Longitudinal Examination of the Skeletal Effects of Selective Serotonin Reuptake Inhibitors and Risperidone in Boys

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ABSTRACT

Objective: In a previous cross-sectional study, we found lower bone mass during treatment with selective serotonin reuptake inhibitors (SSRIs) and risperidone in youths. Here, we evaluate the skeletal effects of these psychotropics at follow-up.

Method: Between April 2005 and July 2011, medically healthy 7- to 17-year-old males treated with risperidone for 6 months or more were enrolled through child psychiatry outpatient clinics and returned for follow-up 1.5 years later. Treatment history was extracted from the medical and pharmacy records. Anthropometric, laboratory, and bone mass measurements were obtained. Multivariable linear regression analyses compared participants who remained on risperidone at follow-up to those who had discontinued risperidone treatment as well as SSRI-treated versus SSRI-unexposed participants.

Results: The sample consisted of 94 boys with a mean age of 11.8 ± 2.7 years at study entry. The majority had an externalizing disorder and had received risperidone and SSRIs for 2.5 ± 1.7 years and 1.6 ± 1.9 years, respectively, at study entry. By follow-up, 26% (n = 24) had discontinued risperidone. Compared to discontinuing risperidone, continuing it was associated with a decline in participants' age-sex-height-race–specific areal bone mineral density (BMD) *z* score at the lumbar spine ($P < .04$) and failure to increase radius trabecular volumetric BMD ($P < .03$), after accounting for significant covariates. In addition, receiving an SSRI was associated with reduced lumbar spine areal BMD *z* score and radius trabecular volumetric BMD at both study entry ($P < .02$ and $P < .03$, respectively) and follow-up ($P < .06$ and $P < .03$, respectively), but without further decline between the 2 visits.

Conclusions: Chronic SSRI treatment in children and adolescents is associated with reduced, albeit stable, bone mass for age, while chronic risperidone treatment is associated with failure to accrue bone mass.

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Selective serotonin reuptake inhibitors (SSRIs) and second-generation antipsychotics (SGAs) are widely prescribed, often long-term. Therefore, in order to optimize patient care, attention is increasingly paid to the safety of extended use of psychotropics, particularly regarding cardiovascular risk.[1–5]

One potential, but largely neglected, side effect is the risk for loss of bone mass,[6,7] leading to osteopenia/osteoporosis. Osteoporosis is estimated to affect around 3.5% of the US population, resulting in billions of dollars in annual costs related to fractures and disability.[8] Most antipsychotics cause hyperprolactinemia, which persists in a significant proportion of patients during chronic use[9,10] and has been linked to osteopenia in patients with prolactin-secreting pituitary adenomas.[11] However, additional processes, perhaps more directly related to the drugs' pharmacodynamics, could also interfere with skeletal metabolism during SGA treatment.[12,13] Similarly, SSRIs have been implicated in loss of bone mass and increased fracture risk.[6,14] This can occur by disrupting functional serotonin signaling in bone cells peripherally[14,15] and modulating sympathetic nervous system activity centrally, through hypothalamic serotonin 5-HT_{2C} receptors.[16,17]

Previously, we examined skeletal health in a group of boys in extended risperidone treatment and found an inverse association between prolactin serum concentration and trabecular volumetric bone mineral density (vBMD) at the ultradistal radius as measured using peripheral quantitative computed tomography (pQCT).[18] Furthermore, SSRI use was associated with lower vBMD at the ultradistal radius as well as lower age-sex–specific areal bone mineral density (aBMD) *z* score at the lumbar spine, measured using dual-energy x-ray absorptiometry (DXA).[18] DXA is the most widely used method to assess bone mass, particularly in clinical settings, but pQCT has the additional advantages of generating a true estimate of BMD and isolating trabecular from cortical bone.[19,20] Trabecular bone is more metabolically active and, consequently, more susceptible to the effect of various metabolic factors (eg, hormonal, toxic, pharmacologic).[19,20] Here, we describe the outcome of the bone measurements in participants who returned for follow-up 18 months after study entry. Specifically, we examined the skeletal effects of SSRI treatment and continuing versus discontinuing risperidone, between study entry and follow-up. We anticipated that the use of these medications would be associated with lower bone mass.

