Predictors of Placebo Response in Adults With Attention-Deficit/Hyperactivity Disorder: Data From 2 Randomized Trials of Osmotic-Release Oral System Methylphenidate

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ABSTRACT

Objective: To find potential correlates of placebo response in adults with attention-deficit/hyperactivity disorder (ADHD) and gain insights into why placebo response may be high in clinical trials.

Method: Post hoc analysis of placebo data from 2 randomized controlled trials of osmotic-release oral system (OROS) methylphenidate in adults with ADHD defined according to the *Diagnostic and Statistical Manual of Mental Diseases,* Fourth Edition: the Long-Acting Methylphenidate in Adults with ADHD (LAMDA-I) study (2005–2006, 5 weeks, n = 95) and the LAMDA-II study (2008–2009, 13 weeks, n = 97). The primary efficacy measure was the Conners' Adult ADHD Rating Scale-observer rated, short version (CAARS:O-SV). Predictors of CAARS:O-SV change were assessed using a random-intercepts model with demographic and disease-related parameters as independent variables. Sensitivity analyses were conducted using the CAARS self-report (CAARS:S-S) and a categorical response criterion (improvement of > 30% in CAARS:O-SV), and in subjects who completed the study.

Results: In LAMDA-I, mean ± SD change in CAARS:O-SV was −7.6 ± 9.9 with placebo and −11.9 ± 10.6 with OROS methylphenidate. Higher baseline CAARS score ($P = .007$) and lower educational achievement ($P = .014$) were significantly associated with greater improvement in placebo-treated subjects. In LAMDA-II, mean ± SD change in CAARS:O-SV was −10.4 ± 11.0 and −14.1 ± 10.7 in subjects receiving placebo and OROS methylphenidate, respectively. Variables significantly associated with greater placebo response were higher baseline CAARS:O-SV ($P = .019$), shorter time since ADHD diagnosis ($P < .045$), and younger age ($P = .014$). None of the sensitivity analyses challenged the outcomes.

Conclusions: Possible predictors of placebo response in adults with ADHD include higher severity of ADHD symptoms, younger age, shorter time since diagnosis, and lower educational level.

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Scientific interest in the placebo effect has grown over the past 2 decades, and this attention may be driven largely by the failure of many clinical trials in pain, anxiety, and depression to differentiate between placebo and active treatment. A review of the US Food and Drug Administration database of antidepressant trials, for example, found that 36% of studies overall and 52% of studies of new antidepressants failed to show superiority over placebo.[1] Notably, the size of placebo effects in trials of psychiatric conditions such as depression or schizophrenia is increasing over time for reasons that are not clear.[2–4]

The role of the placebo effect in responses to medication for psychiatric conditions is poorly understood; placebo effects vary across different conditions and also according to psychological factors such as meaning, belief, faith, and hope.[5] For example, studies of placebo responses of 90% have been reported in some trials of drugs for depression or anxiety, while placebo responses in obsessive-compulsive disorder are lower than those in other anxiety-based Axis I conditions. Placebo responses in attention-deficit/hyperactivity disorder (ADHD) and schizophrenia are also generally lower than those seen in depression and anxiety disorders.

Many reasons for the placebo effect have been suggested, including response bias in clinical trials using subjective outcomes as a result of the patient's profound desire to get better, increased medical attention as a result of being in an experimental study of a new treatment, or even an unconscious wish by the person to please the physician by getting better or by giving "correct" answers to questions.[6] Larger placebo responses also appear to be associated with physical interventions, such as devices or sham procedures.[7] Recent research has provided initial insights into the neurobiological basis of placebo responses.[8–11] For example, reward-processing circuits in the brain may play a role with regard to expectations of drug efficacy and clinical improvement. Similarly, pathways of classical behavioral conditioning may also play a role,[10] while studies of analgesia have shown that placebo responses can be blocked by the opioid antagonist naloxone, suggesting the involvement of endogenous opioids in placebo responses to pain.[6] Specific causes of placebo effects are, however, difficult to quantify and have largely resisted correction by modification of subject requirements and trial design. Design strategies, such as including a placebo lead-in before randomization or carrying out 2 consecutive double-blind treatment stages, have been suggested, although the benefits of such strategies remain to be confirmed.[12,13]

