# Iron Homeostasis During Risperidone Treatment in Children and Adolescents

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## ABSTRACT

***Objective:*** Previous cross-sectional evidence has linked antipsychotic-related weight gain to reduced body iron concentration. Using longitudinal data, we examined the association between changes in weight following risperidone initiation or discontinuation and ferritin concentration.

***Method:*** Study 1: Between April 2004 and September 2007, participants were enrolled from outpatient settings in a prospective randomized clinical trial comparing the efficacy of risperidone monotherapy to the combination of risperidone and behavior therapy in targeting disruptive behavior in 4- to 13-year-old children with *DSM-IV-TR*–based autism spectrum disorder. Study 2: Medically healthy 7- to 17-year-old participants in long-term open-label risperidone treatment at study entry returned for follow-up 1.5 years later, between July 2007 and July 2011. Available blood samples were used to measure ferritin. Linear multivariable regression analysis tested the association between ferritin concentration and change in age-sex–specific body mass index (BMI) *z* score between study entry and endpoint, adjusting for relevant confounders.

***Results:*** Study 1 sample consisted of 73 participants (85% males, mean age: 7.7 ± 2.4 years). After 18.0 ± 2.0 weeks on risperidone, their BMI *z* score increased by 0.93 ± 0.70 points and ferritin concentration declined by 6.8 ± 13.3 µg/L. After adjusting for age and sex, change in BMI *z* score was inversely correlated with percent change in ferritin concentration (β = −18.3, $P < .003$). Study 2 participants had all been receiving risperidone at study entry. At follow-up, 1.5 ± 0.3 years later, risperidone was discontinued in 26 of the 96 who were included in the analysis. Neither change in BMI *z* score nor in ferritin concentration was different between those who continued versus discontinued risperidone. However, a reduction in BMI *z* score between study entry and follow-up was associated with higher ferritin concentration at follow-up in participants who discontinued risperidone compared to those who continued it ($P = .01$).

***Conclusions:*** Risperidone-related weight gain is associated with a reduction in body iron reserves, which appears to improve with weight loss following risperidone discontinuation. Preliminary evidence suggests that risperidone may also directly inhibit iron absorption.

***Trial Registration:*** ClinicalTrials.gov Identifier: NCT00080145

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Iron plays a significant role in brain function.[1] Iron is incorporated in various structural and transport proteins.[2] It is also a cofactor of various enzymes, such as tyrosine hydroxylase, the rate-limiting enzyme for catecholamine synthesis.[3] Iron deficiency in rats results in reduced density of the dopamine transporter and the dopamine $D_1$ and $D_2$ receptors in the basal ganglia.[4–8] In children, iron deficiency has been associated with cognitive impairment, including motor, attention, and memory dysfunction.[9] Such deficits have been observed even in the absence of anemia because available body iron is prioritized to hemoglobin synthesis during iron depletion.[10,11] In clinical samples, low serum ferritin concentration (a marker of body iron stores) has additionally been associated with more severe attention-deficit/hyperactivity disorder (ADHD) symptoms and poorer response to psychostimulants.[12–15]

Previously, we found significant iron depletion in a group of children and adolescents treated chronically with risperidone.[16] Moreover, after adjusting for relevant factors, including risperidone and 9-hydroxy-risperidone concentration, we found that body iron concentration was inversely associated with prolactin concentration. This is presumably secondary to a reduction in dopamine $D_2$ receptor density in the anterior pituitary, induced by iron depletion.[4–8] We further found that body iron concentration was inversely associated with weight gain that followed the initiation of risperidone treatment.[16]

As our previous study lacked pre-risperidone estimates of iron stores, we here attempt to replicate the association between antipsychotic-induced weight gain and reduced body iron concentration, using data from the second Research Units on Pediatric Psychopharmacology (RUPP) Autism Network risperidone trial[17,18] (referred to as Study 1, henceforth). Further, we extend our previous findings by examining the impact of risperidone discontinuation on ferritin concentration, given that we recently completed a follow-up assessment on the participants in the original study[19] (referred to as Study 2, henceforth). We hypothesized that weight loss following risperidone discontinuation would be associated with an increase in ferritin concentration, reflecting improved iron status.