METHOD

Participants

As previously described,[18] 7- to 17-year-old patients treated with risperidone for 6 months or more were enrolled in the study between April 2005 and October 2009, irrespective of the indication for risperidone. Concurrent treatment at study entry with additional psychotropics, but not with other antipsychotics, was allowed. In fact, 54% of the participants were receiving SSRIs concurrently.[18,21] Participants with chronic medical conditions were excluded, as were pregnant females and those receiving hormonal contraception. Eighteen months after study entry, the participants returned for a follow-up between July 2007 and July 2011, when study

Clinical Points

- Following extended treatment, risperidone was associated with progressive bone loss in youths, while SSRIs were associated with reduced, but stable, bone mass.
- While the long-term impact on fracture risk is presently unknown, clinicians should continue to monitor the long-term safety of psychotropic medications, particularly in youths, and to promote healthy lifestyle habits, including nutrition and physical activity.

entry assessments were repeated. This study was approved by the local Institutional Review Board. After providing a complete description of the study, we obtained written assent from children ≤ 14 years of age, and written consent from adolescents and parents or guardians.

Procedures

All medication use was recorded from the medical and pharmacy records.[18,22] During both research visits, anthropometric measurements were obtained following a standard protocol, and pubertal stage was recorded.[18,22]

A best-estimate diagnosis, following the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*),[23] was generated based on a review of the psychiatric record, often supplemented by a clinical interview (conducted by C.A.C.), a standardized interview of the parent using the National Institute of Mental Health Diagnostic Interview Schedule for Children (DISC-IV),[24] and the Child Behavior Checklist.[25]

Daily calcium and vitamin D intake during the week prior to enrollment was estimated using the 2004 Block Kids Food Frequency Questionnaire[26] and physical activity was assessed by asking the parents to compare their child's usual level of physical activity to their peers', using a 5-point Likert scale.[27]

A blood sample was obtained to measure prolactin, testosterone, 2 markers of bone formation (osteocalcin and bone-specific alkaline phosphatase), a marker of bone resorption (collagen type I C-telopeptide [CTX]), and trough (ie, before the morning dose) serum risperidone and 9-hydroxyrisperidone concentrations (referred to, henceforth, as risperidone concentration). Due to funding considerations, the bone turnover markers were added at a later point in the study, making them available primarily at follow-up. Only measurements from samples obtained in the morning, from participants who were fasting, were included in the analyses.

Following the same protocol described previously,[18] vBMD at the nondominant ultradistal radius was measured with pQCT using a Stratec XCT-2000 scanner, software version 6.0 (Stratec, Inc, Pforzheim, Germany). Trabecular vBMD was measured as the mean density of the 90% central area of the bone's cross section, while total vBMD encompassed the entire bone mass, including the thin cortical shell. Compromised pQCT scans, eg, by movement, were rejected. A Hologic QDR DELPHI-4500A unit (Hologic, Inc, Bedford, Massachusetts) was used to estimate bone mineral content (BMC) and aBMD in the lumbar spine (L1–L4). Quality-control and calibration of the equipment were performed daily.

Data Analysis

Compared to participants who dropped out of the study (n = 43), those who returned for follow-up (n = 108) were less likely to have had a history of child maltreatment (6% vs 16%, P = .05) but more likely to be male (93% vs 79%, P = .02), to suffer from an autism spectrum disorder (18% vs 2%, P < .02), and to have been receiving an antidepressant (63% vs 40%, P < .02).[22]

Because the number of female participants who returned for follow-up was small (n = 7), and because BMD is strongly affected by sex, we restricted the analyses to boys.[18] Three boys were excluded due to the onset of hypothyroidism (n = 2) or type 1 diabetes by follow-up. Further, risperidone-treated participants whose serum risperidone concentration was undetectable at study entry or at follow-up were excluded due to suspected treatment nonadherence. Body mass index (BMI) was computed as weight/height^2 (kg/m^2), and height and BMI age-sex–specific *z* scores were generated based on the 2000 Centers for Disease Control and Prevention normative data.[28] Age-sex-height-race–specific *z* scores for lumbar spine BMC and aBMD were generated following the Bone Mineral Density in Childhood Study.[29] Using the laboratory-determined normal ranges, hyperprolactinemia was defined as a prolactin concentration > 15.2 ng/mL.