Clinical Points

- There is a substantial incremental benefit of active treatment over placebo in adults with attention-deficit/hyperactivity disorder (ADHD).
- Patient characteristics, such as knowledge about the disorder, age, and educational level, may affect placebo response in ADHD.
- Further research in ADHD, such as meta-analysis and meta-regression analysis of placebo response in placebo-controlled trials, would be valuable.

In children with ADHD, empirical studies and review of the literature show little evidence that placebo treatment can produce significant changes in behavior or cognitive function,[14] perhaps resulting from a lack of insight into their problems. The same review[14] did suggest, however, that adults tend to evaluate children more positively if they believe they have received medication and are more likely to attribute improvements to medication, even if no active drug has been administered. Studies have shown, however, that subjective measures are more susceptible to placebo effects than objective measures in children with ADHD.[15] A range of factors have been identified as playing a role in the placebo response, although results of individual studies are contradictory.[16,17]

Placebo responses in clinical trials of adults with ADHD vary widely, with reported improvements (reductions) in Conners' Adult ADHD Rating Scale-observer rated, short version (CAARS:O-SV),[18] ranging from 6.0 to 10.4 points.[19–22] In contrast with pediatric data, information on predictors of placebo responses in adults with ADHD is limited, although Waxmonsky et al[17] analyzed data from a 4-week study of lisdexamfetamine dimesylate in 420 adults aged 18–55 years and found no association between placebo response and demographic characteristics, previous therapy, adverse events, or symptom changes.

We analyzed data from 2 large, randomized placebo-controlled trials of osmotic-release oral system (OROS) methylphenidate to describe the incremental effect of treatment and the time course of placebo responses and examine their predictive factors in adults with ADHD. The 5-week Long-Acting Methylphenidate in Adults with ADHD (LAMDA-I) study[19] and the 13-week LAMDA-II study[20] had similar patient populations but differed with regard to duration, dosing of OROS methylphenidate (including titration protocols), and presence or absence of an open-label extension.

METHOD

Study Design

This was a post hoc analysis of data from the placebo arms of 2 randomized controlled trials of OROS methylphenidate: LAMDA-I (ClinicalTrials.gov identifier: NCT00246220), conducted at 51 sites in 13 European countries in 2005–2006, and LAMDA-II (EudraCT number: 2007–002111-82), conducted at 42 sites in 11 European countries in 2008–2009. Twenty-one investigators participated in both studies.

All investigators in the 2 studies were psychiatrists with at least 2 years of clinical experience in the field of adult ADHD diagnosis and treatment. In addition, all investigators who performed ratings for CAARS:O-SV assessments were required to successfully complete formal training and be certified as a rater.

Eligible participants in both studies were aged 18–65 years with ADHD according to the criteria of the *Diagnostic and Statistical Manual of Mental Diseases*, Fourth Edition, Text Revision (*DSM-IV-TR*)[23] and confirmed by the Conners' Adult ADHD Diagnostic Interview for *DSM-IV* (CAADID)[18]; subjects were required to have had a chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before 7 years of age, and a score of ≥ 24 at screening on the CAARS:O-SV.

After a washout period of up to 4 weeks, subjects were randomly allocated to treatment for 5 weeks (LAMDA-I; OROS methylphenidate 18, 36, or 72 mg or placebo [1:1:1:1]) or 13 weeks (LAMDA-II; 54 or 72 mg or placebo [1:1:1]). In LAMDA-I, subjects allocated to 72 mg initially received 36 mg for 4 days and 54 mg for 3 days. In LAMDA-II, all subjects initially received 36 mg for 7 days. All doses (including placebo) were given as 2 capsules per day. The primary efficacy measure in both studies was the CAARS:O-SV; the CAARS self-report (CAARS:S-S) was included in both studies as a secondary efficacy measure. Full details of the LAMDA-I and LAMDA-II studies have previously been published.[19,20]

