Effects of Psychiatric Disorders and Psychotropic Medications on Prolactin and Bone Metabolism

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Objective: Osteoporosis occurs in common psychiatric conditions and causes significant morbidity. Many neuroleptic medications can cause hyperprolactinemia, which can then potentially be associated with bone loss. Few reviews have thus far addressed this issue. We have consolidated information from studies that examined effects of psychiatric conditions and their treatment on bone metabolism.

Data Sources: We searched PubMed for original articles and reviews published between 1976 and 2004 that described changes in bone metabolism in psychiatric disorders and examined prolactin elevations with neuroleptic medications. Keywords used were *major depressive disorder, bipolar disorder, schizophrenia, bone density, bone metabolism, hyperprolactinemia, typical antipsychotics,* and *atypical antipsychotics.*

Study Selection and Data Extraction: 160 articles published in peer-reviewed journals were identified and are summarized, with greater emphasis given to data from larger, controlled studies.

Data Synthesis: Schizophrenia and major mood disorders are often associated with perturbations in bone metabolism related to factors including nutritional alterations, smoking, and hypogonadotropic hypogonadism, with or without medication-induced hyperprolactinemia. Polydipsia can contribute to bone loss in schizophrenia, whereas hypercortisolemia is often associated with low bone density in depression. Lithium in bipolar disorder and thyroid-stimulating hormone–suppressive doses of L-thyroxine have a negative impact on bone health. Mood stabilizers such as carbamazepine and valproate can also affect bone density. Hyperprolactinemia may lead to bone loss only if associated with untreated amenorrhea in women or testosterone deficiency in men. Some atypical neuroleptics, by causing lesser elevations in prolactin, may therefore have a less marked impact on bone than typical neuroleptics.

Conclusions: Because significant morbidity is associated with low bone density and many psychiatric conditions may have a negative impact on bone metabolism, bone density evaluation should be considered an integral component of chronic medical care of these disorders, and risk factors should be identified and addressed.

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Certain psychiatric disorders are now known to be associated with low bone mineral density (BMD), including schizophrenia, schizoaffective states, major depression, and bipolar disorder.[1–6] Eating disorders, especially those associated with low body mass index (BMI) and lean body mass such as anorexia nervosa, are well known to be associated with osteopenia and osteoporosis and have been extensively reviewed in other publications.[7–10] A decrease in BMD at the hip by about 10% has been associated with a greater than 40% increase in fracture rates over a 10-year period,[11] and once lost, bone mass in this population may be difficult to gain back. Psychotropic medications, including a number of antidepressants, antipsychotics, and benzodiazepines, have side effects that include sedation, orthostatic hypotension, and dyskinesias, which may predispose patients on treatment with these medications to falls. Depression is also an independent risk factor for falls and subsequent fractures. Psychiatric disorders and medications used in their treatment can sometimes lead to reproductive abnormalities resulting in estrogen deficiency in women and testosterone deficiency in men. This hypogonadal state is also a major risk factor for bone loss, whether it occurs in asso-

Table 1. Psychiatric Disorders and Bone Metabolism

Psychiatric Disorder	Bone Density	Bone Turnover	Predisposing Factors for Low Bone Density
Schizophrenia and schizoaffective states	May be ↓[2,3,16,160]	Insufficient data	Hypogonadism (associated with illness, induced by medication, or both) Inadequate or excessive exercise Undernutrition Smoking Polydipsia
Major depression and other depressive states	May be ↓[4–6,104–106]	↓[4] ↑[107]	Hypogonadism (associated with illness, induced by medication, or both) Hypercortisolism Loss of appetite and weight loss Inadequate or excessive exercise
Bipolar disorder	Normal[148,149] ↓[146]	Insufficient data	Hypogonadism (associated with illness, induced by medication, or both) Lithium-induced hyperparathyroidism Low 25 (OH) vitamin D levels in association with carbamazepine or valproate

Symbols: ↓ = decreased, ↑ = increased.

ciation with the underlying disorder or as a consequence of medication-induced hyperprolactinemia.

In this review, we focus on the effects of psychiatric disorders such as schizophrenia and major mood disorders and their treatment on bone metabolism. Publications were identified by searching PubMed for original articles and reviews published between 1976 and 2004 that described changes in bone metabolism in psychiatric disorders and examined prolactin elevations with neuroleptic medications. Keywords used were *major depressive disorder, bipolar disorder, schizophrenia, bone density, bone metabolism, hyperprolactinemia, typical antipsychotics,* and *atypical antipsychotics.* One hundred sixty articles published in peer-reviewed journals were identified and are summarized, with greater emphasis given to data from larger, controlled studies.

SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDERS

Factors that predispose patients with schizophrenia and schizoaffective disorders to impaired bone metabolism and low BMD include hypogonadism in association with the disease itself or due to hyperprolactinemia from use of neuroleptic medications, inadequate exercise and exposure to sunlight, undernutrition, smoking, and polydipsia (Table 1). Hypogonadism has been described in patients with schizophrenia independent of prolactin elevations[12,13] and is attributed to the dysregulation in dopamine transmission that may underlie psychosis or to hypogonadotropic hypogonadism resulting from the stress of the illness itself. Canuso et al.[12] reported menstrual dysfunction in 50% of subjects treated with antipsychotics with prolactin-sparing potential, none of whom had hyperprolactinemia. Estrogen is protective to bone and prevents bone resorption,[14] and hypogonadism is a well-known cause of low bone density. The prevalence of hyperprolactinemia in patients being treated with neuroleptics and the effects of high levels of prolactin on bone metabolism are described in the section Neuroleptics, Hyperprolactinemia, and Bone Metabolism. Almost 85% of all schizophrenics smoke daily,[15] and a direct toxic effect of smoking on osteoblasts has been described. In addition, smoking interferes with the protective effects of estrogen on bone mineralization.

Polydipsia has been reported in as many as 10% of all patients suffering from schizophrenia and in a number of small series and case reports has been shown to contribute to bone loss.[3] The mechanism of bone loss is presumably due to increased urinary calcium excretion, a potential cause of low BMD seen in this group.

Baastrup et al.[16] reported lower bone mineral content at the radius in patients with schizophrenia independent of the kind of medication used. As many as 25% of elderly chronic schizophrenia patients have been reported to have had at least 1 nontraumatic osteoporotic fracture.[2] Meaney et al.[17] demonstrated low bone density in 57% of men and 32% of women with schizophrenia and showed that chlorpromazine equivalence of neuroleptic medications predicts bone density measures in these patients.

Neuroleptics, Hyperprolactinemia, and Bone Metabolism

Regulation of prolactin secretion. Prolactin is secreted by lactotroph cells in the anterior pituitary gland, and its secretion is tonically inhibited by the hypothalamic secretion of dopamine, the predominant prolactin-inhibiting factor. Dopamine acts on D_2 receptors on lactotrophs in the anterior pituitary to inhibit prolactin gene transcription and release.[18] Conversely, serotonin (5-HT) is stimulatory to prolactin secretion and acts through the 5-HT_{1A} and 5-HT_2 receptors.[19,20]

Hyperprolactinemia and bone metabolism. Hyperprolactinemia, primarily studied in patients with prolactin-secreting pituitary tumors, has been well documented to cause bone loss in adult men[21–23] and women[24–28] and in adolescents.[29] The extent of osteopenia or osteoporosis correlates with the presence of hypogonadism and the

Table 2. Effects of Hormones and Cytokines on Bone Turnover

Substance	Effect on Bone Formation	Effect on Bone Resorption
Hormones		
Estrogens	↔/↑	↓
Testosterone	↑	↓ (after aromatization to estrogen)
Growth hormone	↑	↔/↓
Insulin-like growth factor-1	↑	↔
Cortisol	↓	↑
Parathyroid hormone (PTH)	↑ (with intermittent dosing)	↑ (with continuous dosing or endogenous PTH)
Cytokines		
TNF-α, IL-1 and IL-6, PGE-2, RANKL	?	↑
TGF-β, osteoprotegerin	?	↓

Abbreviations: IL = interleukin, PGE-2 = prostaglandin-2, RANKL = receptor activator of NF-κB ligand, TGF-β = transforming growth factor-β, TNF-α = tumor necrosis factor-α. Symbols: ↓ = decreased, ↑ = increased, ↔ = no change, ? = unknown.

duration rather than the degree of hyperprolactinemia. High prolactin levels have an inhibitory effect on the hypothalamic pulsatile release of gonadotropin-releasing hormone (GnRH) and inhibit the positive feedback effect of estradiol levels on luteinizing hormone secretion. The primary mechanism of bone loss is the resulting hypogonadism, which occurs in a subset of both women and men with hyperprolactinemia.[22,25,30] Bone density is normal in women with hyperprolactinemia who continue to have regular menses and thus are not hypogonadal.[25,26]

The effects of hyperprolactinemic amenorrhea and/or estrogen deficiency on bone loss can vary depending on the age at onset. For example, in adults, estrogen is important in maintaining established bone mass. However, estrogen also plays an important role in attainment of peak bone mass. Estrogen is necessary for the secretion of cytokines such as osteoprotegerin and transforming growth factor-β (TGF-β), which inhibit osteoclast differentiation and activation and stimulate apoptosis of these cells, and it also inhibits secretion of other cytokines such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and prostaglandin-2 (PGE-2), which stimulate osteoclast differentiation and activation and inhibit apoptosis[14] (Table 2). In adolescents, rising levels of estrogen are initially associated with rising levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1),[31] which are anabolic to bone,[32] and higher levels of estrogen in late adolescence result in decreased bone resorption. These 2 processes, both of which are estrogen dependent, are responsible for attainment of peak bone mass, 90% of which is achieved by the end of the second decade of life.[33]