**Clinical Points**

- Antipsychotic-induced weight gain is associated with a reduction in body iron reserves.
- In the general population, low iron stores have been associated with impaired cognitive and emotional functioning. In patients with ADHD, low iron stores have been associated with more severe symptoms and poorer response to treatment.
- However, the clinical impact of low iron stores during antipsychotic treatment remains to be examined.

## METHOD

### Study 1

***Participants.*** The aims and methods of the parent study have been described previously.[17,18] This multisite multiphase randomized trial (Clinical Trial Registration NCT00080145), conducted between April 2004 and September 2007, compared risperidone (n = 49) with the combination of risperidone and behavioral therapy (n = 75) to target disruptive behavior in 4- to 13-year-old children with autism spectrum disorder (ASD).[17] The participants had to be psychotropic-drug–free for at least 2 weeks, have an IQ ≥ 35 or mental age ≥ 18 months, and be seizure-free for ≥ 6 months, or, if taking antiepileptic agents, be on a stable dose of antiepileptics for 4 weeks. Exclusion criteria included pregnancy, prior adequate trial of risperidone, a diagnosis of Rett's disorder or childhood disintegrative disorder, and other significant psychiatric or medical conditions. At the end of week 8, poor responders were prescribed aripiprazole (n = 12), and the participants were followed for up to 24 weeks.

***Procedures.*** The institutional review boards of the participating sites approved the investigation, and the parents or legal guardians provided written informed consent.

Height and weight were measured following a standard protocol. The presence of ASD was established by clinical evaluation using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[20] criteria and corroborated by the Autism Diagnostic Interview–Revised.[21]

A blood sample was obtained to measure red blood cell count and hemoglobin concentration. Additional aliquots of plasma were stored at −80°C and used to measure ferritin concentration.

### Study 2

***Participants.*** The aims and methods of the parent study have been described previously.[19,22] Briefly, 7- to 17-year-old patients treated with risperidone for at least 6 months were recruited, regardless of psychiatric diagnosis. Patients receiving concurrent treatment with antipsychotics other than risperidone were excluded. Also excluded were patients with neurologic or medical conditions and female patients who were pregnant or receiving hormonal contraception. Between July 2007 and July 2011, 72% of the participants returned for a follow-up research visit 18 months after study entry, at which time study entry assessments were repeated. Few differences were present between those who returned for follow-up versus those who did not, including being less likely to have had a history of child maltreatment but being more likely to be male, to suffer from ASD, and to have been receiving an antidepressant.[19]

***Procedures.*** The study was approved by the University of Iowa Institutional Review Board. Written assent was obtained from children younger than 14 years old and consent from adolescents and from parents of all patients.

Height and weight were measured following a standard protocol.[19] Iron intake during the week prior to study entry and follow-up was estimated using the 2004 Block Kids Food Frequency Questionnaire.[23] This questionnaire also queries about multivitamin use, assuming that each tablet contains 18 mg of iron.

A best-estimate diagnosis, following the *DSM-IV-TR*, was generated based on a review of the psychiatric record supplemented by a brief clinical interview, and a standardized interview of the parent using the National Institute of Mental Health Diagnostic Interview Schedule for Children.[24]

A morning blood sample was obtained to measure serum ferritin and C-reactive protein (CRP), among other assays.

### Data Analysis

Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$). BMI measurements were converted into age-sex–specific *z* scores.[25]

In Study 1, the baseline visit was before risperidone was started, while the follow-up visit was when the last plasma sample was available. Ferritin is the most widely used marker of body iron stores; however, being an acute phase reactant, it increases during acute inflammation, potentially masking low iron stores.[26] Therefore, participants with a change in ferritin concentration of more than 75% (Study 1) or with a CRP ≥ 10 mg/L (Study 2), suggesting acute inflammation, were excluded as were participants with relatively high ferritin concentrations (ie, > 130 µg/L).

Multivariable linear regression analysis examined the association between change in BMI *z* score between the baseline and follow-up visits and ferritin concentration, adjusting for potential confounders. In Study 2, continuous and categorical variables were compared across participants who continued versus discontinued risperidone using the Student *t* test and Fisher Exact test, respectively.

