/cap.2017.0099>.
- Atkinson, S.D., Prakash, A., Zhang, Q., Pangallo, B.A., Bangs, M.E., Emslie, G.J., March, J.S., 2014. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J. Child Adolesc. Psychopharmacol.* 24, 180–189. <https://doi.org/10.1089/cap.2013.0146>.
- Berard, R., Fong, R., Carpenter, D.J., Thomason, C., Wilkinson, C., 2006. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J. Child Adolesc. Psychopharmacol.* 16, 59–75. <https://doi.org/10.1089/cap.2006.16.59>.
- Berk, M., Mohebbi, M., Dean, O.M., Cotton, S.M., Chanan, A.M., Dodd, S., Ratheesh, A., Amminger, G.P., Phelan, M., Weller, A., MacKinnon, A., Giorlando, F., Baird, S., Incerti, L., Brodie, R.E., Ferguson, N.O., Rice, S., Schäfer, M.R., Mullen, E., Hetrick, S., Kerr, M., Harrigan, S.M., Quinn, A.L., Mazza, C., McGorry, P., Davey, C. G., 2020. Youth depression alleviation with anti-inflammatory agents (YoDA-A): a randomised clinical trial of rosvastatin and aspirin. *BMC Med.* 18 <https://doi.org/10.1186/s12916-019-1475-6>.
- Birmaher, B., Brent, D., AACAP Work Group on Quality Issues, Bernet, W., Bukstein, O., Walter, H., Benson, R.S., Chrisman, A., Farchione, T., Greenhill, L., Hamilton, J., Keable, H., Kinlan, J., Schoettle, U., Stock, S., Ptakowski, K.K., Medicus, J., 2007. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J. Am. Acad. Child Adolesc. Psychiatry* 46 (11), 1503–1526. <https://doi.org/10.1097/chi.0b013e318145ae1c>.
- Carrozzino, D., Patierno, C., Fava, G.A., Guidi, J., 2020. The Hamilton rating scales for depression: a critical review of clinimetric properties of different versions. *Psychother. Psychosom.* <https://doi.org/10.1159/000506879>.
- Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J.P.A., Geddes, J.R., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391, 1357–1366. [https://doi.org/10.1016/S0140-6736\(17\)32802-7](https://doi.org/10.1016/S0140-6736(17)32802-7).
- Cipriani, A., Zhou, X., Del Giovane, C., Hetrick, S.E., Qin, B., Whittington, C., Coghill, D., Zhang, Y., Hazell, P., Leucht, S., Cuijpers, P., Pu, J., Cohen, D., Ravindran, A.V., Liu, Y., Michael, K.D., Yang, L., Liu, L., Xie, P., 2016. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 388, 881–890. [https://doi.org/10.1016/S0140-6736\(16\)30385-3](https://doi.org/10.1016/S0140-6736(16)30385-3).
- Cohen, D., Deniau, E., Maturana, A., Tanguy, M.L., Bodeau, N., Labelle, R., Breton, J.J., Guile, J.M., 2008. Are child and adolescent responses to placebo higher in major depression than in anxiety disorders? A systematic review of placebo-controlled trials. *PLoS One*. <https://doi.org/10.1371/journal.pone.0002632>.
- Cornelius, J.R., Bukstein, O.G., Douaihy, A.B., Clark, D.B., Chung, T.A., Daley, D.C., Wood, D.S., Brown, S.J., 2010. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. *Drug Alcohol Depend.* 112, 39–45. <https://doi.org/10.1016/j.drugalcdep.2010.05.010>.
- Cornelius, J.R., Bukstein, O.G., Wood, D.S., Kirisci, L., Douaihy, A., Clark, D.B., 2009. Double-blind placebo-controlled trial of fluoxetine in adolescents with comorbid

- major depression and an alcohol use disorder. *Addict. Behav.* 34, 905–909. <https://doi.org/10.1016/j.addbeh.2009.03.008>.
- Cox, G.R., Callahan, P., Churchill, R., Hunot, V., Merry, S.N., Parker, A.G., Hetrick, S.E., 2014. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst. Rev.* <https://doi.org/10.1002/14651858.CD008324.pub3>.