In young women, sustained estrogen production is necessary for maintenance of bone mass. Therefore, depending on the stage of life in which hyperprolactinemia occurs, associated hypogonadism may result in a failure to attain peak bone mass (if hyperprolactinemia occurs in the adolescent years) or an inability to maintain bone mass (if hyperprolactinemia occurs in young adult life), with increased risk for fractures in later life. Hypoestrogenism in postmenopausal women is associated with increased skeletal remodeling and bone loss, with an increased risk of osteoporotic fractures.[34] However, the onset of hyperprolactinemia in a postmenopausal woman who is already estrogen deficient would not be expected to result in additional bone loss. Estrogen deficiency, whether due to hyperprolactinemia or other causes of hypogonadism, results in decreased inhibition of osteoclast differentiation and activation and increased apoptosis through interactions with proinflammatory cytokines. New bone remodeling sites are also activated.[35] Recovery from osteopenia follows normalization of levels of gonadal steroids (estrogen/progesterone in women and testosterone in men) after prolactin levels normalize,[22,36] although complete recovery may not occur.[29]

Clinical features associated with hyperprolactinemia. The extent of elevation of prolactin necessary before symptoms such as galactorrhea or hypogonadism occur is highly variable. Prolactin levels above 60 to 100 ng/mL are likely to be associated with galactorrhea and hypogonadism, and clinical features suggestive of hypogonadism include menstrual irregularities or amenorrhea in women and decreased libido in both men and women (reviewed in Wieck and Haddad[20] and Meaney and O'Keane[37]). Men may also develop gynecomastia and impotence. Hyperandrogenic features may be evident in women as a consequence of decreased sex hormone binding globulin levels, which result in higher levels of free testosterone. Prolactin may also directly stimulate the secretion of dehydroepiandrosterone sulfate (DHEA-S), a testosterone precursor from the adrenal glands. In the absence of clinical features of hypogonadism, hyperprolactinemia is not a risk factor for osteoporosis.[26]

Conventional (typical) neuroleptics and hyperprolactinemia. Prolactin levels are typically normal in untreated patients with schizophrenia[38,39] but are frequently elevated in patients treated with conventional neuroleptics.[40] Typical neuroleptics elevate prolactin levels by blocking dopaminergic inhibition of prolactin secretion, and the degree of hyperprolactinemia depends on the percentage occupancy of D_2 receptors.[41] The degree of prolactin elevation with typical neuroleptics such as chlorpromazine, thiorid-

azine, trifluoperazine, butaperazine, and haloperidol correlates with their relative clinical potencies.[42] Maximal prolactin elevations occur 1 to 2 hours after administration of a single subtherapeutic dose of a typical neuroleptic and return to baseline over a period of about 6 hours. With repeated administration of a neuroleptic, prolactin levels remain elevated, and Meltzer and Fang[43] demonstrated in their study 3.2- and 3.8-fold rises in serum prolactin levels in all men and women, respectively, 72 hours after treatment initiation. Dose-dependent increases in prolactin secretion occur with conventional neuroleptic doses up to approximately 600 mg of chlorpromazine equivalents.[20,44] The percentage occupancy of D_2 receptor above 50% correlates with the extent of elevation of prolactin above baseline.[41]

Higher levels of prolactin have been observed in women than in men receiving neuroleptics.[39,44,45] The extent of prolactin elevation appears to be dose related, and associated hypogonadism is more likely to occur in women compared with men on treatment with neuroleptics.[44] In a recent review, Kinon et al.[40] reported prolactin levels 2.6 times higher in women compared with men on treatment with neuroleptics. Duration of therapy is an important factor in determining the persistence of hyperprolactinemia in published studies. Some patients treated with conventional neuroleptics develop tolerance to the prolactin-elevating effects of the medication, resulting in serum prolactin normalization following chronic therapy.[46–49] However, other authors[46,50] have reported significantly higher prolactin levels in patients treated for years with conventional neuroleptics compared with healthy controls. In a recent report, the prevalence of hyperprolactinemia in women on treatment with conventional neuroleptics was 48%.[40]

The prevalence of menstrual irregularities has been reported to be in the range of 26% to 91% with the use of conventional antipsychotics,[51–54] and Windgassen et al.[55] observed a 19% prevalence rate of galactorrhea in women treated with these medications. Sexual dysfunction has also been reported, and in one study[54] of 55 adults with schizophrenia, 58% of men and 33% of women on treatment with classical antipsychotics were noted to have sexual dysfunction, and an association was observed between sexual dysfunction and prolactin levels in the men in the study.

