Selective Serotonin Reuptake Inhibitors Reduce Longitudinal Growth in Risperidone-Treated Boys

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Objectives To examine whether selective serotonin reuptake inhibitors (SSRIs) inhibit longitudinal growth in children and adolescents, particularly in the early stages of puberty, using a sample of convenience comprising risperidone-treated boys.

Study design Data from four clinic-based studies in risperidone-treated 5- to 17-year-old boys with no general medical conditions were combined for this analysis. Anthropometric measurements and psychotropic treatment history were extracted from the medical and pharmacy records. Linear mixed effects regression analyses examined the association between SSRI use and change in age-sex-specific height and body mass index z scores, after adjusting for relevant confounders.

Results Risperidone-treated boys (n = 267; age: 12.7 ± 2.7 years), 71% of whom had ever taken an SSRI, contributed to the analysis. After adjusting for age, psychostimulant and antipsychotic use, and time in the study, both the duration of SSRI use as well as the cumulative dose were inversely associated with height z score after age 11 years ($P < .0001$). After adjusting for baseline height, duration of SSRI use was most strongly inversely associated with height z score in Tanner stages 3 and 4 boys who took SSRIs continuously (r = –0.69, $P < .009$). No association was observed with body mass index z score.

Conclusions In risperidone-treated boys, SSRI use is associated with reduced longitudinal growth, particularly in those undergoing puberty. Whether adult height or other metabolic or psychological outcomes are affected remains to be determined. *(J Pediatr 2018;■■:■■-■■).*

Antidepressant medications are among the 3 most commonly prescribed classes of drugs in the US, and their use has increased by nearly 65% between 1999 and 2014.[1] This trend also applies to adolescents,[1,2] where an estimated 4.8% of all prescriptions written for 12- to 19-year-olds are for antidepressants, ranking third after psychostimulants (6.1%) and bronchodilators (5.4%).[3] Given their efficacy and safety profile, selective serotonin reuptake inhibitors (SSRIs) are by far the most widely used class of antidepressants.[2]

Using data from a prospective observational study, we found SSRI use to be inversely associated with longitudinal growth in older adolescents and young adults.[4] This association was most pronounced with fluoxetine,[4] consistent with findings from a relapse prevention study.[5] In this latter clinical trial, 9- to 17-year-old patients randomized to fluoxetine exhibited a smaller increase in their sex-age-specific height over the first 19 weeks of the study (–0.1 vs +.07 z score, $P = .001$).[5] However, by 1 year of treatment, the difference with placebo was no longer significant (–.04 vs +0.15 z score, $P = .130$). Notably, the magnitude of the difference did not appreciably change; however, 65% of the original sample dropped out, reducing statistical power.[6,7] In fact, concerns about the effects of SSRIs on longitudinal growth had been raised in a case series of 4 adolescents (ages 11.6-13.7 years), where growth recovered following treatment discontinuation.[8] In the one case where the SSRI (fluoxetine) was reinstated, nearly 18 months after it had been discontinued, longitudinal growth was suppressed again.[8] These findings are consistent with preclinical evidence showing decreased growth in fluoxetine-treated rats and rhesus monkeys.[9,10]

Our earlier finding of a suppressing effect of SSRIs on growth was unexpected given that the participants were mostly female subjects (60%), of an age (range: 15-20 years) where the potential for additional longitudinal growth would be

BMI	Body mass index
GH	Growth hormone
IGF	Insulin-like growth factor
SSRI	Selective serotonin reuptake inhibitor
TORDIA	Treatment of Resistant Depression in Adolescents

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Funded by a 2005 and a 2007 Young Investigator Award, a Fraternal Order of Eagle Diabetes Research Center pilot grant, and by the National Institutes of Health (RR024979, R21MH080968, and K23MH085005). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agency. J.G. receives funding support from Pfizer Inc and Aeterna Zentaris Inc. The other authors declare no conflicts of interest.