- Davey, C.G., Channen, A.M., Hetrick, S.E., Cotton, S.M., Ratheesh, A., Amminger, G.P., Koutsogiannis, J., Phelan, M., Mullen, E., Harrison, B.J., Rice, S., Parker, A.G., Dean, O.M., Weller, A., Kerr, M., Quinn, A.L., Catania, L., Kazantzis, N., McGorry, P. D., Berk, M., 2019. The addition of fluoxetine to cognitive behavioural therapy for youth depression (YoDA-C): a randomised, double-blind, placebo-controlled, multicentre clinical trial. *Lancet Psychiatry* 6, 735–744. [https://doi.org/10.1016/S2215-0366\(19\)30215-9](https://doi.org/10.1016/S2215-0366(19)30215-9).
- DelBello, M.P., Hochadel, T.J., Portland, K.B., Azzaro, A.J., Katic, A., Khan, A., Emslie, G., 2014. A double-blind, placebo-controlled study of selegiline transdermal system in depressed adolescents. *J. Child Adolesc. Psychopharmacol.* 24, 311–317. <https://doi.org/10.1089/cap.2013.0138>.
- Dinan, T.G., 2000. A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: a pilot study. *Hum. Psychopharmacol.* 15, 461–469. [https://doi.org/10.1002/1099-1077\(200008\)15:6<461::AID-HUP209>3.0.CO;2-J](https://doi.org/10.1002/1099-1077(200008)15:6<461::AID-HUP209>3.0.CO;2-J).
- Durgam, S., Chen, C., Migliore, R., Prakash, C., Edwards, J., Findling, R.L., 2018. A phase 3, double-blind, randomized, placebo-controlled study of vilazodone in adolescents with major depressive disorder. *Pediatr. Drugs* 20, 353–363. <https://doi.org/10.1007/s40272-018-0290-4>.
- Emslie, G.J., Findling, R.L., Yeung, P.P., Kunz, N.R., Li, Y., 2007. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J. Am. Acad. Child Adolesc. Psychiatry* 46, 479–488. <https://doi.org/10.1097/chl.0b013e31802f5f03>.
- Emslie, G.J., Heiligenstein, J.H., Wagner, K.D., Hoog, S.L., Ernest, D.E., Brown, E., Nilsson, M., Jacobson, J.G., 2002. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J. Am. Acad. Child Adolesc. Psychiatry* 41, 1205–1215. <https://doi.org/10.1097/00004583-200210000-00010>.
- Emslie, G.J., John Rush, A., Weinberg, W.A., Kowatch, R.A., Hughes, C.W., Carmody, T., Rintelmann, J., 1997. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch. Gen. Psychiatry* 54, 1031–1037. <https://doi.org/10.1001/archpsyc.1997.01830230069010>.
- Emslie, G.J., Prakash, A., Zhang, Q., Pangallo, B.A., Bangs, M.E., March, J.S., 2014. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J. Child Adolesc. Psychopharmacol.* 24, 170–179. <https://doi.org/10.1089/cap.2013.0096>.
- Emslie, G.J., Ventura, D., Korotzer, A., Tourkodimitris, S., 2009. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J. Am. Acad. Child Adolesc. Psychiatry* 48, 721–729. <https://doi.org/10.1097/CHI.0b013e3181a2b304>.
- Emslie, G.J., Wagner, K.D., Kutcher, S., Krulwicz, S., Fong, R., Carpenter, D.J., Lipschitz, A., Machin, A., Wilkinson, C., 2006. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J. Am. Acad. Child Adolesc. Psychiatry* 45, 709–719. <https://doi.org/10.1097/01.chi.00000214189.73240.63>.
- EudraCT Number 2015-002181-23 - Clinical trial results - EU Clinical Trials Register. URL: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-002181-23/results> (accessed January 2021).
- European Medicines Agency, 2021. Serotonin-specific Reuptake Inhibitors and Serotonin-noradrenaline Reuptake Inhibitors. <https://www.ema.europa.eu/en/medicines/human/referrals/serotonin-specific-reuptake-inhibitors-serotonin-noradrenaline-reuptake-inhibitors>. (Accessed 15 January 2021).