Analysis

All repeated assessments of change from baseline in CAARS:O-SV score for subjects receiving placebo during the treatment period (see Figures 1 and 2) were included in a random-intercepts model as the dependent variable. The ordering of the assessments was taken into account by including an autoregressive covariance structure in the model. The following independent variables were included: baseline total CAARS:O-SV score, being treatment naive (yes/no), country, sex, age, age at ADHD diagnosis, history of mood or anxiety disorder (based on *DSM-IV* criteria), history of drug or alcohol abuse, average treatment adherence, educational achievement, being employed (yes/no), adult ADHD subtype, time since ADHD diagnosis, and family history of ADHD. In the model for the LAMDA-II study, scores on the Drug Use Screening Inventory Revised scales were also included. These variables were first tested for significance in a univariate model, and any variable with a P value < .2 was included in the initial multivariate model. From this initial multivariate model, independent variables were excluded in a backward fashion if $P > .1$ (ie, this was an iterative process in which the least significant variable with $P > .1$ was dropped and the model was rerun) until all independent variables in the model had a P value < .1. Only the results of this final model are included in this article. In case of outliers in the analysis, the impact was checked by rerunning the model without the outlier. None of the outliers had an impact on

the conclusions, so no outliers were excluded. The analysis was also performed on the completing placebo subjects only, as a form of sensitivity analysis that excluded the impact of study withdrawal, and was performed using the CAARS:S-S instead of CAARS:O-SV. Finally, in addition to the primary analysis based on continuous measures of response, the model was repeated using a categorical measure—an improvement of 30% in CAARS:O-SV—as the criterion for response.

RESULTS

Subjects

In total, 95 and 97 subjects received placebo and had postbaseline efficacy data in LAMDA-I and LAMDA-II, respectively. Other than a greater number of patients with a history of mood and anxiety disorders in LAMDA-II, baseline characteristics of subjects in the placebo arms were similar between the 2 studies and did not differ significantly (Table 1).

Table 1. Baseline Characteristics of Subjects Receiving Placebo in the LAMDA-I and LAMDA-II Studies

Characteristic	LAMDA-I (n = 95)	LAMDA-II (n = 97)	*P* Value[a]
Age, mean ± SD, y	34.6 ± 9.6	35.5 ± 8.8	.4990
Age at ADHD diagnosis, mean ± SD, y	31.6 ± 12.5	31.9 ± 12.8	.8697
Sex, n (%)			.2333
Male	59 (62.1)	52 (53.6)	
Female	36 (37.9)	45 (46.4)	
Race, n (%)			.6476
White	93 (95.9)	85 (94.4)	
Asian	1 (1.0)	1 (1.1)	
Black or African heritage	0	1 (1.1)	
Not allowed to ask/other	3 (3.1)	3 (3.3)	
Adult ADHD type, n (%)			.2342
Combined	67 (70.5)	73 (75.3)	
Predominantly inattentive	23 (24.2)	23 (23.7)	
Predominantly hyperactive-impulsive	2 (2.1)	1 (1.0)	
Not specified	3 (3.2)	0	
Family history of ADHD, n (%)	59 (62.1)	53 (54.6)	.2941
History of alcohol/substance use disorder, n (%)	12 (12.6)	20 (20.6)	.1376
History of mood and anxiety disorders, n (%)	33 (34.7)	50 (51.5)	.0187
Prior stimulant use, n (%)	10 (10.5)	10 (10.3)	.9607
Highest education level, n (%)			.1364
Primary school	16 (16.8)	7 (7.2)	
Secondary school	32 (33.7)	40 (41.2)	
High school	32 (33.7)	29 (29.9)	
University	15 (15.8)	21 (21.6)	
Currently employed, n (%)	61 (64.2)	65 (67.0)	.6830
Baseline CAARS:O-SV score, mean ± SD	37.2 ± 7.1	36.5 ± 6.1	.4643

[a] *t* Test for continuous variables; χ^2 test for categorical variables (categories were merged if some had small sample sizes).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CAARS:O-SV = Conners' Adult ADHD Rating Scale-observer rated, short version; LAMDA-I = 5-week Long-Acting Methylphenidate in Adults with ADHD; LAMDA-II = 13-week Long-Acting Methylphenidate in Adults with ADHD.