Portions of this study were presented as a poster at the annual meeting of the American Academy of Child and Adolescent Psychiatry, Washington, DC, October 25, 2017.

https://doi.org10.1016/j.jpeds.2018.05.040

minimal.[4,11] Therefore, in light of evidence suggesting that risperidone does not hinder longitudinal growth,[12,13] we used a sample of convenience, recruited in the context of four independent studies in risperidone-treated boys of a wider age range, in an effort to replicate our findings.[14-18] We hypothesized that SSRIs inhibit longitudinal growth and that this effect is observed in the early stages of puberty.

Methods

Data from 4 studies were combined in this analysis to maximize sample size. Three studies included children and adolescents who had been taking risperidone for at least 6 or 12 months.[15-17,19] The fourth consisted of a longitudinal observational study that included 6 children who had initiated treatment with risperidone within the prior month.[18] In all 4 studies, concurrent treatment with more than 1 antipsychotic medication and chronic medical or neurologic conditions led to exclusion.

All the studies were approved by the local Institutional Review Board. After study description, written consent was obtained from parents or legal guardians and assent from the participants.

At study entry, height was measured by trained nursing staff to the nearest 0.1 cm using a stadiometer (Holtain Ltd, Crymych, United Kingdom) while the participants were standing erect, and weight was recorded to the nearest 0.1 kg using a digital scale (Scaletronix, Wheaton, Illinois) while participants were in indoor clothes without shoes.[20] The medical and pharmacy records were reviewed to extract all available anthropometric measurements and psychotropic treatments, including the start and stop date of each medication.[20] All dosages of psychostimulants were expressed in methylphenidate equivalents for amphetamines (×2).[21] Of note, we sought to verify the reliability of the anthropometric measurements extracted from the medical records. Therefore, we compared the height and weight measurements obtained during the research visits, following standard procedures as described above, to those extracted from the medical records, collected during clinical encounters falling within a month of the research visit (mean ±SD interval = 16 ± 9 days for height, n = 69, and 17 ± 9 days for weight, n = 97).[20] The intraclass correlation coefficients for unadjusted height and weight and for age-sex-specific z cores were all above 0.97 (95% CI 0.93-0.99).[20]

At enrollment, Tanner stage of sexual development, based on pubic hair and genitalia appearance, was evaluated by physical examination conducted by a trained clinician (trained by pediatric endocrinologist) as well as using a self-completed form.[22] Interrater agreement between the physician and self-rating was high (weighted kappa = 0.81, 95% CI 0.74-0.88, n = 74).[21] Self-rating was used when rating by a clinician was unavailable (18% of the assessments). The genitalia rating was used in the analyses below.

A best-estimate diagnosis, following the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*,[23] was generated based on a review of the psychiatric record, supplemented by a standardized interview of the parent using the Diagnostic Interview Schedule for Children[24] (except in 1 small longitudinal study),[18] the Child Behavior Checklist,[25] and a clinical interview conducted by a child psychiatrist.

Statistical Analyses

Body mass index (BMI) was computed as weight/height^2 (kg/m^2) and age-sex-specific height and BMI z scores were generated based on the 2000 Centers for Disease Control and Prevention normative data.[26] As girls comprised only a small minority of the overall sample (8.7%) and because of major sex differences in pubertal development, the current analysis was restricted to boys. Group differences were compared using the Student *t* test for continuous variables and χ^2 or Fisher exact test for categorical ones.

Several sets of analyses were conducted. First, the association between SSRI use and anthropometric measures (height z score and BMI z score) was examined using a linear mixed effects regression.[27] SSRI use was captured in terms of duration and dose of use. The dose of individual SSRIs was converted into a standardized unit (eg, fluoxetine 20 mg = citalopram 20 mg, etc).[22] Given the dramatic change in growth rate during childhood and the low likelihood of SSRI use, all anthropometric observations obtained before age 7 years were excluded a priori. All models included adjustment for age (years) at study entry and for the use of antipsychotics and psychostimulants because of their known effects on BMI and/or longitudinal growth. Participant-specific random intercepts and slopes were used with an unstructured covariance matrix. Duration of study participation was the time metric in the analysis. Maximum likelihood methods were used for estimation, which yielded unbiased estimates under the assumption that the missing data mechanism is ignorable.[28] SSRI use-related variables were analyzed as time-dependent covariates and decomposed into a between-subject and a within-subject component.[29] The former represents a cross-sectional effect, whereas the latter represents an average individual slope effect.