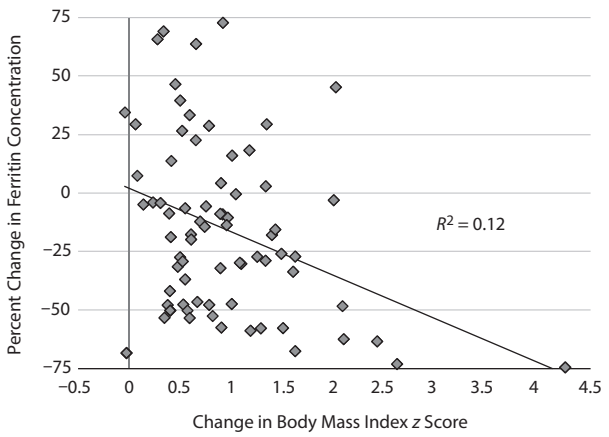
All the statistical tests performed were 2-tailed, using SAS version 9.3 for Windows (SAS Institute Inc, Cary, North Carolina), with statistical significance set at α = .05.

## RESULTS

### Study 1

***Subject characteristics.*** Of the 124 participants randomized to treatment, 79 had plasma samples at baseline and at least 1 follow-up visit. Of those, 6 were excluded due to exhibiting a ferritin concentration > 130 µg/L or a change in concentration of > 75%, leaving 73 participants to be

**Figure 1. Correlation of Percent Change in Ferritin Concentration and Change in Age-Sex–Specific Body Mass Index *z* Score Between Study Entry, Prior to Starting Risperidone, and Follow-Up in Study 1**




included in this analysis. Participants' mean age was 7.7 ± 2.4 years old and 85% (n = 62) were males. Forty-one (56%) had *DSM-IV-TR*–based autistic disorder, 6 (8%) had Asperger's disorder, and 26 (36%) had pervasive developmental disorder not otherwise specified. At baseline, their mean age-sex–specific BMI *z* score was 0.52 ± 1.20 and their mean serum ferritin concentration was 30.3 ± 15.2 µg/L. The follow-up plasma sample was collected at a mean 18.0 ± 2.0 weeks after the baseline measurement.

***Change in ferritin and in BMI z score.*** By follow-up, BMI *z* score had increased by 0.93 ± 0.70 points, and ferritin concentration had declined by 6.8 ± 13.3 µg/L, a 15.2% ± 36.9% reduction. After adjusting for age and sex, baseline ferritin concentration did not predict increase in BMI *z* score ($P > .80$).

After adjusting for age and sex, there was a significant inverse association between change in BMI *z* score and percent change in ferritin concentration ($P < .003$), whereby every 1 point increase in BMI *z* score was associated with an 18.3% reduction in ferritin (Figure 1).

Of note, there was no significant change in red blood cell count or in hemoglobin throughout the trial (mean change: $-0.004 \pm 0.232 \times 10^6/mm^3$, $P > .80$, and mean change: −0.09 ± 0.59 g/dL, $P > .20$, respectively).

### Study 2

***Subject characteristics.*** Of the 108 participants who returned for follow-up, 96 were included in this analysis. Of those, 12 were excluded either for developing a medical condition in the interim period (eg, type 1 diabetes, hypothyroidism) or for lacking a ferritin measurement. The participants were mostly peripubertal and predominantly exhibited externalizing disorders (Table 1). At follow-up, 1.5 ± 0.3 years later, 70 (73%) had continued taking risperidone, 11 (11%) switched to another antipsychotic, and 15 (16%) discontinued all antipsychotic treatment. The last two groups were combined due to small sample size.

***Change in ferritin and in BMI z score.*** By follow-up, neither continuing nor discontinuing risperidone treatment was associated with a significant change in age-sex–specific BMI *z* score (*P* values > .40, Table 1). However, as detailed elsewhere,[19] among those who discontinued risperidone, switching to another antipsychotic was associated with an increase in BMI *z* score, while discontinuing all antipsychotics was associated with a decrease in BMI *z* score (mean = 0.68; 95% confidence interval [CI], 0.31 to 1.04 vs mean = −0.54; 95% CI, −0.80 to −0.28, respectively; $P < .0001$). Further, neither ferritin concentration at follow-up (mean = 13.7 µg/L; 95% CI, 10.2 to 17.1 vs mean = 12.7 µg/L; 95% CI, 4.0 to 21.4 vs mean = 17.1 µg/L; 95% CI, 9.7 to 24.6, respectively) nor the change in ferritin concentration between study entry and follow-up (mean = −1.3 µg/L; 95% CI, −3.9 to 1.4 vs mean = 0.0 µg/L; 95% CI, −5.9 to 5.9 vs mean = 2.5 µg/L; 95% CI, −3.0 to 8.2, respectively) was different between those who continued risperidone, switched to another antipsychotic, or discontinued all antipsychotic treatment (all *P* values > .40).