Placebo Responses

In the 5-week LAMDA-I study, the mean ± SD change in CAARS:O-SV score from baseline to end point in subjects receiving placebo was −7.6 ± 9.9 compared with −11.9 ± 10.5 in patients receiving active treatment. Overall, 27.4% of subjects receiving placebo experienced a decrease (improvement) in CAARS:O-SV score of ≥ 30%. In the 13-week LAMDA-II study, the mean ± SD change in CAARS:O-SV score from baseline to end point in subjects receiving placebo was −10.4 ± 11.0 compared with 12.5 ± 10.4 and 15.7 ± 10.8 with the 2 active treatment dosages. The percentage of placebo subjects achieving an improvement in CAARS:O-SV of ≥ 30% at end point was 45.4%.

In both studies, the greatest increase in separation between placebo and OROS methylphenidate occurred early in the course of treatment (week 1 in LAMDA-I and weeks 1–3 in LAMDA-II), and the difference was maintained for the remainder of the study (Figures 1 and 2). Overall, response in the placebo arm appeared stable over time and was similar—though smaller in magnitude—to that with active treatment.

Factors Associated With Placebo Response

Variables significantly associated with change in CAARS:O-SV score in the mixed-effects model are shown in Table 2. When using CAARS:S-S instead of CAARS:O-SV, a response criterion of 30% improvement in CAARS:O-SV or limiting the analysis to patients who completed the study did not affect the outcomes of the model for either study (data not shown).

Baseline severity. In both studies, placebo-treated subjects with a high CAARS:O-SV score at baseline were significantly more likely to experience improvement than those with a low baseline score.

Education. In LAMDA-I, educational achievement was significantly associated with change in CAARS:O-SV score, with subjects having primary school as their highest level of education more likely to experience an improvement while receiving placebo. Educational achievement was not significantly associated with change in CAARS:O-SV score in LAMDA-II.

Age. In LAMDA-II, age was significantly associated with change in CAARS:O-SV score, with older subjects more likely to experience an improvement during placebo treatment. The opposite appeared to be true in LAMDA-I, with a nonsignificant trend ($P = .066$) toward greater improvement in younger subjects.

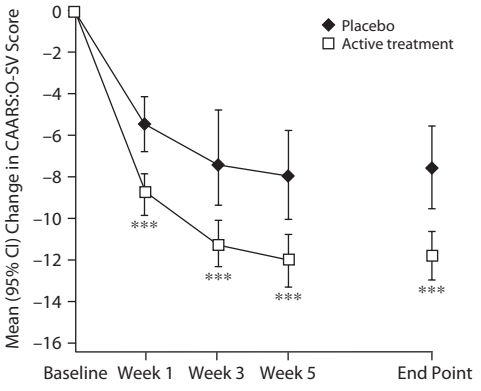
Time since ADHD diagnosis. In LAMDA-II, patients with longer time since ADHD diagnosis experienced less improvement on CAARS:O-SV, but this effect was not seen in LAMDA-I.

Family history of ADHD. In LAMDA-II there was a nonsignificant trend to a greater improvement on CAARS:O-SV in subjects with a family history of ADHD ($P = .076$).