Next, we aimed to investigate whether the effect of SSRIs is different before compared with following the onset of puberty. To that end, all anthropometric data available between ages 7 and 10.99 years defined the "prepubertal" phase. At age 11 years and after, a given participant could contribute to the "pubertal" data as long as they had not received an SSRI prior to age 11 years, to avoid any carry-over effect. This strategy was used because Tanner stage was only available at study entry, not when SSRIs were started.

Finally, in a sensitivity analysis, we restricted the overall sample to boys who, once prescribed SSRIs, took them continuously (SSRI-continuously). Moreover, we excluded participants whose SSRI treatment was less than 6 months, to ensure an adequate exposure period. Only participants with baseline height measurements obtained within 60 days of starting SSRIs were included. We reasoned that height was unlikely to appreciably change, as a result of SSRI use, within this relatively short period of time. A group consisting of participants who had never taken SSRIs (SSRI-never) was selected. Given that these participants had not been on SSRIs, an

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Table I. Baseline demographic and clinical characteristics of the overall sample, divided in boys who had never been treated with SSRIs vs those who had (mean ±SD, unless noted otherwise)

	Never on SSRI n = 77	SSRI n = 190	*P* value
Age, y	11.5 ± 2.6	13.1 ± 2.6	**<.0001**
Tanner stage I/II/III/IV/V (%)	39/21/8/15/17	22/15/15/22/27	**<.03**
White race, n (%)	57 (74)	164 (86)	**<.02**
Height z score	.17 ± .98	.25 ± .98	>.50
BMI z score	.43 ± 1.11	.60 ± 1.10	>.20
Psychiatric characteristics			
Attention deficit hyperactivity disorder, n (%)	74 (96)	168 (88)	***<.06***
Disruptive behavior disorder, n (%)	69 (90)	173 (91)	>.70
Depressive disorder, n (%)	1 (1)	11 (6)	>.10
Anxiety disorder, n (%)	5 (6)	77 (41)	**<.0001**
Autism spectrum disorder, n (%)	6 (8)	46 (24)	**<.003**
Tic disorder, n (%)	12 (16)	40 (21)	>.30
Duration of SSRI treatment, y	0	2.52 ± 2.11	**<.0001**
SSRI dose, unit	0	.88 ± 1.00	**<.0001**
Daily dose of risperidone, mg/kg	.03 ± .02	.03 ± .03	>.20
Risperidone for irritability/aggression, n (%)	59 (81)	161 (85)	>.30
Psychostimulant use, n (%)	60 (82)	106 (64)	**<.006**
Daily dose of psychostimulants, mg/kg	1.27 ± .65	1.26 ± .55	>.90

Significant results ($P < .05$) are bolded and marginally significant results ($P < .10$) are bolded and italicized.
SSRI dose was standardized across agents: One SSRI unit was defined as being equivalent to a daily dose of 20 mg of fluoxetine or citalopram, or 50 mg of sertraline, or 10 mg of escitalopram.

observational period of comparable duration was selected to define "baseline" anthropometric measurements and compute a change score. The Pearson correlation coefficient was used to examine the linear association between SSRI use and the anthropometric measures.

All hypothesis tests were 2-tailed with a significance level of $P < .05$, and analyses used procedures from SAS v 9.4 for Windows (SAS Institute Inc, Cary, North Carolina).