By design, all participants were taking risperidone at study entry. At follow-up, 74% (n = 70) were still taking it, with 17% (n = 16) discontinuing all SGA treatment and 9% (n = 8) switching to another SGA.[22]

Because no differences in bone measurements were observed between boys discontinuing all SGA treatment and those switching to another SGA, the groups were combined (Risperidone Discontinuation group) and compared to those who continued risperidone (Risperidone Continuation group) using Student *t* test for continuous variables and χ^2 test for categorical variables.

To examine the skeletal effects of SSRIs, 2 groups were identified: (1) those who were not receiving SSRIs either at study entry or at follow-up (No SSRI, n = 37) and (2) those who were taking SSRIs at both visits (SSRI group, n = 44). The remaining participants were too few, including those who took SSRIs at study entry but not at follow-up (n = 8), and vice versa (n = 5).

Multivariable linear regression analysis examined the association between continuing versus discontinuing risperidone and skeletal outcomes at study entry and follow-up, adjusting for relevant covariates as informed by our previous work.[18] Similar analyses examined the effect of SSRIs on skeletal health. Cohen *d* effect size was generated by dividing the difference in group-specific least squares means by the residual of the relevant multivariable linear regression model. All hypothesis tests were 2-tailed with a significance level of $P < .05$, and analyses were conducted

using procedures from SAS version 9.3 for Windows (SAS Institute Inc, Cary, North Carolina).

RESULTS

Participants

A total of 94 boys, 70 (74%) of whom were in the Risperidone Continuation group, returned for follow-up and met the criteria for inclusion in this analysis (Table 1). By far, the most common diagnoses were attention-deficit/hyperactivity disorder (n = 83, 88%) and disruptive behavior disorders (n = 82, 87%), with depressive disorder afflicting only a minority (n = 4, 4%). Risperidone was prescribed primarily (78%) for irritability and aggression.

SSRIs and Skeletal Outcomes

We first examined the skeletal outcomes in those participants who were consistently either on or off SSRIs both at study entry and follow-up (Table 2 and Figure 1). After adjusting for relevant confounders, treatment with SSRIs was associated with reduced bone mass at the lumbar spine and ultradistal radius at both study entry and follow-up. These associations were not appreciably altered with further adjustment for the anxious/depressed, withdrawn/depressed, or internalizing problems *t* scores of the Child Behavior Checklist obtained at follow-up, none of which significantly contributed to the model (all *P* values > .90). However, the change between both research visits was not significant.

After adjusting for stage of genitalia development, height *z* score, and the rate of change in height in the period between study entry and follow-up, we found that SSRI treatment was marginally associated with lower osteocalcin concentration at follow-up (β = −23.3, 95% confidence interval [CI], −47.3 to 0.7, Cohen *d* = 0.54, *P* < .06). However, there was no significant association with CTX (*P* > .10) or bone-specific alkaline phosphatase (*P* > .90).

Risperidone and Skeletal Outcomes

Next, we examined the association between continuing versus discontinuing risperidone by follow-up and the skeletal outcomes (Table 2 and Figure 1). No significant difference was found in any of the skeletal measures at study entry between the 2 risperidone treatment status groups (ie, Risperidone Continuation vs Risperidone Discontinuation). This finding is expected as all participants were on risperidone treatment at that point. There were also no significant differences at follow-up. However, after including the study entry lumbar spine aBMD *z* score (*P* < .0001) in the model, in addition to age, height *z* score, and BMI *z* score, the Risperidone Discontinuation group had a marginally significantly higher lumbar spine aBMD *z* score at follow-up (β = 0.17, 95% CI, −0.03 to 0.37, Cohen *d* = 0.42, *P* < .10). This is consistent with the significantly different change in lumbar spine aBMD *z* score between study entry and follow up, between the 2 groups (Table 2 and Figure 1). In fact, lumbar spine aBMD *z* score significantly declined (β = −0.13, 95% CI, −0.23 to −0.03, *P* = .01) between study entry and follow-up in the Risperidone Continuation group but did not change in the Risperidone Discontinuation group (*P* > .30). This association was attenuated when additional adjustment was made for anxious/depressed (Cohen *d* = 0.45, *P* < .09), withdrawn/depressed (Cohen *d* = 0.49, *P* < .06), or internalizing problems *t* scores (Cohen *d* = 0.45, *P* < .09) of the Child Behavior Checklist obtained at follow-up, none of which significantly contributed to the model (all *P* values > .50). Further, accounting for SSRI treatment status did not alter the findings.