DISCUSSION

The results of the present study suggest that the placebo response in adults with ADHD is a genuine phenomenon, with a similar overall pattern and stability, though smaller magnitude, to the response seen in subjects receiving active

Figure 1. Change in CAARS:O-SV Score Over Time in Patients Receiving Placebo or Active Treatment in the LAMDA-I Study (intention-to-treat population)

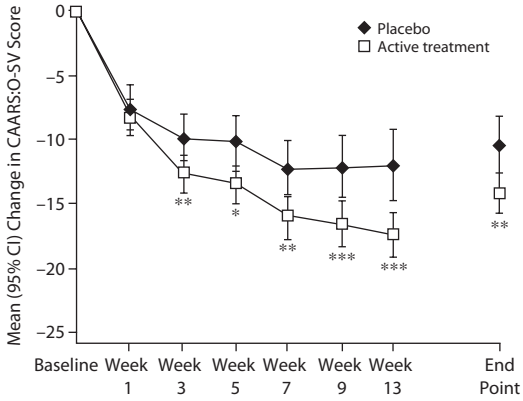


	Baseline	Week 1	Week 3	Week 5	End Point
Placebo, n	95	94	92	88	95
Active treatment, n	299	298	285	266	299

***$P \leq .0001$.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CAARS:O-SV = Conners' Adult ADHD Rating Scale-observer rated, short version; LAMDA-I = 5-week Long-Acting Methylphenidate in Adults With ADHD.

Figure 2. Change in CAARS:O-SV Score Over Time in Patients Receiving Placebo or Active Treatment in the LAMDA-II Study



	Baseline	Week 1	Week 3	Week 5	Week 7	Week 9	Week 13	End Point
Placebo, n	97	97	90	82	75	71	68	97
Active treatment, n	182	179	158	145	130	122	114	182

*$P < .05$; **$P < .01$; ***$P \leq .001$.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CAARS:O-SV = Conners' Adult ADHD Rating Scale-observer rated, short version; LAMDA-II = 13-week Long-Acting Methylphenidate in Adults With ADHD.

Table 2. Variables in the Final Model Associated With Change in CAARS:O-SV Score in Subjects Receiving Placebo in the LAMDA-I and LAMDA-II Studies

Variable	Point Estimate	*P* Value
LAMDA-I study		
Age	−0.144	.066
Baseline CAARS:O-SV score	−0.295	.007
Time	−0.078	.003
Highest level of education		
Primary school	−6.629	.014
Secondary school	−1.898	.409
High school	0.529	.817
University	0	…
LAMDA-II study		
Age	0.245	.014
Time	−0.043	< .001
Baseline CAARS:O-SV score	−0.326	.019
No family history of ADHD	3.096	.076
Time since ADHD diagnosis	0.203	.045

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CAARS:O-SV = Conners' Adult ADHD Rating Scale-observer rated, short version; LAMDA-I = 5-week Long-Acting Methylphenidate in Adults With ADHD; LAMDA-II = 13-week Long-Acting Methylphenidate in Adults With ADHD.

treatment. The greatest incremental benefit of OROS methylphenidate occurred early in the course of the 2 studies, and the level of response was then stable for the remainder of the treatment period. While improvement in CAARS:O-SV scores over time was observed in patients receiving placebo, it is possible that this result is related to discontinuations in patients who failed to respond to placebo treatment, leading to a placebo response that appears artificially high, particularly in later stages of the studies. In the Extended-Release Methylphenidate for Adults with ADHD study of extended-release methylphenidate versus placebo, for example, the discontinuation rate in patients receiving placebo was significantly lower than in those receiving active treatment.[24] While the rate of discontinuation in patients receiving placebo in the LAMDA studies was not noticeably higher than in those receiving active treatment in the early part of the study, patients receiving placebo were more likely to discontinue as a result of lack of efficacy than those receiving active treatment.[20,25]

The size of the placebo responses in the LAMDA-I and LAMDA-II study differed, both in terms of change in CAARS:O-SV score and percentage of subjects achieving ≥ 30% improvement in CAARS:O-SV. The inclusion and exclusion criteria for the 2 studies were the same, and there were no obvious differences in baseline characteristics, other than a significantly higher incidence of mood and anxiety disorders in LAMDA-II. This finding, together with the lack of clear patterns of predictors in terms of patient characteristics, leads to the hypothesis that trial design characteristics may be decisive. The larger placebo response in LAMDA-II may be partly related to the longer study duration, as patients who do not feel a benefit from treatment may be more likely to persist with a short-term study than a longer-term study. This effect has previously been observed in trials of antidepressants,[26–28] although a meta-regression analysis of 35 placebo-controlled trials of antipsychotics for patients with schizophrenia found the placebo responses were larger in shorter studies.[29] The lower placebo response may also be related to the presence of an open-label extension to LAMDA-I in which all patients received an optimized OROS methylphenidate regimen[30]; patients who did not respond to placebo had additional motivation to remain in the study, which may have reduced the overall level of the placebo response.

