Ther Adv Psychopharmacol

[2013] 3(5) 278–293

DOI: 10.1177/

2045125313487548

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Possible mechanisms for the skeletal effects of antipsychotics in children and adolescents

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Abstract: The increasing use of antipsychotics (APs) to treat pediatric psychiatric conditions has led to concerns over the long-term tolerability of these drugs. While the risk of cardiometabolic abnormalities has received most of the attention, preclinical and clinical studies provide preliminary evidence that APs can adversely impact bone metabolism. This would be most concerning in children and adolescents as suboptimal bone accrual during development may lead to increased fracture risk later in life. However, the potential mechanisms of action through which APs may impact bone turnover and, consequently, bone mineral content are not clear. Emerging data suggest that the skeletal effects of APs are complex, with APs directly and indirectly impacting bone cells through modulation of multiple signaling pathways, including those involving dopamine D₂, serotonin, adrenergic, and prolactin receptors, as well as by affecting gonadotropins. Determining the action of APs on skeletal development is further complicated by polypharmacy. In children and adolescents, APs are frequently coprescribed with psychostimulants and selective serotonin reuptake inhibitors, which have also been linked to changes in bone metabolism. This review discusses the mechanisms by which APs may influence bone metabolism. Also covered are preclinical and pediatric findings concerning the impact of APs on bone turnover. However, the dearth of clinical information despite the potential public health significance of this issue underscores the need for further studies. The review ends with a call for clinicians to be vigilant about promoting optimal overall health in chronically ill youth with psychopathology, particularly when pharmacotherapy is unavoidable.

Keywords: antipsychotics, bone metabolism, hyperprolactinemia, osteoporosis, psychopathology, skeletal development

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Introduction

The use of antipsychotic (AP) medications in children and adolescents has rapidly grown over the last two decades, with second-generation APs forming the lion's share [Comer *et al.* 2010; Olfson *et al.* 2010, 2012]. In fact, within certain clinical groups, up to 4% of children are receiving an AP [Cooper *et al.* 2006; Crystal *et al.* 2009]. This widespread use likely reflects the increasing evidence supporting APs' efficacy in a variety of psychiatric conditions, optimizing functioning, and possibly reducing the need for institutionalization [FDA, 2006, 2007, 2009; Zuddas *et al.* 2011]. However, concerns have been raised about

the long-term safety of APs, particularly since many pediatric psychiatric conditions are chronic, often requiring extended treatment [Vitiello *et al.* 2009]. In fact, across a variety of disorders, symptoms recur following the discontinuation of the AP or even despite continued therapy [Research Units on Pediatric Psychopharmacology Autism Network, 2005; Reyes *et al.* 2006a; Findling *et al.* 2010].

Much attention has been paid to AP-related weight gain and cardiometabolic abnormalities, particularly in children and adolescents [Calarge *et al.* 2009a; Correll *et al.* 2009]. However, less

research has explored other potential long-term side effects such as impaired skeletal development. This is of significance in light of accumulating evidence in adults implicating APs in suboptimal bone mineral density (BMD) [Bilici *et al.* 2002; Abraham *et al.* 2003; Becker *et al.* 2003; Meaney *et al.* 2004; Howes *et al.* 2005; Jung *et al.* 2006; Meaney and O'Keane, 2007; Kishimoto *et al.* 2008]. If AP treatment were to begin earlier in life, children and adolescents may be prevented from optimizing their peak bone mass and placed at a heightened risk for the later emergence of osteoporosis [NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001]. Osteoporosis is a taxing condition both financially, with costs estimated at US\$10–15 billion annually in the USA for treatment of fractures alone, as well as personally due to reduced quality of life and increased morbidity and mortality [NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001].

This paper briefly describes skeletal development to highlight the importance of optimizing peak bone mass, reviews the mechanisms through which APs might affect bone metabolism, summarizes the evidence linking APs to skeletal health in animals as well as in children and adolescents, and ends by underscoring the need for clinicians to be mindful of the potential long-term implications of the skeletal effects of psychotropics.

Bone mineral density during development

Peak bone mass achieved by early adulthood is a strong predictor of future BMD [NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001]. More than 85% of peak skeletal mass is accrued before age 18, making bone development during this phase critical for lifelong skeletal health [Theintz *et al.* 1992; Rauch and Schoenau, 2001]. Importantly, failure to achieve peak bone mass before young adulthood (e.g. in youth with prolactin-secreting adenomas) cannot necessarily be compensated for at a later stage [Colao *et al.* 2000]. Moreover, age-related bone loss is directly correlated with peak bone mass and even a 5–10% reduction in peak BMD (equivalent to a reduction of BMD between 0.5 and 1 SD) can increase the incidence of future fractures substantially [Matkovic *et al.* 1995; Matkovic, 1996]. In sum, whether genetic or environmental, processes that impact bone mass accrual during development have the potential to

increase the lifetime risk of osteoporosis and fractures [Carrie Fassler and Bonjour, 1995; Duntas, 2001].