Similarly, after adjusting for study entry trabecular vBMD (*P* < .0001), in addition to age, BMI *z* score, and physical activity, the Risperidone Continuation group had a significantly lower trabecular vBMD at follow-up (β = −19.7, 95% CI, −33.8 to −5.6, Cohen *d* = 1.03, *P* < .008). In fact, trabecular vBMD was unchanged between study entry and follow-up in the Risperidone Continuation group (*P* > .80) but increased in the Risperidone Discontinuation group (*P* < .002). This association was not appreciably altered by adjusting for the anxious/depressed, withdrawn/depressed, or internalizing problems *t* scores obtained at follow-up, none of which significantly contributed to the model (all *P* values > .20). Further, taking SSRI treatment status into account did not alter the findings. A similar, albeit attenuated, pattern of findings emerged when ultradistal radius total vBMD was examined.

No significant associations were found between the risperidone treatment status groups and the bone turnover markers at follow-up, after adjusting for stage of genitalia development, height *z* score, and the rate of change in height in the period between study entry and follow-up (all *P* values > .50).

Prolactin and Skeletal Outcomes

None of the Risperidone Discontinuation participants exhibited hyperprolactinemia at follow-up, while 48% (n = 32) of the Risperidone Continuation group did. After adjusting for lumbar spine aBMD *z* score at study entry, height and BMI *z* scores at follow-up, and risperidone treatment status at follow-up, prolactin concentration at follow-up was positively associated with lumbar spine aBMD *z* score (β = 0.009, *P* < .02). Of note, the effect of risperidone treatment status that was marginally significant in the more reduced model described earlier became significant when prolactin concentration was added to the model (*P* < .02). In contrast, prolactin concentration at follow-up was not significantly associated with radius trabecular vBMD at follow-up, after accounting for trabecular vBMD at study entry and age, BMI *z* score, physical activity, and risperidone treatment status at follow-up. Adjusting for SSRI exposure did not alter the results.

DISCUSSION

To our knowledge, this is the first study to prospectively examine the skeletal effects of commonly used psychotropics in youths. Using DXA and pQCT focused on trabecular bone sites, we found that risperidone and SSRIs are both associated

Table 1. Demographic, Anthropometric, and Laboratory Characteristics of All Participants and Participants Divided by Whether Risperidone Was Continued vs Discontinued by Follow-Up[a,b]