Results

Longitudinal Association between SSRIs and Longitudinal Growth after Age 7 Years

Of 299 enrolled participants, 26 (8.7%) were female and, thus, excluded from the analysis. Another 6 (2%) participants were excluded either because of age restriction (ie, <7 years old) or missing data (n = 5). The demographic and clinical characteristics of the 267 participants included in this first analysis are summarized in Table I. They contributed a combined 4592 height measurements.

Linear mixed regression analysis was used to examine the association of SSRI use with height z score. After adjusting for age, psychostimulant use, antipsychotic use, and time, a significant inverse longitudinal association (ie, within-subject effect) between the cumulative dose of SSRI used and height z score was observed ($P < .02$, Table II). However, after adjusting for the same variables, there was neither a significant cross-sectional (ie, between-subject effect) nor a longitudinal association between cumulative SSRI treatment duration and height z score (Table II). Adjusting for race, which was different between the groups, did not alter the findings.

Effect of Puberty

When the analysis was restricted to observations obtained between ages 7 and 10.99 years, after adjusting for age, psychostimulant use ($P < .06$), antipsychotic use, and time ($P < .02$), there was no significant longitudinal association between cumulative SSRI treatment duration or dose and height z score (participants n = 259, height observations n = 2659, Table II). However, the cumulative SSRI dose was positively associated (cross-sectionally, but not longitudinally) with height z score ($P < .04$), and the association with duration of treatment failed to reach significance ($P < .09$, Table II).

In contrast, when the analysis was restricted to observations obtained after age 11 years (participants n = 83, observations n = 901), with no prior SSRI exposure, the findings were quite different. After adjusting for age, psychostimulant use ($P < .0001$), antipsychotic use, and time ($P < .06$), there was

Table II. Parameter estimates (±SEs) from linear mixed effects regression analysis models for age-sex-specific height z scores

	Full sample		Age 7-10.99 y		Age ≥11 y	
	Duration	Dose	Duration	Dose	Duration	Dose
Baseline age	–.01 ± .05	–.01 ± .05	–.03 ± .07	–.05 ± .07	.01 ± .07	.01 ± .07
Psychostimulant use	.01 ± .02	.01 ± .02	***–.04 ± .02***	***–.04 ± .02***	**.14 ± .04**	**.14 ± .04**
Antipsychotic use	.00 ± .01	.00 ± .01	.02 ± .02	.02 ± .02	–.04 ± .03	–.04 ± .03
Time	**.04 ± .01**	**.04 ± .01**	**.03 ± .01**	**.03 ± .01**	***.05 ± .03***	***.05 ± .03***
SSRI effect						
Between-subject	.70 ± .46	.45 ± .31	***.86 ± .50***	**.73 ± .34**	–.00 ± .86	–.12 ± .53
Within-subject	–.03 ± .02	**–.04 ± .02**	–.04 ± .03	–.05 ± .03	**–.17 ± .04***	**–.12 ± .03**

Significant results ($P < .05$) are bolded and marginally significant results ($P < .10$) are bolded and italicized.
Duration: refers to the cumulative duration of SSRI treatment. Dose: refers to the cumulative dose of SSRI treatment. Between-subject effect represents a cross-sectional effect, whereas within-subject effect represents an average individual slope effect.
*The following suggests that, in boys 11 years and older, keeping baseline age and psychostimulant and antipsychotic use constant, for every one year of continuous SSRI treatment, height z score will be smaller by .17 point compared to not taking SSRIs at all.

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a significant inverse longitudinal association between height z score and the cumulative SSRI treatment duration ($P < .0001$) as well as the cumulative SSRI dose ($P < .0001$, **Table II**). Of note, controlling for the duration of psychostimulant use (as opposed to whether psychostimulants were used or not) did not alter the findings (within-subject effect β for duration of SSRI use = –0.18 ± .04, $P < .0001$). In addition, adjusting for the total number of comorbid psychiatric disorders ($P > .60$) also did not alter the findings substantially.