After adjusting for age, sex, and ferritin concentration at study entry, there was a significant interaction effect between change in BMI *z* score and being on risperidone at follow-up in predicting ferritin concentration at follow-up ($P < .04$). In fact, a reduction in BMI *z* score between study entry and follow-up was associated with higher ferritin concentration at follow-up in participants who discontinued compared to those who continued risperidone. No difference in ferritin was observed among those whose BMI *z* score increased (Figure 2A). A similar finding was observed with change in ferritin concentration between study entry and follow-up, after adjusting for the same variables (Figure 2B). Excluding the participants who switched to an antipsychotic other than risperidone by follow-up did not alter these findings.

## DISCUSSION

Previously, using cross-sectional data, we found an inverse association between weight gain and iron status in children and adolescents who had received risperidone for a mean of 2.4 years.[16] Here, we extend those findings by (1) showing that baseline ferritin concentration does not moderate weight gain associated with antipsychotic treatment; (2) replicating the association between weight gain and reduction in body iron concentration, using a longitudinal design; (3) finding that ferritin concentration improves following weight loss after antipsychotic discontinuation; and (4) suggesting that risperidone might inhibit iron absorption, independently of its potential to cause weight gain.

By design, the participants had already been taking risperidone for at least 6 months prior to entry into Study 2. Therefore, it may be possible that the participants' pre-risperidone iron status was compromised, somehow predisposing them to excessive weight gain. Findings from Study 1 address this concern by showing not only that the participants with ASD had largely normal body iron status before starting risperidone, but also that there was no association between their baseline ferritin concentration

**Table 1. Demographic and Clinical Characteristics of the Study 2 Sample Overall and Split Based on Risperidone Treatment Status at Follow-Up**

| Characteristic | Total Sample N = 96 | Risperidone Continuation n = 70 | Risperidone Discontinuation n = 26 | *P* Value |
|---|---|---|---|---|
| Males, n (%) | 88 (92) | 66 (94) | 22 (85) | > .20 |
| Age, y, mean ± SD | 13.2 ± 2.7 | 13.3 ± 2.8 | 12.9 ± 2.4 | > .50 |
| Tanner stage I/II/III/IV/V, % | 18/21/14/17/30 | 18/21/18/13/31 | 19/23/4/27/27 | > .30 |
| Change in BMI *z* score, mean ± SD[a] | −0.04 ± 0.63 | −0.04 ± 0.46 | −0.05 ± 0.96 | > .90 |
| Dietary iron intake, mg/d, mean ± SD[b] | 15.8 ± 7.7 | 16.0 ± 8.0 | 15.0 ± 6.9 | > .50 |
| Multivitamin use, n (%) | 22 (23) | 19 (27) | 3 (12) | > .10 |
| Ferritin concentration, µg/L, mean ± SD | 14.1 ± 14.4 | 13.7 ± 15.9 | 15.3 ± 9.7 | > .50 |
| Ferritin change, µg/L, mean ± SD[a] | −0.5 ± 9.4 | −1.3 ± 9.7 | 1.3 ± 8.5 | > .20 |
| Psychiatric disorders, n (%) | | | | |
| Attention-deficit/hyperactivity disorder | 86 (90) | 63 (90) | 23 (88) | > .80 |
| Disruptive behavior disorder | 84 (88) | 64 (91) | 20 (77) | < .06 |
| Anxiety disorder | 28 (29) | 21 (30) | 7 (27) | > .70 |
| Tic disorder | 25 (26) | 17 (24) | 8 (31) | > .50 |
| Autism spectrum disorder | 18 (19) | 12 (17) | 6 (23) | > .50 |
| Depressive disorder | 5 (5) | 3 (4) | 2 (8) | > .50 |

[a]Refers to change between study entry and follow-up. Ferritin concentration was available at both visits for 71 participants.
[b]This combines intake from food and supplements (ie, multivitamins); 4 participants with invalid dietary data were excluded.

and the magnitude of weight gain following the initiation of risperidone.