Mechanisms potentially linking antipsychotics to bone metabolism

Most APs block the dopamine D₂ receptors [Richelson and Souder, 2000]. Dopamine released by tuberoinfundibulum neurons in the arcuate nucleus of the mediobasal hypothalamus activate dopamine D₂ receptors on pituitary lactotrophs, tonically inhibiting prolactin release [Halbreich *et al.* 2003; Shibli-Rahhal and Schlechte, 2009]. Thus, during AP treatment, hyperprolactinemia often ensues, particularly since lactotrophs dopamine D₂ receptors are highly sensitive to the D₂-blocking activity of APs [Langer *et al.* 1977]. Amenorrhea due to prolactin-secreting pituitary adenomas is associated with low spinal bone mass [Shibli-Rahhal and Schlechte, 2009]. Hyperprolactinemia may inhibit the pulsatile secretion of gonadotropin-releasing hormone, thereby impairing gonadotropin secretion and causing hypogonadism [Klibanski *et al.* 1980; Biller *et al.* 1992; Schlechte *et al.* 1992; Shibli-Rahhal and Schlechte, 2009]. Sex hormones play a critical role in bone metabolism and hypogonadism (e.g. menopause) is associated with a drastic reduction in bone mass [Phillip and Lazar, 2003]. Therefore, concerns have been raised that, similar to prolactin-secreting pituitary adenomas, AP-induced hyperprolactinemia may lead to bone loss by causing hypogonadism [Abraham *et al.* 2003].

However, the mechanism by which hyperprolactinemia leads to bone loss is likely not limited to its effects on the hypothalamic–pituitary–gonadal axis since eugonadal patients with hyperprolactinemia may exhibit bone loss and fail to completely recover bone mass after treatment [Schlechte *et al.* 1983; Greenspan *et al.* 1989]. Moreover, adolescents with prolactin-secreting adenomas exhibit significantly reduced BMD for age despite progressing through puberty normally [Colao *et al.* 1998, 2000].

Of note, prolactin appears to directly affect the skeleton through the prolactin receptor expressed by osteoblasts [Clement-Lacroix *et al.* 1999; Seriwatanachai *et al.* 2008a, 2008b, 2009]. In fact, knockout mice lacking the prolactin receptor gene exhibit a dramatic reduction in bone formation and, consequently, low BMD [Clement-Lacroix *et al.* 1999]. Conversely, activation of the prolactin receptor inhibits osteoblast differentiation and

matrix mineralization, with reduced alkaline phosphatase concentration [Coss *et al.* 2000; Seriwatanachai *et al.* 2009]. Thus, while a certain basal level of prolactin is necessary for skeletal health, excess prolactin seems detrimental.

Importantly, findings across preclinical studies vary depending on their design, including duration of prolactin exposure, cell culture, and the stage of differentiation of osteoblasts when exposed to prolactin [Charoenphandhu *et al.* 2008; Seriwatanachai *et al.* 2008a, 2008b, 2009]. For instance, the receptor activator of nuclear factor κ B ligand to osteoprotegerin (RANKL/OPG) ratio increased when osteoblast-like MG-63 cells were incubated with prolactin for 48 h in a nondexamethasone-enriched medium, denoting increased osteoclastic bone resorption [Seriwatanachai *et al.* 2008b]. However, human pre-osteoblasts (SV-HFO) showed no change in the RANKL/OPG ratio following a 21-day exposure to prolactin in a dexamethasone-enriched medium [Seriwatanachai *et al.* 2009]. In addition, Charoenphandhu and colleagues found that cultured primary osteoblasts treated with prolactin for 48 h showed decreased expression of certain genes involved in osteoblast differentiation, including *runx2*, a transcriptional regulator of the alkaline phosphatase gene [Charoenphandhu *et al.* 2008]. Furthermore, exposure to prolactin for 5 days did not change osteoblast mineralization capacity [Charoenphandhu *et al.* 2008]. In contrast, in the human pre-osteoblast cell line, Seriwatanachai and colleagues found increased *runx2* expression at day 5 of osteoblast differentiation, while mineralization capacity was decreased after 14 days of prolactin exposure [Seriwatanachai *et al.* 2009].

Further evidence implicating prolactin in bone turnover comes from studies in rats showing reduced bone turnover following treatment with bromocriptine, an inhibitor of prolactin secretion [Lotinun *et al.* 1998, 2003]. Interestingly, while endogenous prolactin levels increase bone turnover in pregnant rats, exogenous prolactin administration decreases it [Lotinun *et al.* 1998].