- Findling, R.L., McCusker, E., Strawn, J.R., 2020. 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.* 30, 355–365. <https://doi.org/10.1089/cap.2019.0176>.
- Findling, R.L., Pagano, M.E., McNamara, N.K., Stansbrey, R.J., Faber, J.E., Lingler, J., Demeter, C.A., Bedoya, D., Reed, M.D., 2009. 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* 3. <https://doi.org/10.1186/1753-2000-3-11>.
- Food and Drug Administration, 2021a. Depression Medicines | FDA. <https://www.fda.gov/consumers/free-publications-women/depression-medicines>. (Accessed 14 January 2021).
- Food and Drug Administration, 2021b. Suicidality in Children and Adolescents Being Treated With Antidepressant Medications. <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescent-s-being-treated-antidepressant-medications>. (Accessed 15 January 2021).
- Forti-Buratti, M.A., Saikia, R., Wilkinson, E.L., Ramchandani, P.G., 2016. Psychological treatments for depression in pre-adolescent children (12 years and younger): systematic review and meta-analysis of randomised controlled trials. *Eur. Child Adolesc. Psychiatry*. <https://doi.org/10.1007/s00787-016-0834-5>.
- Freeman, M.P., Pooley, J., Flynn, M.J., Baer, L., Mischoulon, D., Mou, D., Fava, M., 2017. Guarding the gate: remote structured assessments to enhance enrollment precision in depression trials. *J. Clin. Psychopharmacol.* 37, 176–181. <https://doi.org/10.1097/JCP.0000000000000669>.
- Gabbay, V., Freed, R.D., Alonso, C.M., Senger, S., Stadterman, J., Davison, B.A., Klein, R. G., 2018. A double-blind placebo-controlled trial of omega-3 fatty acids as a monotherapy for adolescent depression. *J. Clin. Psychiatry* 79. <https://doi.org/10.4088/JCP.17m11596>.
- Goodyer, I.M., Dubicka, B., Wilkinson, P., Kelvin, R., Roberts, C., Byford, S., Breen, S., Ford, C., Barrett, B., Leech, A., Rothwell, J., White, L., Harrington, R., 2008. A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. In: *The ADAPT trial*. *Health Technol. Assess. (Rockv)*, p. 12. <https://doi.org/10.3310/hta12140>.
- Hetrick, S.E., McKenzie, J.E., Bailey, A.P., Sharma, V., Moller, C.I., Badcock, P.B., Cox, G. R., Merry, S.N., Meader, N., 2021. New generation antidepressants for depression in children and adolescents: a network meta-analysis. *Cochrane Database Syst. Rev.* 2021 <https://doi.org/10.1002/14651858.CD013674.PUB2>.
- Iftene, F., Predescu, E., Stefan, S., David, D., 2015. Rational-emotive and cognitive-behavior therapy (REBT/CBT) versus pharmacotherapy versus REBT/CBT plus pharmacotherapy in the treatment of major depressive disorder in youth; a randomized clinical trial. *Psychiatry Res.* 225, 687–694. <https://doi.org/10.1016/j.psychres.2014.11.021>.
- Ignaszewski, M.J., Waslick, B., 2018. Update on randomized placebo-controlled trials in the past decade for treatment of major depressive disorder in child and adolescent patients: a systematic review. *J. Child Adolesc. Psychopharmacol.* <https://doi.org/10.1089/cap.2017.0174>.
- Iovieno, N., Papakostas, G.I., 2012. Correlation between different levels of placebo response rate and clinical trial outcome in major depressive disorder: a meta-analysis. *J. Clin. Psychiatry*. <https://doi.org/10.4088/JCP.11r07485>.
- Iovieno, N., Papakostas, G.I., Feeney, A., Fava, M., Mathew, S.J., Iosifescu, D.I., Murrough, J.W., Macaluso, M., Hock, R.S., Jha, M.K., 2021. Vortioxetine versus placebo for major depressive disorder: a comprehensive analysis of the clinical trial dataset. *J. Clin. Psychiatry* 82. <https://doi.org/10.4088/JCP.20R13682>.