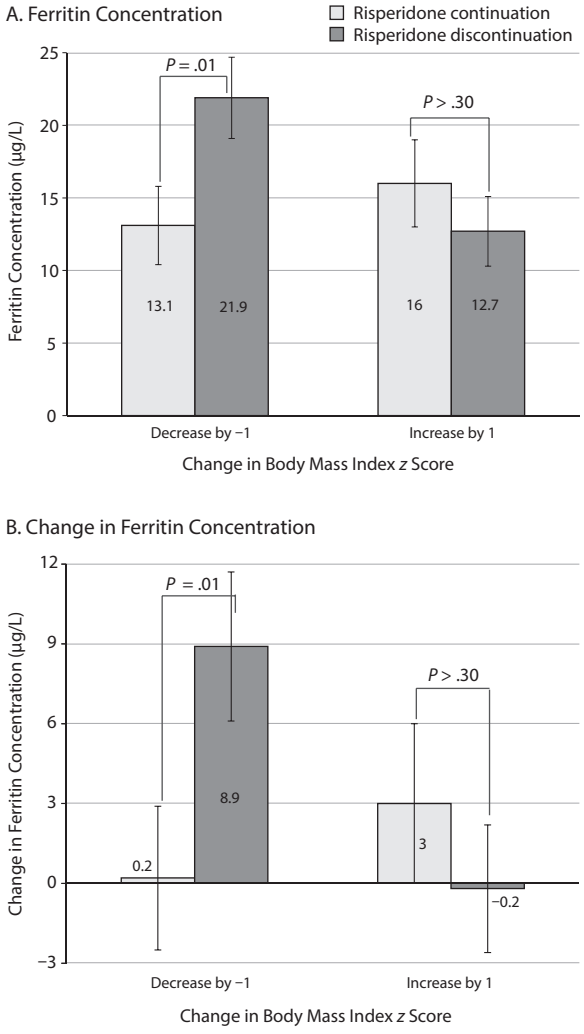
Additionally, with ferritin measurements available at baseline and follow-up, Study 1 confirms the inverse association between weight gain and reduction in body iron concentration. This is predictable given the substantial risperidone-associated increase in BMI *z* score observed in Study 1, consistent with evidence linking rapid growth with reduction in body iron reserves.[27–29] A large portion of the newly added weight, following antipsychotic treatment, may be adipose tissue. Thus, although its need for vascularization might be smaller than that of lean tissue, it will nevertheless still place further demand for iron on a system already strained to meet the needs related to normal growth in children and adolescents. It is also possible that the accumulation of adipose tissue promotes inflammation, consequently inducing the release of hepcidin from the liver. Hepcidin down-regulates the iron transport protein ferroportin, thereby potently inhibiting intestinal iron absorption.[16,30,31] In fact, childhood obesity has been associated with iron depletion, a finding mediated at least in part by increased hepcidin.[30–33]

In further support of the association between change in weight during antipsychotic treatment and changes in body iron reserves, we found that the discontinuation of risperidone resulted in the resolution of the excessive age-inappropriate weight gain.[19] This was correlated with an improvement in ferritin concentration. As detailed elsewhere,[19] those who discontinued risperidone still gained significant weight between study entry and follow-up, but with a less steep trajectory, compared to those who continued taking risperidone, a rate slow enough for their sex-age–specific BMI *z* score to return to its pre-risperidone baseline through normal maturation by the follow-up visit. This increase in weight, necessary for growth and development during childhood and adolescence, still requires iron for vascularization and normal cellular functions, which perhaps explains the only partial repletion of body iron reserves by follow-up, despite the fact that iron dietary intake was within the recommended range.[34]

Of interest, there was a significant interaction effect between change in BMI *z* score and risperidone treatment status in predicting change in ferritin concentration. Among participants whose BMI *z* score increased at follow-up, ferritin concentration did not significantly change, regardless of whether risperidone was continued or not. This is quite likely due to the fact that ferritin was already strikingly low (ie, floor effect). In contrast, among participants whose BMI *z* score decreased, ferritin concentration improved only in those who discontinued risperidone. This suggests that risperidone may be directly inhibiting iron absorption, thereby suppressing the beneficial effect of BMI *z* score reduction on iron status. This finding is not explained by sample characteristics because the range of BMI *z* score change between study entry and follow-up among those who continued on risperidone was −1.2 to 0.95, while the range for those who discontinued all antipsychotic treatment was −1.93 to 0.15. Further, the findings were not altered by excluding those participants who switched to a different antipsychotic.