In addition to its direct effect on bone cells, prolactin may alter bone mass by enhancing the absorption of calcium by the small intestine [Mainoya, 1975; Charoenphandhu *et al.* 2001; Tudpor *et al.* 2005]. This effect is also complex since, beyond a certain concentration, prolactin may actually decrease calcium absorption [Manna *et al.* 2001; Tanrattana *et al.* 2004]. In fact,

excessive prolactin is thought to inactivate its own receptor by inhibiting dimerization [Fuh *et al.* 1993; Ilondo *et al.* 1994].

An alternative, under-investigated, mechanism linking hyperprolactinemia to low BMD may involve parathyroid hormone related peptide (PTH-RP), a hormone which activates bone resorption in selected contexts. PTH-RP increases in lactating women, whose circulating prolactin concentration is also elevated, and is inversely associated with lumbar BMD in patients with prolactin-secreting tumors [Kovacs and Chik, 1995; Stiegler *et al.* 1995]. Thus, by increasing prolactin and, consequently, promoting the release of PTH-RP, APs may adversely affect bone metabolism. However, this mechanism has not been explored in AP-treated patients.

Furthermore, APs may affect bone health independently of their effect on prolactin. In fact, APs, particularly second-generation APs, modulate serotonergic and adrenergic receptors [Richelson and Souder, 2000]. A number of functional serotonin receptors [e.g. 5-hydroxytryptamine 1A (5-HT_{1A}), 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}] along with the serotonin transporter have been identified in bone cells [Bliziotis *et al.* 2001; Westbroek *et al.* 2001; Yadav *et al.* 2008]. This has recently stimulated great interest in understanding the role of serotonin in bone metabolism [Warden *et al.* 2010]. In fact, circulating serotonin has been implicated in reduced bone formation [Yadav *et al.* 2008; Modder *et al.* 2010], by activating the 5-HT_{1B} receptor on osteoblasts [Yadav *et al.* 2008]. This activation reduces the expression of the transcription factor cyclic adenosine monophosphate response element binding protein, which in turn decreases the expression of cyclin D1, reducing osteoblast proliferation [Yadav *et al.* 2008]. Consistent with this finding, 5-HT_{1B} knockout mice display increased bone formation and bone mass [Yadav *et al.* 2008]. While the affinity for the 5-HT_{1B} receptor of commonly used APs is generally low, it does vary across the different compounds [Roth *et al.* 2004]. Therefore, it is conceivable that some APs may promote bone formation by blocking the 5-HT_{1B} receptor. The skeletal effect of blocking the 5-HT_{2A} receptor, which most APs have a high affinity for [Roth *et al.* 2004], is less clear. This receptor is expressed on osteoblasts [Bliziotis *et al.* 2001] but 5-HT_{2A} receptor knockout mice display normal bone formation and resorption and no deficit in osteoblast proliferation [Yadav *et al.* 2008]. In contrast, 5-HT_{2B} receptor knockout mice exhibit impaired osteoblast

recruitment and proliferation resulting in deficient cortical and trabecular BMD [Locker *et al.* 2006; Collet *et al.* 2008; Baudry *et al.* 2010]. Thus, APs may also interfere with bone mineralization by blocking the 5-HT_{2B} receptor [Bymaster *et al.* 1999]. However, by blocking the 5-HT_{2C} receptors in neurons of the ventromedial hypothalamus, APs may attenuate the inhibition of the sympathetic nervous system by serotonergic signaling from the raphe nuclei [Ducy, 2011]. This, in turn, activates skeletal β_2 -adrenergic receptors, which negatively impact bone metabolism [Karsenty and Ducy, 2006]. Of note is that most APs have a very low affinity for β -adrenergic receptors [Leysen *et al.* 1992]. However, several APs have high affinity for α_{1A} - and α_{1B} -adrenergic receptors [Roth *et al.* 2004]. Human osteoblasts express α_{1A} -adrenergic receptors and stop proliferating when treated with α_1 antagonists [Huang *et al.* 2009]. Expression of α_{1B} -adrenergic receptor mRNA has also been demonstrated in human osteoclasts [Togari, 2002], suggesting that these receptors may have a role in osteoclast regulation. This would be consistent with recent evidence linking risperidone to increased osteoclast proliferation in mouse cell culture [Motyl *et al.* 2012].

Finally, it is also possible for APs to hinder bone metabolism by impairing muscular function, either directly or indirectly (e.g. by inducing sedation, thereby reducing physical activity) [Safer, 2011]. In fact, muscular contractions are the major cause of physiological loading, which, in turn, determines bone modeling and remodeling activity [Frost, 1987]. Therefore, reduced bone mass during AP treatment may reflect, at least in part, the decreased load bearing strain placed on the skeleton [Frost, 1987; Schoenau, 2005; Fricke and Schoenau, 2007].

In sum, APs may influence skeletal development through various mechanisms with overlapping or opposing effects (Figure 1). These include the release of prolactin, with or without secondary hypogonadism, and the modulation of serotonergic and adrenergic signaling, sympathetic nervous system activity, and perhaps muscular function as well. The overall impact on bone metabolism is difficult to predict but is necessary to establish empirically due to the potential long-term health sequelae.

