The Effect of Psychostimulants on Skeletal Health in Boys Co-Treated with Risperidone

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Objectives To examine the skeletal effects of chronic psychostimulant treatment in children and adolescents.

Study design Medically healthy 5- to 17-year-old males from 4 different clinic-based studies were combined for this analysis. They were divided by psychostimulant use into 3 groups: none to negligible, intermittent, and continuous use. Most (95%) had also received risperidone for 6 months or more. Treatment history was extracted from medical and pharmacy records. Anthropometric and bone measurements, using dual-energy x-ray absorptiometry and peripheral quantitative computed tomography, were obtained at each research visit. Multivariable linear regression analysis models examined whether age-sex-specific height Z-score and skeletal outcomes differed among the 3 psychostimulant-use groups.

Results The sample consisted of 194 males with a mean age of 11.7 ± 2.8 years at study entry. The majority had an externalizing disorder. There was no significant difference across the 3 treatment groups in height Z-score or in skeletal outcomes at the radius, lumbar spine, or whole body. One hundred forty-four boys had valid follow-up skeletal data 1.4 ± 0.7 years after study entry. Again, neither height Z-score nor the skeletal outcomes were different among those who remained on psychostimulants between the 2 visits, started psychostimulants anew, or had not taken psychostimulants.

Conclusions Following chronic treatment, psychostimulants did not appear to significantly affect bone mass accrual in children and adolescents taking risperidone. There was a small, but statistically not significant, negative impact on longitudinal growth. *(J Pediatr 2015;166:1449-54)*.

Attention deficit hyperactivity disorder is characterized by inattention, hyperactivity, and impulsivity, impairing functioning across a variety of settings.[1] Its prevalence ranges between 2.5% in adults and 5% in children.[1] Although a number of interventions are available, psychostimulants are the most effective at targeting attention deficit hyperactivity disorder symptoms.[2] The use of these drugs continues to grow worldwide.[3-5]

Concerns have been raised about the potential for psychostimulants to stunt longitudinal growth.[6-8] This effect appears to plateau over extended periods of treatment,[7] and it remains unclear whether adult height is impacted.[9-11]

Preclinical work in 4-week-old male rats treated for 13 weeks suggests that psychostimulants may interfere with bone metabolism, resulting in reduced bone mass and increased bone fragility.[12] The femur and tibia exhibited these changes, but not the vertebrae. Further, low bone mass and increased fragility recovered within 5 weeks following medication discontinuation.[12] The mechanisms involved in the possible skeletal effects of psychostimulants have not been established but may involve the downstream effects of dopamine transporter blockade,[13] height suppression,[7] hormonal alterations,[14,15] or nutritional insufficiency because of medication-induced anorexia.

Aside from a small (n = 10) pilot study,[16] the skeletal effects of psychostimulants have not been examined in children and adolescents. If, as suggested by preclinical findings,[12] extended psychostimulant treatment hinders bone mass accrual, then the clinical impact could be significant given that peak bone mass accrued by early adulthood is a major determinant of lifetime risk of osteoporosis and fractures.[17]

Thus, we undertook an analysis of data from several pediatric studies to examine skeletal health following chronic treatment with psychostimulants.

aBMD	Areal bone mineral density
BMC	Bone mineral content
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
LS	Lumbar spine
MPH	Methylphenidate
pQCT	Peripheral quantitative computed tomography
SSRI	Selective serotonin reuptake inhibitor
TBLH	Total body less head
vBMD	Volumetric bone mineral density

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We anticipated that psychostimulant use will be associated with a clinically significant reduction in bone mass.

Methods

Data from 4 studies were combined in this analysis to maximize sample size (**Table I**; available at www.jpeds.com). Study 1 involved 152 participants, 7- to 17-years-old, who had received risperidone for at least 6 months. One hundred eight (71%) returned for an additional follow-up visit, 1.5 ± 0.3 years after study entry.[18] Study 2 was cross-sectional and involved eight 10- to 18-year-olds treated with risperidone for at least 1 year. Study 3 consisted of a randomized trial (n = 46) examining the skeletal effects of calcium and vitamin D supplementation in 5- to 17-year-old boys taking risperidone for at least 1 year and exhibiting hyperprolactinemia. Study 4 consisted of a longitudinal observational study (n = 17) involving 5- to 16-year-old, largely antipsychotic-naïve, participants, 6 of whom had initiated treatment with risperidone within the prior month. In all 4 studies, chronic medical or neurologic conditions, concurrent treatment with more than 1 antipsychotic medication, or pregnancy led to exclusion.