Characteristic	Total Sample N = 94	Risperidone Continued n = 70	Risperidone Discontinued n = 24	*P* Value[b]
Race/ethnicity, n (%)				
White	78 (83)	57 (81)	21 (88)	> .70
African American	11 (12)	9 (13)	2 (8)	
Other	3 (3)	2 (3)	1 (4)	
Hispanic	2 (2)	2 (3)	0	
Age, y				
At study entry	11.8 ± 2.7	11.9 ± 2.7	11.4 ± 2.4	> .40
At follow-up	13.3 ± 2.7	13.4 ± 2.8	13.0 ± 2.4	> .50
Tanner stage, % I/II/III/IV/V				
At study entry	33/20/19/23/4	35/17/19/23/6	29/29/21/21/0	> .50
At follow-up	15/21/15/18/30	15/21/19/13/32	17/21/4/33/25	> .10
Body mass index (BMI) *z* score				
At study entry	0.51 ± 1.08	0.39 ± 1.13	0.86 ± 0.85	***< .07***
At follow-up	0.44 ± 1.10	0.37 ± 1.11	0.66 ± 1.08	> .20
Risperidone treatment duration, y				
At study entry	2.48 ± 1.66	2.66 ± 1.69	1.96 ± 1.47	***< .08***
At follow-up	3.66 ± 1.83	4.07 ± 1.73	2.47 ± 1.58	**< .0001**
SSRI treatment group, n (%)[c]				
SSRI group	44 (47)	31 (44)	13 (54)	> .20
No SSRI group	37 (39)	31 (44)	6 (25)	
Inconsistent SSRI group	13 (14)	8 (11)	5 (21)	
SSRI treatment duration, years				
At study entry	1.63 ± 1.89	1.65 ± 2.03	1.57 ± 1.46	> .80
At follow-up	2.39 ± 2.37	2.34 ± 2.51	2.53 ± 1.92	> .70
Calcium intake, mg/d				
At study entry	1,059.8 ± 360.7	1,097.5 ± 357.0	951.7 ± 356.7	***< .09***
At follow-up	1,010.1 ± 389.9	1,024.0 ± 397.3	969.9 ± 373.2	> .50
Vitamin D intake, IU/d				
At study entry	319.4 ± 164.3	332.0 ± 166.4	283.0 ± 156.0	> .20
At follow-up	296.4 ± 187.0	316.2 ± 268.4	239.5 ± 181.7	**< .05**
Prolactin, ng/mL				
At study entry	21.8 ± 14.2	20.7 ± 13.4	24.9 ± 16.2	> .20
At follow-up	14.2 ± 12.8	17.4 ± 13.5	5.5 ± 3.4	**< .0001**
Testosterone, ng/mL				
At study entry	180.2 ± 188.8	174.7 ± 192.9	195.4 ± 180.4	> .60
At follow-up	298.9 ± 219.0	295.3 ± 217.0	307.9 ± 228.6	> .60
Skeletal variables[d]				
LS BMC *z* score				
At study entry	0.03 ± 0.92	0.06 ± 0.97	−0.05 ± 0.79	> .60
At follow-up	−0.03 ± 0.90	−0.01 ± 0.96	−0.10 ± 0.71	> .60
LS aBMD *z* score				
At study entry	0.22 ± 0.99	0.23 ± 1.01	0.17 ± 0.92	> .80
At follow-up	0.15 ± 1.00	0.12 ± 1.01	0.25 ± 0.98	> .50
Radius total vBMD, mg/cm^3				
At study entry	327.9 ± 55.3	330.1 ± 54.6	320.6 ± 58.9	> .50
At follow-up	335.5 ± 54.4	333.4 ± 51.7	343.1 ± 65.1	> .50
Follow-up osteocalcin, ng/mL	78.9 ± 53.2	75.6 ± 50.7	88.3 ± 59.8	> .30
Follow-up collagen type I C-telopeptide (CTX), ng/mL	2.62 ± 0.91	2.57 ± 0.93	2.77 ± 0.85	> .30
Follow-up bone-specific alkaline phosphatase, U/L	161.0 ± 64.7	160.7 ± 68.5	161.7 ± 55.9	> .90

[a]Mean ± SD unless noted otherwise.
[b]Significant results ($P < .05$) are bolded; results that are marginally significant ($P < .10$) are bolded and italicized.
[c]Three groups were generated based on whether participants were taking SSRIs at study entry and follow-up (SSRI group), at neither visit (no SSRI group), or at only 1 of the 2 visits (inconsistent SSRI group).
[d]Age-sex-height-race–specific *z* scores were generated using published normative data.[29] vBMD data are available for 69 participants at study entry and 62 at follow-up, after excluding compromised scans.
Abbreviations: aBMD = areal bone mineral density, BMC = bone mineral content, LS = lumbar spine, SSRI = selective serotonin reuptake inhibitors, vBMD = volumetric bone mineral density.

with reduced bone mass but with differing trajectories. In fact, while SSRIs were associated with reduced bone mass at both study entry and follow-up without an apparent worsening over time, risperidone was associated with increasingly significant failure to accrue bone mass, as would otherwise be expected for the age of the participants.

Attention is increasingly focused on promoting preventive medicine. At the same time, it has become widely recognized that many chronic diseases have their onset in childhood and adolescence. This would certainly apply to osteopenia and osteoporosis, particularly as age-related bone loss is directly related to peak BMD achieved by young adulthood.[8] The

Table 2. Results of Multivariable Linear Regression Analyses Examining the Skeletal Impact of SSRI Treatment and of Continuing vs Discontinuing Risperidone by Follow-Up[a]