Preclinical studies

Understanding the mechanisms of AP-induced skeletal changes is necessary for developing

treatment strategies that might minimize the impact of these drugs on growth and bone mass. However, the majority of preclinical studies to date describe the effects of APs on bone and related systems but have not tested specific mechanisms with loss or gain of function approaches. Nonetheless, the following reports support clinical observations and provide clues as to how APs may directly or indirectly modulate bone metabolism.

In a study of 9- to 24 month-old male pigtail macaques (equivalent to 4–8-year-old children), neither risperidone nor quetiapine had any significant effect on body weight or skeletal growth measurements during the 6 months of treatment (3 months at low dose, followed by 3 months at high dose) or the 3 months of post-drug monitoring [Sackett *et al.* 2010]. However, low-dose risperidone (0.025 mg/kg) transiently reduced total areal BMD and significantly elevated prolactin compared with placebo and 2 mg/kg quetiapine. Despite increasing the dose of risperidone to 0.05 mg/kg, areal BMD recovered within the high-dose treatment period and prolactin concentrations decreased, albeit they remained above those of placebo or quetiapine (4 mg/kg). These findings are promising in that risperidone did not permanently hinder skeletal growth or BMD. However, the small sample size per treatment group ($n = 10$) might have limited statistical power, particularly since risperidone-treated macaques appeared to have numerically lower BMD in the post-drug phase. Furthermore, because drug metabolism varies by species, it is not clear whether the oral doses of the medications, which are similar to those used in humans, resulted in comparable serum concentrations. Moreover, the effects of hyperprolactinemia-induced hypogonadism could not be addressed as the macaques were prepubertal. Finally, the length of treatment was relatively short; many patients prescribed APs might take them throughout childhood and adolescence.

Work in rodents has also helped shed light on the skeletal impact of APs. For instance, Costa and colleagues found that male Sprague–Dawley rats treated daily, from 6 to 12 weeks of age, with the prolactin-sparing second-generation AP clozapine (10 mg/kg) had reduced total areal BMD compared with vehicle and haloperidol (0.25 mg/kg) treated rats [Costa *et al.* 2011]. In addition, both haloperidol and clozapine lowered body weight and clozapine alone transiently lowered testosterone levels. Clozapine reduced tibia trabecular bone volume/total volume (BV/TV) and

Figure 1. Mechanisms by which risperidone impacts bone formation and resorption. Risperidone inhibits osteoblastic α_1 -adrenergic receptors (α_1 -ARs) and serotonin [5-hydroxytryptamine (5-HT)] receptors. Inhibition of α_1 -ARs negatively regulates osteoblasts. The impact of osteoblastic 5-HT receptor inhibition remains to be elucidated. Inhibition of dopamine D_2 receptors (D_2 R) on pituitary lactotrophs leads to increased prolactin (PRL) concentration, impacting multiple signaling pathways. PRL activates osteoblastic prolactin receptors (PRLRs), negatively regulating osteoblasts. PRL activates PRLRs in the gastrointestinal (GI) tract to increase calcium absorption, allowing for increased bone mineralization [*absorption is enhanced by PRL only up to a certain point, beyond which absorption is decreased]. PRL decreases estrogen (E_2) and testosterone (T) concentrations, promoting bone resorption. It increases levels of parathyroid hormone-related peptide (PTHrP), activating the PTH type 1 receptor (PTH1R) and stimulating the production of receptor activator of nuclear factor κ B ligand (RANKL); RANKL positively regulates osteoclasts. Inhibition of the 5-HT $_{2C}$ receptors of ventromedial hypothalamic (VMH) neurons leads to increased sympathetic nervous system (SNS) signaling, activation of osteoblastic β_2 adrenergic receptors (β_2 -ARs), and decreased production of cyclin D1 by osteoblasts; this negatively regulates osteoblasts. Similarly, blockade of the 5-HT $_{2B}$ receptor may reduce osteoblast recruitment and proliferation. Conversely, blockade of the 5-HT $_{1B}$ receptor may promote bone formation by increasing cyclin D1 and, consequently, osteoblast proliferation. Risperidone may also reduce mechanical loading, thereby affecting bone modeling and remodeling.

trabecular number, as well as cortical perimeter but not thickness. The investigators then examined whether clozapine could cause any direct effects on bone turnover by treating bone cells with clozapine and haloperidol *in vitro*. Clozapine, but not haloperidol, at concentrations comparable to human serum levels (1 μ M), significantly reduced osteoblast proliferation ([3 H]-thymidine incorporation) and differentiation (% mineralized area). In addition, osteoclast differentiation from

primary and RAW264.7 (osteoclast cell line) cells was significantly reduced only with supraphysiologic levels of clozapine (5–10 μ M) but not with haloperidol. Therefore, if clozapine is directly modulating bone remodeling, it is likely inhibiting osteoblast proliferation and differentiation. However, indirect activation of osteoclasts could not be ruled out *in vivo* because the primary outcomes of the study were metabolic and did not include histomorphometric measurements.