Atypical neuroleptics and hyperprolactinemia. It has been suggested that atypical antipsychotic drugs including clozapine, olanzapine, quetiapine, ziprasidone, risperidone, amisulpride, zotepine, and aripiprazole[20] have preferential high affinities for 5-HT_{2A} serotonin receptors and relatively low affinities for D_2-dopamine receptors. The atypical antipsychotics differ as regards their effect on prolactin secretion, which has been thought to reflect their relative affinities for the D_2 and 5-HT_2 receptors, with greater D_2 and lesser 5-HT_2 receptor antagonism often related to increases in prolactin levels. For example, treatment with risperidone, an atypical with a high in vitro potency for D_2 inhibition,[56] has often been reported to result in elevations in prolactin levels, not only in adults[40,57–62] but also in children and adolescents.[63,64] In a large study of adults treated with neuroleptic medications, Kinon et al.[40] reported hyperprolactinemia in 88% of female patients treated with risperidone. Findling et al.[64] demonstrated that in children and adolescents, prolactin levels increase almost 4-fold after 1 to 2 months of receiving 0.02 to 0.06 mg/kg/day of risperidone but then decrease to almost normal levels by 3 to 5 months of therapy. The prevalence of menstrual irregularities has been reported to be in the range of 8% to 48% with risperidone,[40,65] and sexual dysfunction has been reported in as many as 43% of schizophrenia patients on risperidone treatment.[66] Therefore, in examining potential long-term effects of prolactin secretion on bone, there are 2 important factors to consider. First, if hyperprolactinemia occurs, is it temporary or chronic? Second, does hyperprolactinemia cause disturbances in gonadal hormone secretion resulting in amenorrhea and low estrogen levels in women and low testosterone levels in men?

In patients with symptomatic drug-induced hyperprolactinemia, it is uncertain whether reducing prolactin levels in patients using dopamine agonists such as cabergoline can cause psychiatric destabilization as prolactin levels are normalized. Dopamine agonist treatment in patients with hyperprolactinemia due to pituitary tumors has been rarely reported to cause behavioral changes including psychosis. Some reports suggest that an elevation in prolactin levels with risperidone is associated with an improvement in psychotic symptoms,[67] while other reports[68,69] suggest that the degree of prolactin elevation does not correlate with treatment efficacy. Tollin[68] demonstrated that dopamine agonist therapy normalizes prolactin levels without causing a worsening of psychosis in patients with risperidone-induced hyperprolactinemia. Similar results have been reported in small retrospective studies in children, with cabergoline effectively decreasing prolactin levels without causing any side effects.[69] Amisulpride/sulpiride are also known to increase prolactin levels, and as much as a 10-fold increase in levels above baseline has been reported.[70]

In contrast, other atypical neuroleptics such as olanzapine result in more modest prolactin elevations than equivalent therapeutic doses of risperidone[71] or haloperidol.[72,73] Replacing risperidone with olanzapine in women with risperidone-induced hyperprolactinemia has been noted to result in normalization of prolactin levels and an improvement in reproductive and sexual function.[74] Olanzapine and clozapine have also been observed to decrease prolactin levels in patients with treatment-induced hyperprolactinemia.[62] Conversely, addition of risperidone[58] or haloperidol[75] treatment in patients receiving clozapine

monotherapy was reported to result in an elevation in prolactin levels, and the latter was associated with increased D_2 receptor occupancy from 55% to 79%. Turrone et al.[59] demonstrated normal prolactin levels in patients receiving olanzapine or clozapine. In a study of children and adolescents receiving antipsychotic drugs, 100% of the group receiving haloperidol, 70% of the group receiving olanzapine, and 0% of the group receiving clozapine had prolactin levels that were above the upper limit of normal.[76]

Quetiapine,[59,77,78] aripiprazole,[61] and ziprasidone[79] do not appear to be associated with persistent hyperprolactinemia. Quetiapine is associated with much lower prolactin levels than risperidone and with a lower incidence of sexual dysfunction.[80] Hyperprolactinemia induced by other neuroleptics has also been shown to resolve when patients are switched to quetiapine.[81] Takahashi et al.[82] reported recovery of menstrual function in 72% of women with risperidone- or haloperidol-induced amenorrhea who were switched to quetiapine. Aripiprazole is a dopamine D_2 receptor partial agonist that has partial agonist activity at serotonin 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. In one study examining the effects of risperidone versus aripiprazole, 6 mg/day of risperidone was associated with a 5-fold increase in prolactin levels, whereas 20 to 30 mg/day of aripiprazole led to a decrease in prolactin levels.[61] Ziprasidone has a 5-HT_{2A}/D_2 receptor-binding ratio of approximately 8:1, among the highest of its class. It is also a potent 5-HT_{1A}R agonist and a 5-HT_{1D}R and 5-HT_{2C}R antagonist, and it blocks the reuptake of both 5-HT and norepinephrine. It has low-to-modest affinity for histamine (H_1) and α_1-adrenoceptors and a negligible affinity for muscarinic (M_1) receptors.[83] This combination of effects may be responsible for the low incidence of general adverse events with ziprasidone, including a low incidence of persistent prolactin elevation, despite the fact that its in vitro potency for the D_2 receptor is equivalent to that of haloperidol.[56] Switching to ziprasidone has been reported to result in a decrease in prolactin levels in patients previously on treatment with risperidone or conventional neuroleptics and weight loss in patients previously on treatment with olanzapine and risperidone.[84]

Kapur et al.[85] demonstrated that dissociation between central and peripheral effects of atypical antipsychotics is explained by the differential occupancy of D_2 receptors in the striatum versus in the pituitary. The ratio of striatal/pituitary effective $dose_{50}$ (ED_{50}) values for D_2 occupancy was high for amisulpride and risperidone and low for quetiapine and olanzapine, suggesting that dissociation between central and peripheral D_2 receptor occupancy is a major determinant of the degree of prolactin elevation observed at therapeutic doses. Lower prolactin levels associated with atypical antipsychotics are quite likely a consequence of transient or low levels of D_2 receptor occupancy.[77] According to studies of D_2 receptor binding affinity and effects on prolactin levels, it appears that the prolactin-raising potency is highest for sulpiride, followed by risperidone, haloperidol, quetiapine, olanzapine, and clozapine.