Another effect observed in trials of antidepressants that may be relevant is the tendency for the size of the placebo effect and the size of medication responses to increase over time[2]; similar increases in placebo response over time have

been observed in studies of patients with schizophrenia.[3,4] As LAMDA-I was conducted in 2005–2006 and LAMDA-II was conducted in 2008–2009, a similar effect may be occurring in ADHD, although the variability in trial designs and outcome measures used makes it difficult to assess this. One possible explanation may be the increasingly strict limiting of patients in clinical trials to those patients without comorbidities. This leads to inclusion of relatively healthy patients—especially compared with a real-life setting, where comorbidities occur commonly. It seems likely that patients with numerous or severe comorbidities will be far less susceptible to placebo responses and that earlier studies included more patients with comorbidities. This does not, however, explain the difference between LAMDA-I and LAMDA-II, as the inclusion criteria were the same. Interestingly, a study of an extended-release formulation carried out in 2004–2006 also reported a high placebo response (42%) using the Wender–Reimherr Adult Attention Deficit Disorder Scale.[24] Another factor that may play a role in placebo responses in trials of antidepressants is the number of study sites; an analysis of short-term trials of antidepressant treatment in children found that number of study sites was the strongest predictor of placebo response.[31] The LAMDA-I and LAMDA-II studies were conducted at 51 and 42 sites, respectively, and this difference may have predisposed LAMDA-I to an increased placebo response, although it is interesting to note that the placebo response was higher in LAMDA-II, despite fewer study sites. It is possible that number of patients per site is also an important factor (average number of patients per site in LAMDA-I was 7.9; LAMDA-II, 6.6). Study site recruitment rate has also been identified as a predictor of placebo response in a study of placebo responses in patients with neuropathic pain.[32]

The analysis of factors that may predict placebo response in subjects with ADHD receiving OROS methylphenidate showed that baseline CAARS:O-SV score was the only consistently significant factor between the 2 studies. Although a genuinely greater effect of placebo in patients with more severe disease cannot be ruled out, this is likely to be a regression to the mean effect: subjects with a large CAARS:O-SV score at baseline (ie, a high level of impairment) are likely to experience larger improvements over time simply because they have the greatest scope for improvement.

The effect of age on placebo response was unclear. In LAMDA-II, older subjects were significantly less likely to respond to placebo. This is consistent with the significant effect observed for time since diagnosis of ADHD and may reflect increased familiarity of these subjects with the condition and the potential impact of treatment, making them less susceptible to psycho-education. Similarly, the effect of educational status on placebo response differed between the 2 studies, with a lower level of education associated with greater chance of improvement in the placebo group in LAMDA-I, but not LAMDA-II.

In adults with other psychiatric conditions, studies of factors associated with placebo responses are also limited. In a small study[33] of patients with schizophrenia, the only factor found to predict placebo response was baseline severity, with greater responses in patients with higher symptom scores, which the authors attribute to regression to the mean. An analysis of 97 subjects from 4 clinical trials of antidepressants found that older age was associated with a trend to greater placebo response,[34] as found in LAMDA-I but not LAMDA-II. The same study also found that married individuals were more likely to experience a placebo response, but that duration of illness and educational level had no effect. An analysis of 4 studies of escitalopram also found that duration of illness was not associated with placebo response.[35] In a pooled analysis of 3 clinical trials of lamotrigine in patients with neuropathic pain, baseline severity and, as noted above, study site recruitment rate were identified as predictors of placebo response.[32] Similarly, baseline severity was also identified as a significant predictor in a study of placebo responses in patients with cancer-related fatigue.[36]