Recently, Motyl and colleagues characterized the bone effects of risperidone with two different drug delivery strategies: male 3.5-week-old mice were administered 1 mg/kg/day of risperidone in their food; and female 8-week-old mice were administered 0.5 mg/kg/day of risperidone by subcutaneous osmotic minipump [Motyl *et al.* 2012]. Both studies were focused on metabolic complications and whether they were associated with bone loss. Oral administration of risperidone reduced body mass, percent body fat, and trabecular BV/TV, which was largely attributed to increased osteoclast parameters by histomorphometry. Consistent with this, *in vitro* application of risperidone (concentrations comparable to human serum concentrations) to primary osteoclast cultures increased osteoclast differentiation. Because bone loss could be associated with lower body mass, the investigators then treated female mice (which are more likely to gain weight on atypical APs) using osmotic minipump delivery. In this case, risperidone did not alter body composition, insulin or glucose tolerance, or uterine weight, but did decrease BV/TV and bone formation parameters, leaving resorption parameters unchanged. Due to the substantial differences in study design, it is not possible to determine what factors (age, gender, dose, delivery method) contributed to the disparate findings. The authors concluded that bone changes could not be solely related to metabolic dysfunction or body composition changes.

In addition to the effects of some second-generation APs on bone turnover, some studies have also found significant changes from typical APs. For example, Oh-ie and colleagues found that 10 mg/kg/day of chlorpromazine (CPZ) reduced serum and marrow alkaline phosphatase activity and increased serum acid phosphatase activity in 25-day-old rats, suggesting reduced bone formation and increased resorption respectively [Oh-ie *et al.* 2002]. Interestingly, these serum changes were completely blocked and marrow changes were ameliorated by coadministration of CPZ with 25 ng/kg 1 α -hydroxyvitamin D₃. Unfortunately, this study only examined serum markers of remodeling, but did not address changes in trabecular or cortical bone mass.

In another related study, Kunimatsu and colleagues examined the effects of long-term (daily oral gavage for 6 months) CPZ and haloperidol on prolactin and BMD in female rats [Kunimatsu *et al.* 2010]. They administered 2 and 10 mg/kg haloperidol and 25 and 50 mg/kg CZP to induce

changes in reproductive organs. As expected, all dosing strategies increased serum prolactin and caused significant mammary gland acinous hyperplasia, as well as uterine atrophy and a trend toward low estradiol, suggesting hypogonadism. In addition, CPZ increased osteocalcin and both CPZ and haloperidol increased urinary deoxypyridinoline, suggesting increased bone turnover. Consistent with this notion, trabecular, but not cortical, BMD in the femur was significantly reduced by all treatments compared with that of untreated rats. Hyperprolactinemia and indicators of hypogonadism improved after a 3-month drug-free phase; however, trabecular BMD did not normalize. Importantly, the medicated rats were less active and gained less weight than untreated rats, both of which could cause significant changes in trabecular BMD.

In sum, preclinical studies suggest that both typical and second-generation APs can alter bone metabolism. However, the mechanism(s) of these effects remain elusive since, as noted above, the drugs may affect bone cells directly and indirectly. Future, hypothesis-driven studies examining loss or gain of function models or cotreatment strategies will be essential for better understanding potential underlying mechanisms.

Clinical studies in children and adolescents

Hyperprolactinemia. Hyperprolactinemia commonly follows the onset of AP treatment in children and adolescents [Sikich *et al.* 2008; Roke *et al.* 2009; Safer, 2011]. The incidence of this adverse event varies across APs due to their differential neuroreceptor binding affinity as well as differences in study design, duration of follow up, age and sex composition of the study population, dose of the AP, and the concurrent use of other psychotropics. For instance, it has been estimated that acute (i.e. ≤ 12 weeks) treatment with risperidone in children and adolescents is associated with an average increase in prolactin concentration of nearly 21 ng/ml compared with placebo [Pringsheim *et al.* 2011]. With prolactin reference values typically ranging from 3 to 25 ng/ml, such an increase is substantial, placing many individuals above the upper limit of normal. Similarly, compared with placebo, treatment for 3 and 6 weeks with olanzapine was associated with a nearly 31-fold increase in the risk of hyperprolactinemia, although the magnitude of the elevation is smaller than that observed with risperidone [Tohen *et al.* 2007; Kryzhanovskaya *et al.* 2009;

Pringsheim *et al.* 2011]. Quetiapine has also been associated with hyperprolactinemia while ziprasidone and clozapine tend to be prolactin sparing [Roke *et al.* 2009]. In contrast, aripiprazole reduces prolactin concentration below normal in nearly two-thirds of treated children, likely due to its partial dopamine agonist activity [Safer *et al.* 2013]. Of note, changes in prolactin concentration have been observed during AP treatment across a variety of psychiatric disorders [Roke *et al.* 2009; Pringsheim *et al.* 2011].