- Johnson, D., Dupuis, G., Piche, J., Clayborne, Z., Colman, I., 2018. Adult mental health outcomes of adolescent depression: a systematic review. *Depress. Anxiety* 35, 700–716. <https://doi.org/10.1002/da.22777>.
- Keller, M.B., Ryan, N.D., Strober, M., Klein, R.G., Kutcher, S.P., Birmaher, B., Hagino, O. R., Koplewicz, H., Carlson, G.A., Clarke, G.N., Emslie, G.J., Feinberg, D., Geller, B., Kusumakar, V., Papatheodorou, G., Sack, W.H., Sweeney, M., Wagner, K.D., Weller, E.B., Winters, N.C., Oakes, R., McCafferty, J.P., 2001. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J. Am. Acad. Child Adolesc. Psychiatry* 40, 762–772. <https://doi.org/10.1097/00004583-200107000-00010>.
- Kjærgaard, M., Arfwedson Wang, C.E., Waterloo, K., Jorde, R., 2014. A study of the psychometric properties of the Beck depression inventory-II, the Montgomery and Åsberg depression rating scale, and the hospital anxiety and depression scale in a sample from a healthy population. *Scand. J. Psychol.* 55, 83–89. <https://doi.org/10.1111/sjop.12090>.
- Li, Y., Huang, J., He, Y., Yang, J., Lv, Y., Liu, H., Liang, L., Li, H., Zheng, Q., Li, L., 2019. 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.* 29, 712–720. <https://doi.org/10.1089/cap.2019.0022>.
- Lipari, R.N., Park-Lee, E., 2019. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health.
- Locher, C., Koehlin, H., Zion, S.R., Werner, C., Pine, D.S., Kirsch, I., Kessler, R.C., Kosowsky, J., 2017. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. *JAMA Psychiatry* 74, 1011–1020. <https://doi.org/10.1001/jamapsychiatry.2017.2432>.
- Malhi, G.S., Bassett, D., Boyce, P., Bryant, R., Fitzgerald, P.B., Fritz, K., Hopwood, M., Lyndon, B., Mulder, R., Murray, G., Porter, R., Singh, A.B., 2015. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust. N. Z. J. Psychiatry* 49 (12), 1087–1206. <https://doi.org/10.1177/0004867415617657>.
- Mandoki, M.W., Tapia, M.R., Tapia, M.A., Sumner, G.S., Parker, J.L., 1997. Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol. Bull.* 33, 149–154.
- March, J.S., 2004. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for adolescents with depression study (TADS) randomized controlled trial. *J. Am. Med. Assoc.* 292, 807–820. <https://doi.org/10.1001/jama.292.7.807>.
- Meister, R., Abbas, M., Antel, J., Peters, T., Pan, Y., Bingel, U., Nestoriuc, Y., Hebebrand, J., 2020. 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*. <https://doi.org/10.1007/s00787-018-1244-7>.
- Melvin, G.A., Tonge, B.J., King, N.J., Heyne, D., Gordon, M.S., Klimkeit, E., 2006. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J. Am. Acad. Child Adolesc. Psychiatry* 45, 1151–1161. <https://doi.org/10.1097/01.chi.0000023157.21925.71>.
- National Institute for Health and Care Excellence, 2021. Recommendations | Depression in children and young people: identification and management | Guidance | NICE. <https://www.nice.org.uk/guidance/ng134>. (Accessed 15 January 2021).
- Oud, M., de Winter, L., Vermeulen-Smit, E., Bodden, D., Nauta, M., Stone, L., van den Heuvel, M., Taher, R.A.I., de Graaf, I., Kendall, T., Engels, R., Stikkelbroek, Y., 2019. Effectiveness of CBT for children and adolescents with depression: a systematic review and meta-regression analysis. *Eur. Psychiatry*. <https://doi.org/10.1016/j.eurpsy.2018.12.008>.