	SSRI Treatment Group Status		Risperidone Treatment Group Status	
	β Estimate, 95% CI	Cohen *d*	β Estimate, 95% CI	Cohen *d*
Dual-Energy x-Ray Absorptiometry or DXA-Based Measures[b]				
LS aBMD *z* score				
At study entry	**−0.48 (−0.88 to −0.08)**	**0.44**	0.13 (−0.30 to 0.56)	0.15
At follow-up	***−0.38 (−0.78 to 0.01)***	***0.44***	0.15 (−0.33 to 0.45)	0.17
Change[c]	0.08 (−0.11 to 0.26)	0.21	**−0.20 (−0.40 to −0.00)**	**0.52**
LS BMC *z* score				
At study entry	***−0.35 (−0.74 to 0.03)***	***0.42***	0.13 (−0.29 to 0.54)	0.15
At follow-up	**−0.40 (−0.75 to −0.04)**	**0.51**	0.06 (−0.33 to 0.45)	0.07
Change[c]	−0.08 (−0.26 to 0.09)	0.22	−0.04 (−0.22 to 0.14)	0.12
Peripheral Quantitative Computed Tomography or pQCT-Based Measures[d]				
Trabecular vBMD				
At study entry	**−22.9 (−42.9 to −2.91)**	**0.64**	6.0 (−14.8 to 26.8)	0.17
At follow-up	**−28.6 (−53.2 to −3.9)**	**0.68**	−5.4 (−31.8 to 21.1)	0.13
Change[c]	−4.4 (−19.2 to 10.4)	0.22	**−21.3 (−34.9 to −7.7)**	**1.18**
Radius total vBMD				
At study entry	***−26.1 (−55.9 to 3.7)***	***0.49***	0.6 (−30.8 to 32.1)	0.01
At follow-up	**−29.0 (−57.6 to −0.4)**	**0.60**	−9.2 (−40.8 to 22.5)	0.18
Change[c]	−13.6 (−34.3 to 7.2)	0.47	−14.9 (−36.5 to 6.7)	0.51

[a]Significant results ($P < .05$) are bolded, and results that are marginally significant ($P < .10$) are bolded and italicized.
[b]DXA-based measurements were converted into age-sex-height-race–specific *z* scores. The analyses were adjusted for age and age-sex–specific height and BMI *z* scores. In addition, the "change" analyses were also adjusted for the corresponding skeletal measurement at study entry as well as for change in height and BMI *z* scores between study entry and follow-up.
[c]Refers to change in the respective measurements between study entry and follow-up.
[d]The analyses were adjusted for age, physical activity, and BMI *z* score. In addition, the "change" analyses were also adjusted for the corresponding skeletal measurement at study entry as well as for time interval between study entry and follow-up.
Abbreviations: aBMD = areal bone mineral density, BMC = bone mineral content, BMI = body mass index, DXA = dual-energy x-ray absorptiometry, LS = lumbar spine, pQCT = peripheral quantitative computed tomography, SSRI = selective serotonin reuptake inhibitors, vBMD = volumetric bone mineral density.

concern is that even a moderate reduction in peak BMD could significantly increase the incidence of osteoporotic fractures.[8,30,31] Therefore, the reduction in BMD we observed could have significant long-term health implications, as continued treatment, beyond a certain age,[32] may prevent psychotropic-treated youths from reaching their optimal peak bone mass. Such effects are especially troublesome as these medications are widely used, often for extended periods, thereby leaving those who care for psychiatrically ill youths in a difficult position, having to choose between treating a youth's ongoing distressing and impairing condition and placing the youth at risk for long-term sequelae.