In terms of change in raw (unadjusted) height, the same models suggest that, holding all other covariates constant, every 1 year of continuous SSRI use after age 11 years in our participants was associated with a failure to grow by 1 cm ($P = .0012$). All the findings remained virtually unchanged after adjusting for race.

Of note, after adjusting for the same variables, neither SSRI treatment duration nor SSRI dose was longitudinally associated with BMI z score either before or after age 11 years, although SSRI treatment duration was nearly significantly associated with it, longitudinally, before age 11 years ($\beta = 0.105$, SE = .054, $P < .06$).

Effect of Continuous SSRI Use

Finally, following the criteria described earlier, 2 subgroups of participants (SSRI-continuously vs SSRI-never) were formed (**Table III**). Among SSRI-continuously boys, after adjusting for baseline height z score obtained within 2 months of SSRI initiation, there was an inverse correlation between duration of SSRI exposure and change in height z score (r = –0.30, $P < .05$). Adjusting for the duration of psychostimulant treatment (natural log transformed) did not alter the results. Although this correlation was negligible in Tanner stage 1 (r = –0.10, n = 13) and Tanner stage 5 boys (r = –0.10, n = 14), it was quite large in Tanner stage 3 and 4 boys (r = –0.69, $P < .009$, n = 14, **Figure**). There were only 5 boys in Tanner stage 2. No such association was found between duration of SSRI use and BMI z score (r = .00), after adjusting for baseline BMI z score. Similarly, after adjusting for baseline height z score, no association was found between time and change in height z score in the SSRI-never group. Of note, although not statistically significant, SSRI-continuously participants in Tanner stage 3 and 4 had a numerically smaller height z score compared with those in the SSRI-never group (–0.20 ± 1.25 vs 0.12 ± 0.86, $P > .40$, Cohen d = –0.29).

Table III. Baseline demographic and clinical characteristics of boys who had taken SSRIs continuously and a matched group of never SSRI-treated (mean ± SD, unless noted otherwise)

	Never on SSRI n = 48	SSRI continuously n = 49	*P* value
Age, y	12.6 ± 2.5	13.1 ± 2.8	>.30
Tanner stage I/II/III/IV/V (%)	32/16/7/18/27	28/13/15/15/30	>.70
White race, n (%)	35 (73)	42 (86)	>.10
Height z score			
At study entry	.02 ± 1.00	.01 ± 1.05	>.90
Change since baseline	–.06 ± .61	–.04 ± .52	>.90
Time since baseline height, y	3.1 ± 2.1	3.0 ± 2.1	>.60
BMI z score			
At study entry	.44 ± 1.08	.54 ± 1.07	>.60
Change since baseline	–.10 ± .73	.42 ± .88	**<.003**
Psychiatric characteristics			
Attention deficit hyperactivity disorder, n (%)	46 (96)	44 (90)	>.40
Disruptive behavior disorder, n (%)	43 (90)	38 (78)	>.10
Depressive disorder, n (%)	1 (2)	4 (8)	>.10
Anxiety disorder, n (%)	2 (4)	18 (37)	**<.0001**
Autism spectrum disorder, n (%)	4 (8)	17 (35)	**<.002**
Tic disorder, n (%)	10 (21)	13 (27)	>.50
Duration of SSRI treatment, y	0	2.99 ± 2.08	**<.0001**
SSRI dose, unit	0	1.14 ± .91	**<.0001**
Daily dose of risperidone, mg/kg	.03 ± .01	.04 ± .03	**<.02**
Psychostimulant use, n (%)	39 (81)	31 (63)	**<.05**
Daily dose of psychostimulants, mg/kg	1.29 ± .66	1.26 ± .66	>.80
Duration of psychostimulant treatment, y	4.87 ± 3.06	5.86 ± 2.89	>.10

Significant results ($P < .05$) are bolded.
SSRI dose was standardized across agents: One SSRI unit was defined as being equivalent to a daily dose of 20 mg of fluoxetine or citalopram, or 50 mg of sertraline, or 10 mg of escitalopram.