- Papakostas, G.I., Fava, M., 2009. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials

- in MDD. *Eur. Neuropsychopharmacol.* 19, 34–40. <https://doi.org/10.1016/j.euroneuro.2008.08.009>.
- Papakostas, G.I., Østergaard, S.D., Iovieno, N., 2015. The nature of placebo response in clinical studies of major depressive disorder. *J. Clin. Psychiatry*. <https://doi.org/10.4088/JCP.14r09297>.
- Paxil Japanese Post Marketing Paediatric Study in Depression (Double-blind, Placebo Controlled Study) - Full Text View - ClinicalTrials.gov [WWW Document]. n.d. URL. <https://clinicaltrials.gov/ct2/show/NCT00812812> (accessed 2.18.21).
- Power, R.A., Tansey, K.E., Buttenschon, H.N., Cohen-Woods, S., Bigdeli, T., Hall, L.S., Kutalik, Z., Lee, S.H., Ripke, S., Steinberg, S., Teumer, A., Viktorin, A., Wray, N.R., Arolt, V., Baune, B.T., Boomsma, D.I., Børglum, A.D., Byrne, E.M., Castelao, E., Craddock, N., Craig, I.W., Dannlowski, U., Deary, I.J., Degenhardt, F., Forstner, A.J., Gordon, S.D., Grabe, H.J., Grove, J., Hamilton, S.P., Hayward, C., Heath, A.C., Hocking, L.J., Homuth, G., Hottenga, J.J., Kloeber, S., Krogh, J., Landén, M., Lang, M., Levinson, D.F., Lichtenstein, P., Lucae, S., MacIntyre, D.J., Madden, P., Magnusson, P.K.E., Martin, N.G., McIntosh, A.M., Middeldorp, C.M., Milaneschi, Y., Montgomery, G.W., Mors, O., Müller-Myhsok, B., Nyholt, D.R., Oskarsson, H., Owen, M.J., Padmanabhan, S., Penninx, B.W.J.H., Pergadia, M.L., Porteous, D.J., Potash, J.B., Preisig, M., Rivera, M., Shi, J., Shyn, S.I., Sigurdsson, E., Smit, J.H., Smith, B.H., Stefansson, H., Stefansson, K., Strohmaier, J., Sullivan, P.F., Thomson, P., Thorgeirsson, T.E., Van der Auwera, S., Weissman, M.M., Breen, G., Lewis, C.M., 2017. Genome-wide Association for Major Depression through age at onset stratification: major depressive disorder working Group of the Psychiatric Genomics Consortium. *Biol. Psychiatry* 81, 325–335. <https://doi.org/10.1016/j.biopsych.2016.05.010>.
- Poznanski, E.O., Freeman, L.N., Mokros, H.B., 1985. Children's depression rating scale - revised (September 1984). *Psychopharmacol. Bull.* 21, 979–989.
- Ramsey, L.B., Bishop, J.R., Strawn, J.R., 2019. Pharmacogenetics of treating pediatric anxiety and depression " we advocate for evidence-based guidelines for PGx use in children and adolescents with anxiety and depressive disorders, while planning larger and more comprehensive PGx studies in these patients. " *Pharmacogenomics* 20, 867–870. <https://doi.org/10.2217/pgs-2019-0088>.
- Rice, F., Riglin, L., Lomax, T., Souter, E., Potter, R., Smith, D.J., Thapar, A.K., Thapar, A., 2019. Adolescent and adult differences in major depression symptom profiles. *J. Affect. Disord.* 243, 175–181. <https://doi.org/10.1016/j.jad.2018.09.015>.
- Rice, Frances, Riglin, L., Thapar, A.K., Heron, J., Anney, R., O'Donovan, M.C., Thapar, A., 2019. Characterizing developmental trajectories and the role of neuropsychiatric genetic risk variants in early-onset depression. *JAMA Psychiatry* 76, 306–313. <https://doi.org/10.1001/jamapsychiatry.2018.3338>.