When making a decision to use one neuroleptic medication versus another, it is important to consider the effect of the different neuroleptic agents on prolactin secretion, but this consideration needs to be balanced against the effects of these medications on body weight and glucose and lipid metabolism. Several typical and atypical neuroleptics have been associated with weight gain. However, atypical neuroleptics such as clozapine, olanzapine, risperidone, and quetiapine appear to be more potent as regards effects on weight; followed by phenothiazines such as chlorpromazine, thioridazine, and mesoridazine; followed by haloperidol, with small effects on weight, and molindone, loxapine, and pimozide, which do not cause any increase in weight.[86] Among the newer neuroleptics, long-term treatment with clozapine and olanzapine carries the highest risk of weight gain, followed by risperidone and quetiapine, which have a moderate risk of weight gain (risperidone more than quetiapine).[87,88] Conversely, ziprasidone and aripiprazole have a low risk for inducing an increase in weight.[87] Associated with weight gain are adverse effects on glucose and lipid metabolism. The relative risk of glucose intolerance and type 2 diabetes has been reported to be highest with clozapine and olanzapine, low to moderate for quetiapine and risperidone, and lowest with ziprasidone.[89–97] Olanzapine use is associated with a 20% to 37% increased risk of diabetes compared with risperidone.[94,95] In addition, an increase in cholesterol and triglyceride levels has been demonstrated with use of clozapine and olanzapine.[89,96,98]

Neuroleptics and Bone Density

Data regarding the effects of neuroleptics on bone mass are limited by small patient numbers, limited controls, lack of prospective studies, and multiple confounders. As previously noted, patients receiving neuroleptics may have other factors impacting on bone, such as hypogonadism unrelated to prolactin elevation, poor diet, and cigarette smoking. However, obesity, a significant problem in this population, is protective against bone loss. In addition, data regarding gonadal function are often unavailable. These limitations prevent conclusions regarding effects of neuroleptics on bone. Ataya et al.[99] reported that BMD in 10 women with neuroleptic-induced hyperprolactinemia was at about the 90th percentile when compared with that in controls matched for age, gender, ethnicity, and weight and correlated with the vaginal maturation score, a measure of estrogen exposure. Bilici et al.[100] examined bone density in 75 individuals with schizophrenia on treatment with neuroleptics (typical and atypical) and 20 healthy controls and found that bone density was higher in controls. Inverse correlations were

noted between duration of illness and bone density and durations of neuroleptic therapy and bone density. Similarly, Meaney et al.[17] reported that chlorpromazine equivalence was the most important predictor of low bone density in patients with schizophrenia on treatment with neuroleptics. Recent reports suggest that the use of atypical neuroleptics (with the exception of risperidone) may be less harmful to bone than the use of classical neuroleptics.[60,100]

In a small, recently published cross-sectional study,[60] prolactin levels were noted to be lower in 14 schizophrenia patients treated with olanzapine versus 12 patients treated with risperidone. Bone mineral density measured by dual-energy x-ray absorptiometry (DXA), the gold standard of assessing bone mass and future fracture risk, was not different in the 2 groups. Although the risperidone-treated group had lower bone speed of sound (as assessed by ultrasound) compared with the olanzapine-treated group, the clinical significance of this finding is not established. Another yearlong prospective study[101] of women receiving risperidone versus olanzapine found no differences in BMD in 7 patients with schizophrenia with hyperprolactinemia versus 7 women with schizophrenia but normal levels of prolactin.

AFFECTIVE DISORDERS

The lifetime prevalence of major depressive disorder is as high as 5% to 10% in the general population, and it is the second most common chronic condition encountered in clinical practice, second only to hypertension.[102] The association of depression with alterations in the neuroendocrine axes is well known and includes hypercortisolism, hypogonadism, and alterations in the GH–IGF-1 axis.[103] Over the last decade or so, studies have reported low bone density in both men and women suffering from this debilitating disorder and have attributed it to the neuroendocrine alterations observed in this population (Table 1).