Discussion

We sought to replicate the finding of an adverse effect of SSRIs on longitudinal growth in a large sample of convenience comprising boys enrolled in studies aimed at examining the skeletal effects of risperidone. As predicted, SSRI use was associated with reduced growth in height, particularly in boys in Tanner stages 3 and 4. This effect is of a moderate magnitude of about 1 cm for every 1 year of treatment with SSRIs during adolescence.

Unlike psychostimulants, long-known to cause growth suppression,[30,31] only a few studies have examined the effect of SSRIs on height. As noted earlier, a relapse prevention study found children and adolescents randomized to fluoxetine to exhibit a significantly smaller increase in height by week 19 of the study, compared with those assigned to placebo.[5] This difference disappeared at 1 year, however, likely because of major attrition.[6] In the Treatment of Resistant Depression in Adolescents (TORDIA), there was no difference in the change in height between adolescents randomized to SSRIs vs venlafaxine, over the 24-week duration of the study.[32] However, a reanalysis of the data revealed that although change in height by week 12 was not different between the 2 groups (Cohen d = –.05, 95% CI –0.36, 0.25; favoring SSRIs, SSRI n = 80 and venlafaxine n = 88), by week 24, venlafaxine was associated with a larger increase in height, narrowly missing significance (Cohen d = 0.29, 95% CI –.05, 0.63; SSRI n = 61 and venlafaxine n = 71, David Brent, MD, email communication). Albeit small, this effect is nonetheless striking given that the average age of the participants was about 16 years, with female participants comprising about 70% of the sample.[33] Therefore, most longitudinal growth should have been completed by study enrollment, similar to our earlier study.[11] Moreover, by design, all participants in TORDIA had received SSRIs for at least 8 weeks, the last 4 of which at a dosage equivalent to 40 mg of fluoxetine.[33]

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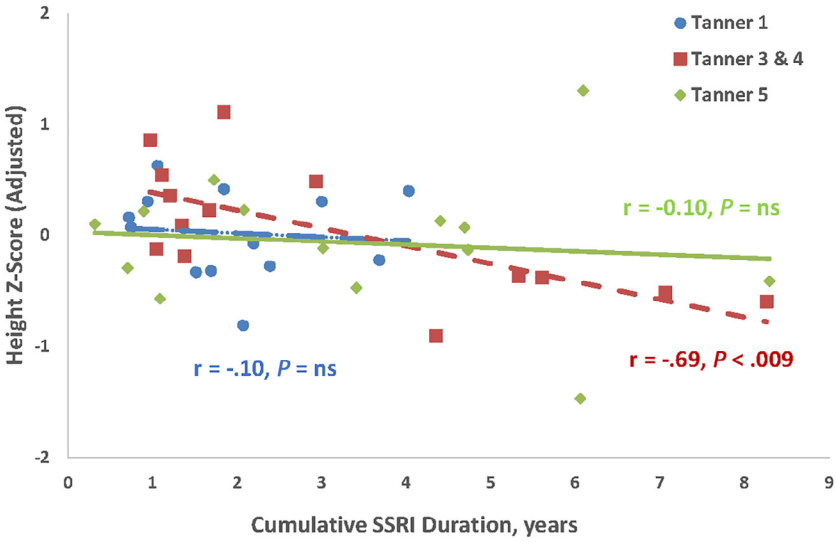

Figure. Linear correlation between duration of use of selective serotonin reuptake inhibitors (SSRIs, in years) and age-sex-specific height z score, across different Tanner stages at study entry, in boys who received SSRIs continuously, for at least 6 months. Height z score is adjusted for height z score at the onset of SSRI treatment. Given that only 5 participants were in Tanner stage 2, they were excluded from this analysis.

Thus, their growth could have already been suppressed, attenuating the effect observed during the course of the study. Finally, venlafaxine has a serotonin reuptake inhibitor activity, potentially leading to growth suppression itself.