- Riggs, P.D., Mikulich-Gilbertson, S.K., Davies, R.D., Lohman, M., Klein, C., Stover, S.K., 2007. A randomized controlled trial of fluoxetine and cognitive behavioral therapy in adolescents with major depression, behavior problems, and substance use disorders. *Arch. Pediatr. Adolesc. Med.* 161, 1026–1034. <https://doi.org/10.1001/archpedi.161.11.1026>.
- Safety and Efficacy of Levomilnacipran ER in Adolescent Participants With Major Depressive Disorder - Full Text View - ClinicalTrials.gov [WWW Document]. n.d. URL. <https://clinicaltrials.gov/ct2/show/NCT02431806> (accessed 2.18.21).
- Salloum, N.C., Fava, M., Ball, S., Papakostas, G.I., 2020. Success and efficiency of phase 2/3 adjunctive trials for MDD funded by industry: a systematic review. *Mol. Psychiatry*. <https://doi.org/10.1038/s41380-020-0646-3>.
- Verduijn, J., Milaneschi, Y., Peyrot, W.J., Hottenga, J.J., Abdellaoui, A., de Geus, E.J.C., Smit, J.H., Breen, G., Lewis, C.M., Boomsma, D.I., Beekman, A.T.F., Penninx, B.W.J.H., 2017. Using clinical characteristics to identify which patients with major depressive disorder have a higher genetic load for three psychiatric disorders. *Biol. Psychiatry* 81, 316–324. <https://doi.org/10.1016/j.biopsych.2016.05.024>.
- Von Knorring, A.L., Olsson, G.I., Thomsen, P.H., Lemming, O.M., Hultén, A., 2006. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J. Clin. Psychopharmacol.* 26, 311–315. <https://doi.org/10.1097/01.jcp.0000219051.40632.d5>.
- Wagner, K.D., Ambrosini, P., Rynn, M., Wohlberg, C., Yang, R., Greenbaum, M.S., Childress, A., Donnelly, C., Deas, D., 2003. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *J. Am. Med. Assoc.* 290, 1033–1041. <https://doi.org/10.1001/jama.290.8.1033>.
- Wagner, K.D., Jonas, J., Findling, R.L., Ventura, D., Saikali, K., 2006. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J. Am. Acad. Child Adolesc. Psychiatry* 45, 280–288. <https://doi.org/10.1097/01.chi.0000192250.38400.9e>.
- Wagner, K.D., Robb, A.S., Findling, R.L., Jin, J., Gutierrez, M.M., Heydorn, W.E., 2004. A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am. J. Psychiatry* 161, 1079–1083. <https://doi.org/10.1176/appi.ajp.161.6.1079>.
- Weihs, K.L., Murphy, W., Abbas, R., Chiles, D., England, R.D., Ramaker, S., Wajsbrot, D. B., 2018. Desvenlafaxine versus placebo in a fluoxetine-referenced study of children and adolescents with major depressive disorder. *J. Child Adolesc. Psychopharmacol.* 28, 36–46. <https://doi.org/10.1089/cap.2017.0100>.
- Weisz, J.R., Kuppens, S., Ng, M.Y., Eckshtain, D., Ugueto, A.M., Vaughn-Coaxum, R., Jensen-Doss, A., Hawley, K.M., Krumholz Marchette, L.S., Chu, B.C., Robin Weersing, V., Fordwood, S.R., 2017. What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice. *Am. Psychol.* 72, 79–117. <https://doi.org/10.1037/a0040360>.
- Zhou, X., Hetrick, S.E., Cuijpers, P., Qin, B., Barth, J., Whittington, C.J., Cohen, D., Del Giovane, C., Liu, Y., Michael, K.D., Zhang, Y., Weisz, J.R., Xie, P., 2015a. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry* 14, 207–222. <https://doi.org/10.1002/wps.20217>.
- Zhou, X., Keitner, G.I., Qin, B., Ravindran, A.V., Bauer, M., Del Giovane, C., Zhao, J., Liu, Y., Fang, Y., Zhang, Y., Xie, P., 2015b. Atypical antipsychotic augmentation for treatment-resistant depression: a systematic review and network meta-analysis. *Int. J. Neuropsychopharmacol.* <https://doi.org/10.1093/ijnp/pyv060>.