The limitations of the present analysis should be borne in mind when interpreting the results. These include the post hoc nature of the analysis and the possibility that important predictive variables may have been missed, as they were not evaluated in the parent studies (such as personality traits and behavioral and motivational measures). Another limitation is that more objective measures of response to treatment, such as actimeters and neuropsychological assessments, were not included. Although these objective measures do not map perfectly on clinical indices of response, they may be useful in calibrating the self-rated treatment outcomes.[37–39]

In conclusion, this analysis of placebo responses in patients with ADHD shows that there is a substantial incremental benefit of active treatment, with early separation between active treatment and placebo remaining stable throughout the studies. Analysis of variables associated with placebo response in adults with ADHD suggests that greater baseline severity, knowledge about the disorder, age, and educational level may affect placebo response. Further work is needed to explore placebo effects in adults with ADHD in greater detail, ideally through a meta-analysis of randomized controlled trials. This work should be extended beyond the study of mere descriptive and clinical characteristics and also focus on neurocognitive and neural variables that might characterize placebo response. In addition, it may be of interest to look at predictors of response to active treatment and how they overlap with, or differ from, predictors of placebo response. Such research has the potential to improve our understanding of the mechanisms involved in response to treatment, either to placebo or to active medication, in adults with ADHD.

Drug names: escitalopram (Lexapro and others), lamotrigine (Lamictal and others), lisdexamfetamine (Vyvanse), methylphenidate (Daytrana, Ritalin, and others).