All the studies were approved by the local Institutional Review Board. After complete description of the study, written assent was obtained from children ≤14 years old, and written consent was obtained from adolescents and parents or guardians.

Procedures

During the research visits, height and weight measurements were obtained following a standard protocol and pubertal stage was recorded.[19,20] The medical and pharmacy records were reviewed to document all psychotropic treatments, including the start and stop date of each drug and its dosage.[19,20] All dosages of psychostimulants were expressed in methylphenidate (MPH) equivalents for amphetamines (×2).[21]

A best-estimate diagnosis, following the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision,[22] was generated based on a review of the psychiatric record, often supplemented by a clinical interview (conducted by C.C.), a standardized interview of the parent using the Diagnostic Interview Schedule for Children, Version-IV (except in study 2),[23] and the Child Behavior Checklist.[24]

Daily calcium and vitamin D intake during the week prior to enrollment was estimated using the 2004 Block Kids Food Frequency Questionnaire,[25] and physical activity was assessed (except in study 2) by asking the parent to compare the child's usual level of physical activity to their peers', using a 5-point Likert scale.[26]

Following the same protocol described previously,[18,20] peripheral quantitative computed tomography (pQCT) scans were obtained at the 4% site of the nondominant radius (rich in trabecular bone), to estimate volumetric bone mineral density (vBMD), and at the 20% site to estimate cortical vBMD. A Stratec XCT-2000 scanner, software version 6.0 (Stratec, Inc, Pforzheim, Germany), was used. Trabecular vBMD was measured as the mean density of the 85% central area of the bone's cross-section, and total vBMD encompassed the entire bone mass, including the thin cortical shell.[18] pQCT scans compromised by movement were rejected. A Hologic QDR DELPHI-4500A dual-energy x-ray absorptiometry (DXA) unit (Hologic, Inc, Bedford, Massachusetts; studies 1 and 2) or a Hologic Discovery A unit (Studies 3 and 4) was used to estimate bone mineral content (BMC) and areal bone mineral density (aBMD) in the lumbar spine (LS) vertebrae L1 through L4 or of the total body less head (TBLH). The 2 DXA units were cross-calibrated using a Hologic anthropomorphic spine phantom, Hologic Whole Body Phantom, Orthometrix Anthropomorphic phantom "Oscar Jr," and 12 human volunteers. Quality-control and calibration of the equipment were performed daily. Although each of the 4 studies acquired at least 1 bone scan, the scan type and skeletal site varied (**Table I**). Studies 1, 2, and 3 measured trabecular vBMD at the 4% radius site. In addition, study 3 measured cortical vBMD at the 20% radius site. Studies 1 and 2 acquired a LS DXA scan, and studies 3 and 4 acquired a TBLH scan.

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.[27] Age-sex-height-race-specific Z-scores for LS and TBLH BMC and aBMD were generated following the Bone Mineral Density in Childhood Study.[28]

Because the number of female participants with a bone scan was relatively small and because there is a strong sex effect on bone mass, we restricted the analyses to boys. As the principal aim of this analysis was to examine the skeletal effects of psychostimulants, the participants were divided in 3 groups: (1) Boys with no exposure to psychostimulants within the 2 years prior to the bone scan (no-MPH, n = 40). This group included participants who never received psychostimulants (n = 26) as well as those who had received them but not for at least 2 years prior to undergoing the bone scan (n = 14). The period of 2 years was set, somewhat arbitrarily, given that psychostimulant holidays allow the rapid recovery of longitudinal growth delays,[7,12] in order to ensure that any potential skeletal effect of psychostimulants would have resolved; (2) The second group consisted of those who had taken psychostimulants continuously (MPH-continuous, n = 91). This included boys who never discontinued psychostimulants (n = 63) as well as those who may have discontinued them at some point but had taken them continuously for 2 years prior to undergoing the bone scan (n = 28); and (3) Finally, boys who took psychostimulants intermittently, including during the 2 years prior to the bone scan formed the third group (MPH-intermittent, n = 63).

To take full advantage of the data available, 2 sets of analyses related to the skeletal outcomes were conducted. First,