Over more extended periods of exposure, prolactin concentration decreases although hyperprolactinemia persists in a substantial number of individuals [Findling *et al.* 2003; Calarge *et al.* 2009b; Kryzhanovskaya *et al.* 2009]. For example, between 30 and 50% of children and adolescents treated with risperidone continue to exhibit this side effect [Findling *et al.* 2003; Calarge *et al.* 2009b]. Hyperprolactinemia is also common during long-term treatment with typical APs as well as with olanzapine [Kryzhanovskaya *et al.* 2009; Roke *et al.* 2009].

In order to explore the tolerability of risperidone during long-term treatment in children and adolescents, Calarge and colleagues recruited 7–17 year-old patients who had received risperidone for at least 6 months [Calarge *et al.* 2009b, 2010]. At study enrollment, psychotropic polypharmacy was allowed but treatment with APs other than risperidone led to study exclusion. A morning fasting blood sample was used to measure prolactin and sex hormones. Nearly 3 years after the onset of risperidone treatment, hyperprolactinemia was present in 50% of the participants. Older age, more advanced pubertal development, and a higher oral dose of risperidone were associated with higher prolactin concentrations whereas treatment with psychostimulants, which potentiates dopaminergic signaling, lowered prolactin [Calarge *et al.* 2009b]. However, these predictors became non-significant when the combined serum concentration of risperidone and 9-hydroxyrisperidone, its major active metabolite, was considered, accounting for about 40% of the variability in prolactin. In addition, prolactin concentration was also associated with variants of the dopamine D₂ receptor gene [Calarge *et al.* 2009b], although this association could not be established by others [Anderson *et al.* 2007]. More recently, we have also linked risperidone-induced hyperprolactinemia to body iron stores, with iron deficiency being associated with higher prolactin

concentration [Calarge and Ziegler, 2013]. Iron deficiency impairs central dopaminergic signaling and studies in rodents have shown a potentiation of prolactin elevation during AP treatment in the context of iron deficiency [Barkey *et al.* 1985].

Sex hormones. Sex hormones play a key role in the growth spurt and bone mineralization [Phillip and Lazar, 2003]. In a combined analysis of children involved in several long-term clinical trials with risperidone, puberty appeared to have progressed normally [Dunbar *et al.* 2004]. This was also suggested by two long-term open-label risperidone studies [Reyes *et al.* 2006b, 2006c]. In none of these studies, however, were serum concentrations of sex hormones directly measured. Moreover, only patients who were able to tolerate risperidone during acute treatment were included, raising questions about the generalizability of the findings. In our work, we found no association between the serum concentration of prolactin and testosterone in risperidone-treated boys, after accounting for pubertal development [Calarge *et al.* 2009b].

The effect of APs on pubertal development and sex hormones is complex since obesity has been associated with earlier onset of puberty. However, as noted above, hyperprolactinemia could induce a hypogonadal state.

Bone mineral density. Little work has been conducted to directly explore skeletal health in children and adolescents receiving AP treatment. In the study cited earlier from our group, risperidone-treated participants underwent dual x-ray absorptiometry (DXA) of the lumbar spine and a peripheral quantitative computed tomography (pQCT) scan of the nondominant ultra-distal radius [Calarge *et al.* 2010]. DXA was used because of its versatility and the availability of age- and gender-specific BMD reference values for children [Zemel *et al.* 2004; Kelly *et al.* 2005]. However, DXA is a projectional technique. Thus, its measurements are based on the bidimensional projection of a tridimensional structure, resulting in only an approximation of bone size. This limitation makes it vulnerable to inaccuracies in estimating BMD, particularly in youth on either extremes of the height percentile curve. In addition, imprecision could also result from inhomogeneities in body composition. In contrast, pQCT defines the tridimensional bone structure allowing measurement of the true total volumetric BMD, which is less influenced by body size

[Pitukcheewanont and Chen, 2005]. The other major advantage of pQCT is its unique ability to differentiate trabecular from cortical bone. Cortical bone is present in the shaft of long bones. In contrast, trabecular bone is present in the metaphyses of long bones and in short bones (like the vertebrae). Trabecular bone is more metabolically active and, consequently, more vulnerable to the effect of factors that alter bone turnover, including hyperprolactinemia [Schlechte *et al.* 1992; Pitukcheewanont and Chen, 2005; Specker and Schoenau, 2005]. Thus, pQCT offers the potential to improve the sensitivity to detect early changes in BMD.