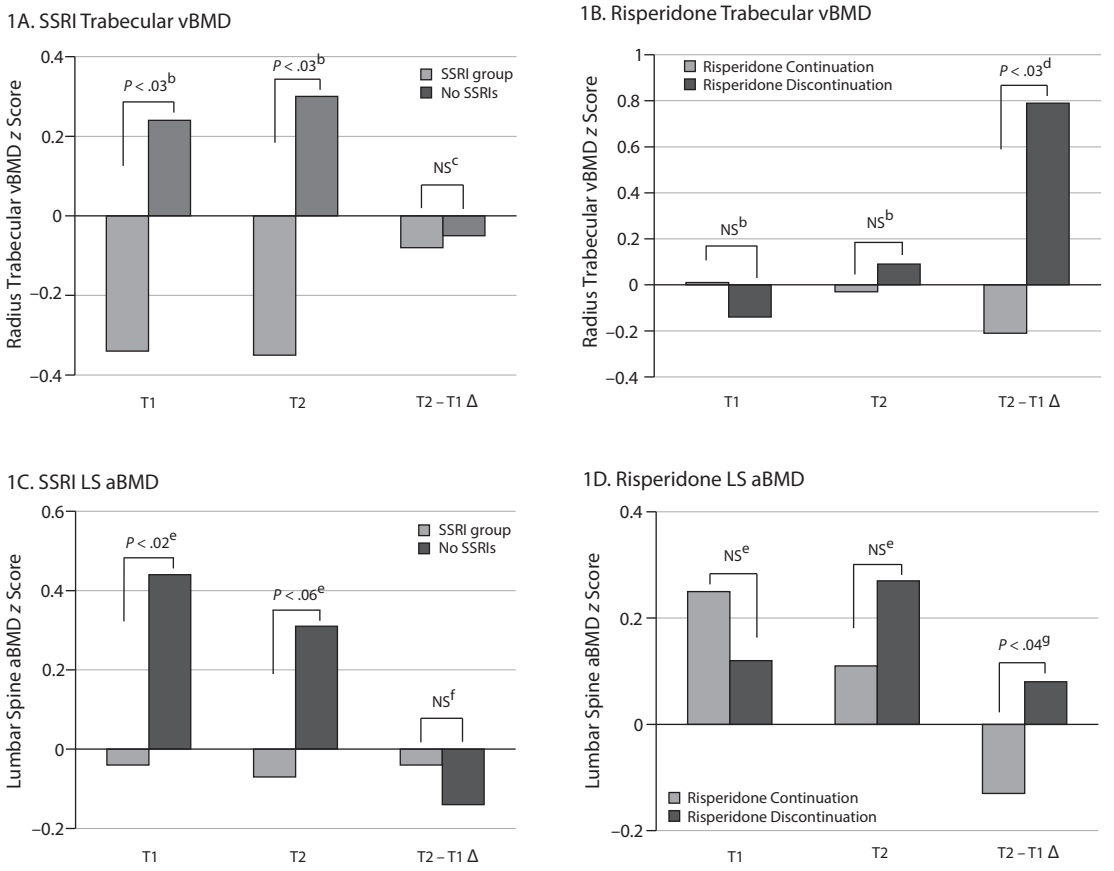
Recently, using data from this same sample, we reported that those who continued on risperidone therapy maintained their moderate increase in BMI *z* score (~0.32 ± 1.11) compared to pre-risperidone values, while those who discontinued all SGAs returned to their pretreatment BMI *z* score, despite having taken risperidone for years.[22] The absence of pre-risperidone skeletal measurements and of an unmedicated control group makes it impossible to determine whether the Risperidone Discontinuation group saw its skeletal outcomes return to normal after discontinuing risperidone. It is hoped that full recovery is possible in the absence of clinical relapse that requires reinstitution of psychotropic treatment.[32] Notably, discontinuing risperidone not only removes the detrimental direct effect of the drug on the skeleton, but also that of associated weight gain.

Elsewhere, we have reviewed the complex mechanisms potentially involved in the skeletal effects of risperidone.[12] Elegant research has also shed light on the skeletal effects of SSRIs.[14] Our findings suggest that these medications may impact bone mass accrual differently, following long-term use. In fact, continued risperidone treatment led to failure to increase trabecular vBMD at the radius. At the lumbar spine, this process translated into a decline in aBMD *z* score between study entry and follow-up. Of note, trabecular vBMD measurements are raw values, while aBMD measurements are adjusted for age and height (as well as for sex and race). This explains why we observed an increase in the former in those who discontinued risperidone, but a decrease in the latter among those who continued risperidone. In contrast, SSRI use was consistently associated with lower bone mass at both visits, but this deficit did not worsen over time. The study, however, did not examine the mechanisms that account for our observations. Preclinical data suggest that psychotropics may interfere with both bone formation and resorption.[12,14,16] We found a trend for osteocalcin to be lower during SSRI treatment, consistent with what has been reported.[14] However, no associations were found between risperidone use and bone turnover markers.