Because the effect of SSRIs on longitudinal growth has not been widely recognized, the underlying pathophysiology has not been investigated. Impaired growth hormone (GH) secretion or activity has been implicated, given that SSRIs alter serotonin signaling, which is known to control GH secretion.[34] In fact, there is some evidence that SSRIs could inhibit GH secretion relatively soon after treatment onset.[8] This may be consistent with our finding of a larger impact in boys in Tanner stages 3 and 4, a period when height velocity is most likely to peak, rendering it most susceptible to disruption.[35] Notably, although GH stimulates longitudinal growth throughout childhood and adolescence, it is during puberty that its secretion most rapidly increases.[36,37] Not only were SSRIs associated with smaller growth following in utero exposure, citalopram was associated with lower cord blood insulin-like growth factor (IGF)-I concentration compared with paroxetine-exposed and unexposed infants.[38] Similarly, SSRIs have been associated with reduction in IGF-1 in adults.[39,40] Notably, GH mediates growth primarily through stimulation of hepatic and peripheral release of IGF-I.[41] Finally, it has been postulated that psychostimulant-induced growth suppression may be due to their anorectic effect.[42,43] This is unlikely in our participants given that their BMI z score was above normal (**Tables I** and **III**). In fact, although severe malnutrition can affect longitudinal growth, the trajectories of change in weight and height are often independent, including in psychostimulant-treated children.[44]

Beyond growth suppression, disrupted GH activity can promote central adiposity,[4,32,45] affect cognitive and emotional processing, and is associated with depression, social isolation, and low overall quality of life.[45] In addition, height itself has psychosocial implications, as evidenced by its association with early life experiences, psychological well-being, future earnings, and longevity.[46-50] Nonetheless, the risk for side effects is but one of several factors that ought to be considered during treatment planning, given the significant distress and impairment associated with untreated depressive and anxiety disorders.[51-53]

This study has several limitations. First, it was based on data from 4 studies where assignment to SSRI treatment was not randomized. Thus, as expected, clear differences in clinical characteristics between SSRI-treated vs never-treated participants were apparent (**Tables I** and **III**). It is not clear; however, that long-term studies like this one are feasible using a randomized placebo-controlled design, for ethical and practical reasons. It is also possible that depressive disorders or psychological distress contributed to our findings, as shown in at least 2 studies.[54,55] However, neither study accounted for antidepressant use. In addition, the rate of depressive disorders in our sample was quite low but there was a significant group difference in anxiety disorders. Finally, both TORDIA and the fluoxetine relapse prevention study only recruited participants with major depressive disorder.[7,33] Another limitation of our study is that Tanner staging was based on genitalia. Future studies should assess testicular size and bone age, which are more accurate markers of pubertal development. Also, almost all the participants were treated with risperidone and a substantial majority with psychostimulants. It is possible that statistical adjustment is insufficient to account for the contribution of polypharmacy to our findings. We also could not verify medication adherence over the long duration of the study. Of note, it was the group of participants not taking SSRIs that was more likely to receive psychostimulants (**Tables I** and **III**). This would have

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biased the findings toward the null hypothesis. Moreover, risperidone has not been associated with longitudinal growth delays.[12,13] Finally, our findings may not apply to female subjects, who formed too small a minority of our participants to be included in this analysis. Given that sex might interact with the metabolic effect of SSRIs,[56,57] future studies should include girls as well as patients from more diverse racial and ethnic backgrounds. Furthermore, a stepwise approach is needed to determine the effect of SSRIs on growth velocity, GH activity, and include a follow up after SSRIs are discontinued as well as into adulthood to determine if the effect is reversible and whether adult height is indeed adversely impacted.

In the meantime, clinicians should continue to closely monitor children and adolescents starting antidepressant treatment to minimize side effects. ■

We thank the families for enrolling in the studies and the research team for conducting the work.

Submitted for publication Feb 10, 2018; last revision received Apr 12, 2018; accepted May 22, 2018

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