In addition to measuring BMD and serum prolactin concentration, the participants' physical activity and dietary intake were assessed [Calarge *et al.* 2010]. Since sex is a major determinant of BMD and since boys composed the vast majority of our sample (88%), we excluded girls from the analyses. The mean age of the participants was 11.9 years [standard deviation (SD) = 2.8] with 36% being prepubertal. The rest were distributed across the other four Tanner stages of pubertal development. The participants had received risperidone for a mean of 2.9 years (SD = 1.9). Most participants suffered from attention deficit hyperactivity disorder (87%) and disruptive behavior disorder (64%), although a wide range of disorders were present, often concurrently. As is frequently the case in AP-treated children and adolescents, polypharmacy was prevalent with psychostimulants (67%), selective serotonin reuptake inhibitors (SSRIs, 54%), and α_2 agonists (27%) being the most commonly co prescribed. After taking into account the stage of sexual development ($p > 0.1$), age-sex-adjusted body mass index (z score ($p < 0.002$), and age-sex-adjusted height z score ($p < 0.02$), prolactin was inversely associated with trabecular BMD at the ultradistal radius. Similar findings were obtained when the analysis was restricted to non-Hispanic white boys. We also found a suggestion for an inverse association between DXA-based total lumbar bone mineral content and prolactin ($p < 0.07$) in white boys but this association was not significant after adjusting for stage of sexual development, vitamin D intake, and estimated physical activity. No significant associations were found between prolactin and the DXA-based cross-sectional area or age-sex-adjusted BMD z score of the lumbar spine.

Importantly, the duration of risperidone treatment did not significantly predict BMD but it

may be that this was not a valid surrogate for the duration of hyperprolactinemia. As noted earlier, prolactin concentration is correlated with serum risperidone concentration, which in turn is closely associated with the oral dose [Calarge *et al.* 2009b]. However, over extended periods of treatment, prolactin concentration could significantly vary depending on the duration of treatment, changes in the oral dose in relation to the growing body weight in youth, treatment adherence, and concurrent medications.

Of note is that the association between prolactin concentration and trabecular BMD at the ultradistal radius was attenuated ($p < 0.07$) when we also considered treatment with SSRIs, which was inversely correlated with trabecular BMD ($p < 0.04$). However, including SSRI treatment in the model did not alter the significant inverse association of prolactin with trabecular BMD in non-Hispanic white boys. SSRIs were also negatively associated with lumbar BMD z score ($p < 0.05$), after accounting for Tanner stage, sex-age-adjusted height and weight z scores, daily intake of calcium, physical activity, and prolactin. Moreover, this association was moderated by variants of the serotonin transporter gene [Calarge *et al.* 2011].

Finally, several studies have reported elevations in alkaline phosphatase during AP treatment [Kumra *et al.* 1996, 1997; Erdogan *et al.* 2008; Pavuluri *et al.* 2010; Geller *et al.* 2012]. In children and adolescents, most circulating alkaline phosphatase consists of the bone isoenzyme [Yang and Grey, 2006]. Therefore, an increase in the concentration of total alkaline phosphatase might reflect a direct effect of APs on bone turnover. This, however, cannot be confirmed (or ruled out) since the bone-specific isoenzyme was not measured in these studies. Alternatively, it is equally likely that the hepatic isoenzyme accounts for this increase due to AP-induced weight gain, potentially leading to steatosis, or due to direct hepatotoxicity [Kumra *et al.* 1996, 1997; Erdogan *et al.* 2008, 2010].

Discussion

Most, albeit not all, APs exhibit a strong affinity for dopamine D_2 receptors [Richelson and Souder, 2000]. By blocking these receptors in the anterior pituitary, APs increase circulating prolactin. This, in turn, could interfere with bone metabolism through direct and indirect effects. In

addition, APs may affect bone health via several other processes, including the modulation of serotonergic and adrenergic signaling. In children and adolescents, impaired skeletal mineralization could have lasting consequences since bone mass acquired by young adulthood is a significant determinant of lifetime fracture risk [NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001].

In general, when an AP is initiated, the immediate concern is symptom control. While APs might be predominantly used to treat psychotic and severe mood disorders in adults, they are commonly used to treat explosive behavior in children and adolescents, in the context of disruptive behavior disorders, pervasive developmental disorders, mood disorders, or psychosis [Findling *et al.* 2008; Comer *et al.* 2010]. Therefore, optimizing the safety of the child and their environment is the absolute priority initially. It is when the acute circumstances dissipate and the child's behavior improves that attention ought to focus on the long-term tolerability of the treatment. Unfortunately, extended use of APs is often necessary lest the underlying psychiatric symptoms return. This makes side effects like hyperprolactinemia particularly challenging since they often go unnoticed, yet might lead to long-term sequelae. In fact, APs in children and adolescents are disproportionately prescribed to boys [Olsson *et al.* 2010, 2012]. In this group, as well as in prepubertal girls, amenorrhea is not a useful marker for problematic hyperprolactinemia. Moreover, some other prolactin-related side effects, like gynecomastia, are difficult to attribute directly to hyperprolactinemia since these can occur in untreated peripubertal youth undergoing normal development [Styne, 2002]. Even galactorrhea can be challenging to identify since stimulation of the nipple is often needed for the release of milk. All of these challenges make it difficult to 'clinically' suspect hyperprolactinemia in children and adolescents before proceeding to laboratory confirmation.