Bone Metabolism

Schweiger et al.[5] first examined lumbar BMD by quantitative computed tomography in 80 depressed men and women more than 40 years old and 57 healthy control subjects. This cross-sectional study reported lower BMD in the depressed group and concluded that major depressive disorder is a risk factor for osteoporosis. In a follow-up study,[6] the authors demonstrated that men and women with depression continued to lose bone mass when examined at least 2 years after the initial study, and the depressed group had significantly lower BMD at follow-up after adjustment for effects of initial BMD, age, and gender. In a subsequent study, Michelson et al.[4] reported similar results using DXA in 24 women (mean ± SD age = 41 ± 8 years) with a past or present history of depression compared with control women matched for age, BMI, menopausal status, and ethnicity. Bone mineral density in women with a history of depression was lower by 6.5% at the lumbar spine, 13.6% at the femoral neck, 13.6% at Ward's triangle, and 10.8% at the femoral trochanter. However, BMD at the radius did not differ between the groups, leading the authors to conclude that trabecular rather than cortical BMD is affected in this disorder. Robbins et al.[104] also reported a negative association between depression scores as assessed by the Center for Epidemiological Studies-Depression scale and hip BMD, most marked in white women, even after adjusting for age, BMI, kilocalories of activity, estrogen use, gender, ethnicity, smoking, and alcohol intake. Every unit increase in the depression score used in this study was associated with a 0.3-mg/cm^2 decrease in total hip BMD. Depressive symptoms accounted for 13% of the variability of hip BMD in white women in this study in an unadjusted model and for 2% of the variability of hip BMD after accounting for the covariates described. Another recent study[105] demonstrated low BMD at different sites in depressed premenopausal women. In a survey of 102 perimenopausal white Portuguese women, Coelho et al.[106] showed higher levels of depressive symptoms in women with osteoporosis than in those with normal BMD and demonstrated that depression was an independent predictor of low bone density even after adjusting for potential confounders.

Michelson et al.[4] reported a decreased bone turnover in women with a history of depression compared with healthy women. In this study, the depressed group had lower levels of both osteocalcin, a marker of bone formation, and deoxypyridinoline, a marker of bone resorption. Conversely, Herran et al.[107] found elevated levels of osteocalcin and of *N*-telopeptide (marker of bone resorption) in 19 depressed women with a mean ± SD age of 44.7 ± 12.1 years compared with 19 age-matched healthy women, suggesting a state of increased bone turnover. Yazici et al.[105] similarly reported elevated levels of deoxypyridinoline, yet another marker of bone resorption, but no differences in levels of osteocalcin in 25 premenopausal women versus 15 healthy control women.

These data suggest that depression is a risk factor for low bone density but are limited in that some studies reported subjects with depressive symptoms but without major depressive disorder.

Mechanism of Low Bone Mineral Density in Depression

Endocrine alterations. Hypercortisolemia has been described in depression in many studies and reviews[4,103,107,108] and has been demonstrated to be the consequence of a greater frequency of episodic hormone release.[109] The increases in cortisol levels are generally small although in the range known to result in reductions in BMD.[110,111] Because depressive disorders are associated with multiple exacerbations and remissions, even these small elevations

of cortisol may contribute to low BMD, with recovery of bone mass being less likely while recurrences continue to occur. In addition, elevations in cortisol levels have been associated with decreased bone turnover,[112,113] as has been noted in at least 1 study of depression and bone metabolism.[4]

Higher levels of proinflammatory cytokines such as interleukin-6 (IL-6) and TNF-α, which activate osteoclastic bone resorption and inhibit osteoclast apoptosis, have been described in depression in some studies,[114] but not in others.[115,116] Herran et al.[107] found no differences in IL-6 levels and correlation between bone markers and IL-6 levels in a study of 19 women with depression and 19 controls.

Hypogonadism may occur in some patients with depression,[103] especially in association with eating disorders, and hypoestrogenism is associated with decreased BMD. However, studies have reported low BMD in depressed individuals even when there was no evidence of hypogonadism.[4] Halbreich et al.,[1] however, did observe an inverse correlation between plasma testosterone levels and lumbar BMD in men with psychiatric disorders.

Alterations in the GH–IGF-1 axis have been described in depressive disorders.[103] Both GH and IGF-1 are bone anabolic and act synergistically to increase BMD. Michelson et al.,[4] however, found no differences in levels of IGF-1 in depressed women versus healthy matched controls, and BMD in the depressed group was significantly decreased despite normal IGF-1 levels. Another group[108] found elevated IGF-1 levels and no changes in GH levels in acutely depressed patients compared with controls.

Loss of appetite and weight loss may occur in major depressive disorder, and extreme undernutrition as seen in people with anorexia nervosa[9,10] can cause low BMD. Major depressive disorder, however, has been demonstrated to be an independent risk factor for low BMD, even after controlling for BMI.[4,5]

Physical activity. Depression may be associated with both decreased or increased activity levels depending on whether psychomotor retardation or agitated depression is present.[4] Both reduced and excessive activity may cause a decrease in BMD. Markedly decreased physical activity is associated with a decrease in lean body mass, an important determinant of BMD,[9,10,117] and decreased biomechanical forces on bone. Excessive activity as seen in athletes, gymnasts, and ballet dancers can also result in low BMD,[117] possibly as a consequence of associated hypogonadism and sometimes undernutrition. Self-reports of exercise patterns did not differ in depressed versus normal women in one study.[4] However, validated exercise questionnaires were not used.