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REFERENCES

1. Khan A, Leventhal RM, Khan SR, et al. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J Clin Psychopharmacol*. 2002;22(1): 40–45.
2. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002; 287(14):1840–1847.
3. Kinon BJ, Potts AJ, Watson SB. Placebo response in clinical trials with schizophrenia patients. *Curr Opin Psychiatry*. 2011;24(2):107–113.
4. Kemp AS, Schooler NR, Kalali AH, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? *Schizophr Bull*. 2010;36(3):504–509.
5. Kradin RL. Placebo response: a consideration of its role in therapeutics. *Curr Psychiatry Rep*. 2011;13(1):37–42.
6. Hróbjartsson A, Kaptchuk TJ, Miller FG. Placebo effect studies are susceptible to response bias and to other types of biases. *J Clin Epidemiol*. 2011;64(11):1223–1229.
7. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev*. 2010;(1):CD003974.
8. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. *Philos Trans R Soc Lond B Biol Sci*. 2011;366(1572): 1859–1869.
9. Zubieta JK, Stohler CS. Neurobiological mechanisms of placebo responses. *Ann N Y Acad Sci*. 2009;1156(1):198–210.
10. Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. *Neuron*. 2008;59(2):195–206.
11. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol*. 2008;59(1):565–590.
12. Chen YF, Yang Y, Hung HM, et al. Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials. *Contemp Clin Trials*. 2011;32(4):592–604.
13. Mallinckrodt CH, Tamura RN, Tanaka Y. Recent developments in improving signal detection and reducing placebo response in psychiatric clinical trials. *J Psychiatr Res*. 2011;45(9):1202–1207.
14. Waschbusch DA, Pelham WE Jr, Waxmonsky J, et al. Are there placebo effects in the medication treatment of children with attention-deficit hyperactivity disorder? *J Dev Behav Pediatr*. 2009;30(2):158–168.
15. Sumner CR, Haynes VS, Teicher MH, et al. Does placebo response differ between objective and subjective measures in children with attention-deficit/hyperactivity disorder? *Postgrad Med*. 2010;122(5):52–61.
16. Newcorn JH, Sutton VK, Zhang S, et al. Characteristics of placebo responders in pediatric clinical trials of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(12):1165–1172.
17. Waxmonsky JG, Waschbusch DA, Glatt SJ, et al. Prediction of placebo response in 2 clinical trials of lisdexamfetamine dimesylate for the treatment of ADHD. *J Clin Psychiatry*. 2011;72(1):1366–1375.
18. Conners C, Erhardt D, Sparrow E. *Conners' Adult ADHD Rating Scales (CAARS): Technical Manual*. North Tonawanda, NY: Multi-Health Systems; 1999.
19. Medori R, Ramos-Quiroga JA, Casas M, et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2008;63(10):981–989.
20. Casas M, Rösler M, Sandra Kooij JJ, et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: a 13-week, randomized, double-blind, placebo-controlled, fixed-dose study [published online ahead of print November 22, 2011]. *World J Biol Psychiatry*.
21. Jain U, Hechtman L, Weiss M, et al. Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. *J Clin Psychiatry*. 2007;68(2):268–277.
22. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. *Biol Psychiatry*. 2003;53(2):112–120.
23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
24. Rösler M, Fischer R, Ammer R, et al. A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder. *Eur Arch Psychiatry Clin Neurosci*. 2009;259(2):120–129.
25. Rösler M, Ginsberg Y, Arngrim T, et al. Correlation of symptomatic improvements with functional improvements and patient-reported outcomes in adults with attention-deficit/hyperactivity disorder treated with OROS methylphenidate. *World J Biol Psychiatry*. [published online ahead of print April 26, 2011]
26. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. *Arch Gen Psychiatry*. 2000;57(4):311–317.
27. Quitkin FM, Rabkin JD, Markowitz JM, et al. Use of pattern analysis to identify true drug response: a replication. *Arch Gen Psychiatry*. 1987; 44(3):259–264.
28. Quitkin FM, McGrath PJ, Stewart JW, et al. Chronological milestones to guide drug change: when should clinicians switch antidepressants? *Arch Gen Psychiatry*. 1996;53(9):785–792.
29. Welge JA, Keck PE Jr. Moderators of placebo response to antipsychotic treatment in patients with schizophrenia: a meta-regression. *Psychopharmacology (Berl)*. 2003;166(1):1–10.
30. Buitelaar JK, Ramos-Quiroga JA, Casas M, et al. Safety and tolerability of flexible dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat*. 2009;5:457–466.
31. Bridge JA, Birmaher B, Iyengar S, et al. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *Am J Psychiatry*. 2009;166(1):42–49.
32. Irizarry MC, Webb DJ, Ali Z, et al. Predictors of placebo response in pooled lamotrigine neuropathic pain clinical trials. *Clin J Pain*. 2009; 25(6):469–476.
33. Taiminen T, Syvalahti E, Saarijarvi S, et al. Prediction of positive placebo response among chronic schizophrenic outpatients. *J Nerv Ment Dis*. 1996;184(2):109–113.
34. Wilcox CS, Cohn JB, Linden RD, et al. Predictors of placebo response: a retrospective analysis. *Psychopharmacol Bull*. 1992;28(2):157–162.
35. Stein DJ, Baldwin DS, Dolberg OT, et al. Which factors predict placebo response in anxiety disorders and major depression? An analysis of placebo-controlled studies of escitalopram. *J Clin Psychiatry*. 2006; 67(11):1741–1746.
36. de la Cruz M, Hui D, Parsons HA, et al. Placebo and nocebo effects in randomized double-blind clinical trials of agents for the therapy for fatigue in patients with advanced cancer. *Cancer*. 2010;116(3): 766–774.
37. Kooij JJ, Middelkoop HA, van Gils K, et al. The effect of stimulants on nocturnal motor activity and sleep quality in adults with ADHD: an open-label case-control study. *J Clin Psychiatry*. 2001;62(12):952–956.
38. In de Braek D, Dijkstra JB, Jolles J. Cognitive complaints and neuropsychological functioning in adults with and without attention-deficit hyperactivity disorder referred for multidisciplinary assessment. *Appl Neuropsychol*. 2011;18(2):127–135.
39. Biederman J, Seidman LJ, Petty CR, et al. Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. *J Clin Psychiatry*. 2008;69(7):1150–1156.