The clinical implications of our findings have yet to be fully examined. In a previous risperidone clinical trial in ASD, there was a statistical trend for ferritin concentration to mediate clinical response to risperidone treatment.[35] However, the number of participants with ferritin measurements at baseline and follow-up was small, restricting statistical power. We have previously found iron status to be inversely correlated with response to stimulants in ADHD and with prolactin concentration during long-term treatment with risperidone.[12,16] We have also found that prolactin was inversely related to bone mass.[22] Therefore, low body iron reserves could possibly impair treatment response as well as medication tolerability. These are hypotheses that deserve further investigation.

**Figure 2. Least Squares Means of Ferritin Concentration at Follow-Up (A) and of Change in Ferritin Concentration Between Study Entry and Follow-Up (B) Among Participants in Chronic Risperidone Treatment, Some of Whom Had Discontinued It by Follow-Up (Study 2)[a]**




[a]The reduction, but not increase, in age-sex–specific body mass index *z* score between study entry and follow-up was associated with a higher ferritin concentration at follow-up and a larger increase in ferritin concentration between study entry and follow-up in those who discontinued risperidone compared to those who continued it.

This study suffers from several limitations. First, budgetary restrictions prohibited the measurement of additional markers that could have shed further light on the magnitude and impact of body iron store depletion. Red blood cell count and hemoglobin concentration were available in Study 1 and were normal. However, follow-up took place only 18 weeks after risperidone initiation, and the fact that these markers are the last to be impacted by iron deficiency suggests that it would have been very unlikely that frank anemia would develop. In Study 2, these markers were not measured. We used a drastic change in ferritin concentration and elevated CRP to exclude cases with acute inflammation, but additional cases of masked iron depletion could still have been missed. Further, a thorough assessment of iron intake may shed more light on whether malnutrition contributed to the findings. This possibility is unlikely, however, as our data suggest that intake was within the recommended range.[34] Finally, further research is necessary to examine whether a similar reduction in body iron concentration is observed during treatment with other antipsychotic medications, and to establish the clinical implications of low iron reserves in this population and determine whether iron supplementation would be indicated.

## CONCLUSIONS

Risperidone-related weight gain may be associated with a reduction in body iron stores. Loss of excessive weight may result in improved iron status but apparently not if risperidone treatment is continued.

### Clinical Significance

Optimizing the safety of antipsychotics is necessary as their use in children and adolescents is widespread. One so-far little appreciated adverse event is the depletion of iron stores as a result of weight gain and/or a direct effect of the medication, specifically risperidone. The full clinical implications of such depletion are unknown but could include reduced treatment efficacy and tolerability given that brain iron deficiency is associated with impaired dopaminergic signaling. Thus, clinicians may need to monitor iron status during long-term risperidone treatment.

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***Drug names:*** aripiprazole (Abilify), risperidone (Risperdal and others).

***Potential conflicts of interest:*** **Dr Aman** has received research contracts, consulted with, or served on advisory boards of Biomarin, Bristol-Myers Squibb, Confluence, Coronado Biosciences, Forest Research, Hoffman LaRoche, Johnson and Johnson, Novartis, Pfizer, ProPhase, and Supernus. **Dr Scahill** reports serving as a consultant for Coronado Biosciences, Bracket, Shire, MedAdvante, and Hoffman LaRoche. He also receives royalties from Oxford Press and Guilford Press. **Dr McCracken** reports serving as a consultant to Roche and receiving research contracts from Roche and Seaside Therapeutics. **Dr Arnold** has received research funding from Curemark, Forest, Lilly, Neuropharm, Shire (as well as NIH and Autism Speaks) and has consulted or been on advisory boards for Pfizer, Tris Pharma, Neuropharm, Novartis, Noven, Organon, Roche, Seaside Therapeutics, and Shire. **Drs Calarge, Ziegler, Del Castillo**, and **McDougle** report no competing interests.

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