Practice guidelines do not recommend universal testing for prolactin during AP treatment [Marder *et al.* 2004; Correll and Carlson, 2006]. This is understandable as there is only a weak correlation between prolactin concentration and side effects [Findling *et al.* 2003]. Moreover, relatively mild hyperprolactinemia, in the absence of hypogonadism, has not been definitively linked to deleterious skeletal sequelae [Shibli-Rahhal and Schlechte, 2009]. In addition, the studies exploring the skeletal effects of AP-induced hyperprolactinemia in

adults are conflicting and have largely failed to use state-of-the-art methods to assess trabecular BMD or to adequately account for important confounding variables, such as physical activity, dietary intake, vitamin D concentration, smoking status, and gonadal activity [Bilici *et al.* 2002; Abraham *et al.* 2003; Becker *et al.* 2003; Meaney *et al.* 2004; Howes *et al.* 2005; Jung *et al.* 2006; Meaney and O'Keane, 2007; Kishimoto *et al.* 2008]. As reviewed earlier, the dearth of information in children and adolescents is also problematic, prohibiting the field from drawing firm conclusions.

What is particularly concerning in children and adolescents is that polypharmacy is increasingly prevalent, particularly among AP-treated patients [dosReis *et al.* 2005; Duffy *et al.* 2005; Crystal *et al.* 2009; Comer *et al.* 2010]. A recent analysis of the National Ambulatory Medical Care Survey data revealed that medications for attention deficit hyperactivity disorder, antidepressants, and APs are the classes of psychotropics most often used in combination [Comer *et al.* 2010]. For example, nearly two-thirds of children receiving risperidone were concurrently prescribed other psychotropics. In our sample of risperidone-treated youth, once risperidone was started, only 1% of the children received risperidone monotherapy for their entire treatment period. Thus, with accumulating evidence linking various psychotropics to bone health, clinicians ought to consider the potential skeletal impact of polypharmacy as opposed to that of individual psychotropics. This task is challenging, particularly in light of evidence suggesting that some psychotropics, like lithium, may promote bone mineralization [Zamani *et al.* 2009; Warden *et al.* 2010].

To complicate matters further, childhood psychopathology is itself associated with lower socioeconomic status, single-parent homes, and poor parental supervision. These factors, in turn, are correlated with deleterious lifestyle habits, including suboptimal diet and physical activity. The essential role adequate nutrition, including calcium and vitamin D intake, and physical activity play in healthy bone development is well established [NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001]. Moreover, a history of maltreatment is relatively common in psychiatrically ill children and adolescents, particularly those treated with APs. Such factors, along with obesity whether idiopathic or iatrogenic due to APs, can affect the

Figure 2. Psychotropic treatment, particularly the use of antipsychotics, is associated with a multitude of factors that might, directly or indirectly, impair bone development in children and adolescents. For instance, childhood psychopathology may be associated with suboptimal lifestyle habits, hormonal changes (e.g. hypercortisolemia), and the concurrent use of several medications that may affect bone metabolism.

onset of puberty and induce subclinical inflammation, thereby influencing bone mineralization.

Albeit somewhat controversial, guidelines issued by the Pediatric Position Development Conference of the International Society of Clinical Densitometry recommend densitometry in certain clinical situations (e.g. osteogenesis imperfecta) [Baim *et al.* 2008; Lewiecki *et al.* 2009]. These include anorexia nervosa but not other psychiatric conditions or treatments with psychotropics. In fact, there is presently insufficient scientific evidence to support routine bone densitometry for ‘screening’ or ‘case finding’ in children and adolescents undergoing psychotropic treatment. Nonetheless, the decision to pursue testing is ultimately a clinical one and must take into account such factors as the number of risk factors, personal history of fractures, and family history. Such a decision may be best made in close collaboration with a specialist since the optimal skeletal site to scan and the appropriate interpretation of the densitometry results can be challenging in children, requiring consideration of factors like pubertal development and height [Baim *et al.* 2008; Bachrach and Sills, 2011].

In sum, the risk factors that place a child at an elevated risk for receiving an AP overlap with those contributing to polypharmacy, suboptimal lifestyle habits, obesity, and early pubertal development. The overall result is a situation where multiple risk factors for impaired skeletal development converge (Figure 2). Therefore, clinicians have a challenging task to not only treat the imminent psychiatric problems but also to optimize health during long-term care to prevent chronic diseases, including osteoporosis. This would, in turn, increase the longevity and quality of life of individuals suffering with mental illness.

Funding

This work was funded by a 2005 NARSAD Young Investigator Award and by the National Institute 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 agencies.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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