In our previous work, using data collected at study entry, we found prolactin to be inversely associated with trabecular vBMD.[18] Bone loss associated with hyperprolactinemia is thought to be mediated primarily by hypogonadism.[11] However, the discovery of functional prolactin receptors on bone cells suggests that a direct effect is likely.[12,33] Surprisingly, after accounting for risperidone treatment status, we found prolactin concentration to be positively associated with lumbar spine aBMD *z* score, but not with trabecular vBMD. This may be due to the complex role prolactin plays in controlling bone metabolism during development.[33–35]

Elsewhere, we describe an inverse association between major depressive disorder, but not generalized anxiety disorder, and low bone mass in older adolescents.[36] This is consistent with published data linking the two,[37] although ours is the first study to examine this question in nearly psychotropic-naive patients. In the present study, adjusting for depressive and anxiety symptom severity, as captured by the Child Behavior Checklist, did not alter the overall pattern of the findings, thereby exhibiting limited to no impact. Further, the rate of major depressive disorder in our participants was low. Nonetheless, we cannot rule out the possibility that the association we found between SSRI use

Figure 1. Radius Trabecular vBMD and Lumbar Spine aBMD *z* Scores During Longitudinal Treatment With Selective Serotonin Reuptake Inhibitors and Risperidone in Boys[a]



[a]Least squares means for standardized radius trabecular vBMD *z* scores and lumbar spine age-sex-height-race–specific aBMD *z* scores at study entry (T1) and at follow-up (T2), and of their change between T1 and T2, across those who were taking a selective serotonin reuptake inhibitor (SSRI) at T1 and T2 vs at neither visit (Figures 1A and 1C), and across those who continued risperidone (Risperidone Continuation) vs discontinued risperidone (Risperidone Discontinuation) by T2 (Figures 1B and 1D).
[b]Adjusted for age, physical activity, and age-sex–specific BMI *z* score at T1 and T2, respectively.
[c]Adjusted for vBMD and BMI *z* scores at T1, as well as change in BMI *z* score and time interval between T1 and T2.
[d]Adjusted for vBMD and BMI *z* scores at T1, age, and change in age-sex–specific BMI *z* score and time interval between T1 and T2.
[e]Adjusted for age and age-sex–specific height *z* score and BMI *z* score at T1 and T2, respectively.
[f]Adjusted for aBMD, height, and BMI *z* scores at T1, as well as change in height and BMI *z* scores between T1 and T2.
[g]Adjusted for aBMD and BMI *z* scores at T1 and change in age-sex–specific BMI *z* score and in daily calcium intake between T1 and T2.
Abbreviations: aBMD = areal bone mineral density, LS = lumbar spine, NS = not significant, T1 = study entry, T2 = 1.5-year follow-up, vBMD = volumetric bone mineral density.

and low bone mass reflects instead an underlying association between depression and skeletal health.

Although this study presents novel findings, it suffers from several limitations. First, the participants were enrolled having already initiated treatment with psychotropics. Therefore, pretreatment measurements are lacking. Further, while this study is focused on risperidone because of its propensity to cause hyperprolactinemia, other antipsychotics have overlapping mechanisms of action.[38] Therefore, it is unclear to what extent our findings extend to other psychotropics. We combined in a single group those who discontinued all SGA treatment by follow-up with those who switched to other SGAs as no differences in the skeletal outcomes were detected between them. Nonetheless, each SGA was represented by 1 to 3 patients, making it impossible to draw reliable conclusions about each drug's potential skeletal effects. We measured bone mass at sites rich in trabecular bone, but examining the skeletal effects of psychotropics on whole body bone mineral content as well as on cortical bone, specifically, can also be informative. Finally, examining the skeletal effects of psychotropics in females and in a more racially and ethnically diverse population is necessary, particularly as women are at the highest risk for osteoporosis and psychotropics are also widely used in individuals from diverse backgrounds.

In sum, the chronic use of risperidone in youths is associated with a progressive decline in trabecular bone mass, while the use of SSRIs is associated with significantly lower, but static, bone mass. Future studies should examine these findings in more representative individuals and identify interventions to reverse or attenuate the skeletal effects of psychotropics as their use is necessary to alleviate the distress and impairment associated with psychopathology.

Drug names: risperidone (Risperdal and others).
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