Antidepressant medications. Animal and human studies have demonstrated an inhibitory effect of antidepressants such as imipramine on hypothalamic secretion of corticotropin-releasing hormone.[118] In addition, a lowering of cortisol levels has been demonstrated following administration of antidepressants, suggesting that antidepressant treatment, by lowering cortisol levels, should result in an improvement in BMD.[119,120] Unlike neuroleptics, most antidepressants do not cause significant hyperprolactinemia. Of the tricyclic antidepressants, minor (1.5- to 2.5-fold) elevations in prolactin have been reported with trimipramine,[120] desipramine,[121] and clomipramine,[122] but not with imipramine.[119,123] Tianeptine, like imipramine, does not appear to increase prolactin secretion.[124] Elevations of prolactin levels have been noted with administration of older monoamine oxidase (MAO) inhibitors such as pargyline (2-fold elevation)[125] and new reversible MAO inhibitors such as moclobemide.[126] In one study of 8 healthy men, administration of methysergide, a serotonin receptor antagonist, prior to administration of moclobemide led to total prevention of the moclobemide-induced increase in prolactin levels.[126] Mirtazapine, a tetracyclic piperazinoazepine analog of mianserin and a noradrenergic and specific serotonergic antidepressant, has not been reported to cause an increase in prolactin values.[127,128] The effects of increases in prolactin values from use of antidepressants on bone metabolism remain to be investigated. An improvement in BMD following use of antidepressant medications has not been demonstrated thus far.

Selective serotonin reuptake inhibitors and neuroendocrine hormonal changes affecting bone metabolism. These drugs have been used very effectively in certain psychiatric conditions such as depression and obsessive-compulsive disorders and include fluoxetine, paroxetine, fluvoxamine, sertraline, and citalopram. The neuroendocrine responses to both acute and chronic administration of these agents have been studied. Evidence suggests the involvement of 5-HT_{1A} and 5-HT_{2A} receptors in adrenocorticotropic hormone secretion[129–131]; 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors in prolactin secretion[132,133]; and 5-HT_{1A} and possibly 5-HT_{1D} receptors in GH secretion.[134,135] Von Bardeleben et al. noted a slight increase in cortisol after a single dose of fluoxetine,[136] and Seifritz et al.[137,138] noted significant increases in cortisol levels after a single intravenous dose of citalopram in humans. Acute administration of a single intravenous dose of citalopram also significantly increases prolactin secretion.[137,138] Spigset and Mjorndal[139] reported increases in prolactin levels after 4 weeks of fluvoxamine treatment. In contrast, long-term administration of selective serotonin reuptake inhibitors (SSRIs) has not resulted in consistent alterations in basal levels of cortisol, prolactin, and growth hormone in animal or human studies (reviewed by Raap and Van de Kar[140]). Although prolactin levels do not usually rise above the normal range during treatment with SSRIs, isolated case reports do exist of galactorrhea and elevations in prolactin in patients treated with fluoxetine,[141] paroxetine,[142,143] and sertraline.[144,145]

BIPOLAR DISORDER

Several medications used to treat bipolar disorder have been reported to have effects on bone. Lithium has a potential negative impact on bone metabolism given the known association of hyperparathyroidism with lithium therapy.[146–150] In addition, doses of L-thyroxine that suppress thyroid-stimulating hormone (TSH) levels have been previously used in the management of individuals with rapid-cycling bipolar disorder,[149] and the adverse effects of such doses of L-thyroxine on bone metabolism are well known.[151,152] A high incidence of hypothyroidism (up to 50%) has been noted in this group, and after administration of L-thyroxine in doses that suppress TSH (T_4 levels approximately 150% of normal), bone loss due to excess thyroid hormone may occur.[153,154] Antipsychotic agents have proven very helpful in the treatment of acute mania and also as maintenance therapy.[155] Atypical neuroleptics are now often added to mood stabilizers and antidepressants in treatment-resistant bipolar disorder and are also used alone in this condition. The effects of neuroleptics on prolactin levels and bone metabolism are described at length in the section Neuroleptics, Hyperprolactinemia, and Bone Metabolism.

Mood Stabilizers and Bone Metabolism

Lithium. Effects of lithium on calcium metabolism and parathyroid hormone (PTH) secretion include elevations in levels of PTH[147,148] and calcium,[148] associated with decreased urinary excretion of calcium.[146,147] An increase in the PTH set point has been recently described in lithium-treated patients.[150] Based on the increased urinary calcium reabsorption, Mak et al.[147] suggested that lithium treatment is associated with decreased rather than increased bone resorption. Indeed, in a cross-sectional study, Nordenstrom et al.[148] found no differences in BMD at the lumbar spine, femoral neck, or total body when lithium-treated patients were compared with age-, gender-, and BMI-matched controls. Similarly, another cross-sectional study noted no differences in lumbar spine or hip BMD in patients treated short-term (0.4–1 year) or long-term (more than 3 years) with lithium.[149] The groups were matched for gender, weight, calcium and lithium intake, and smoking habits. Conversely, in an older prospective study, Plenge and Rafaelsen[146] reported a decrease in bone mineral content as measured by photon absorptiometry within 6 months of lithium treatment, although urinary calcium and phosphate excretion decreased. It is likely that the prospective nature of the latter study versus the cross-sectional nature of the other 2 studies and the different outcome measures used (bone mineral content vs. bone mineral density) accounted for the difference in results. More prospective studies of lithium-treated patients with DXA (the standard for bone density evaluation today) would be useful to better understand the long-term effects of lithium on bone.

