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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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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