Anticonvulsants. Anticonvulsants such as carbamazepine and valproic acid have been used successfully as mood stabilizers and have also been associated with osteopenia,[156–159] with the extent of bone loss being related to the duration of treatment. Low bone density is a consequence of low levels of 25-hydroxy vitamin D.[156–159] Effects of valproate on bone are more marked than those of carbamazepine, especially in children.[156,157]

RECOMMENDATIONS FOR MANAGEMENT AND CONCLUSIONS

Given the significant morbidity associated with osteoporosis, identification of secondary causes of osteoporosis in at-risk populations is critical. Many psychiatric disorders can be associated with low bone density, and disorders such as schizophrenia, depression, and anorexia nervosa are reported to have more significant effects on bone metabolism than others. Thus, it is necessary that a baseline bone density evaluation become an integral component of the chronic management of patients with such disorders. Studies that have been performed examining bone metabolism in psychiatric conditions have primarily been conducted in adults. Although some of these psychiatric disorders are also common in the adolescent years, the effects of disorders such as schizophrenia and depression as well as their treatment on bone metabolism in adolescence have not been described. Adolescence is a crucial time of life for bone mass accrual, and 90% of peak bone mass is achieved by the end of the second decade of life. Thus, it is important to examine baseline bone density nnæ only in adults but also in adolescents suffering from chronic psychiatric disorders, particularly in conditions such as schizophrenia, depression, and anorexia nervosa that are associated with a significant risk of osteoporosis. When the psychiatric condition persists, a follow-up bone density evaluation should be performed in 1 to 2 years depending on the severity of the disorder, the medications being used, and the value of initial bone density to determine whether bone loss has progressed over time.

The DXA procedure is associated with minimal radiation risk and excellent reproducibility. The lumbar spine, hip, and distal radius are the sites commonly assessed. Follow-up bone density testing should ideally be performed on the same DXA machine for optimal comparison with the initial scan. In adults, a T-score of less than –2.5 indicates osteoporosis, while a T-score between –1.0 and –2.5 indicates osteopenia. In contrast, in children, a Z-score of less than –2.5 suggests osteoporosis, while a Z-score between –1.0 and –2.5 suggests osteopenia. The T-score compares the patient's bone density with peak bone density for gender and ethnicity, whereas the Z-score compares the patient's bone density with mean bone density for gender, age, and ethnicity. Because peak bone mass is achieved in early adult life (late second decade to

early third decade), T-scores underestimate bone density measures in children and should never be used in this age group. Evidence of osteoporosis should prompt a referral to an endocrinologist for further management. In addition, it is important to optimize intake of calcium and vitamin D in patients with psychiatric disorders who are at risk for low bone density. Depending on dietary consumption of calcium and vitamin D, in deficient patients, we recommend elemental calcium at a dose of 1300 mg in adolescents and 1500 mg in adults, and 400 to 800 IU of vitamin D daily, to optimize calcium supply and absorption.

An important contributor to low bone density and impaired bone metabolism in psychiatric conditions is neuroendocrine dysregulation induced by the disorder per se, e.g., hypercortisolemia or amenorrhea in depression. In addition, several neuroleptic medications used to treat the condition may contribute to the development of hyperprolactinemia. Other factors that contribute to low bone density include low body weight as a consequence of impaired appetite, decreased levels of physical activity, cigarette smoking, and polydipsia (in schizophrenics). Eliciting a history of smoking in patients with psychiatric disorders is thus important, as is a close attention to body weight, activity levels, and reproductive function in both women and men.

Determination of prolactin levels is essential in those patients treated with neuroleptic medications who have signs and symptoms suggestive of hypogonadism, such as menstrual dysfunction or galactorrhea in women and impotence, gynecomastia, or decreased libido in men. Because hyperprolactinemia without hypogonadism is not a risk factor for osteoporosis, measurement of prolactin levels is usually not necessary in the absence of clinical features suggestive of hypogonadism. In the presence of hyperprolactinemia, it is important to determine whether the elevation in prolactin levels is temporary or chronic. Repeating prolactin level assessment in 3 months is useful in this regard. If hyperprolactinemia is associated with estrogen deficiency in women or low testosterone levels in men, reversal of hypogonadism is important. In some patients, this reversal can be best accomplished by estrogen/progestin replacement in women or physiologic testosterone replacement, preferably by transdermal routes, in men. Switching to another medication can be considered; however, destabilization from a psychiatric standpoint must be considered. The potential of certain medications to increase the risk of bone loss must also be balanced against the risk of obesity and diabetes seen in greater frequency with prolactin-sparing psychotropic medications. These considerations should be important components in assessing the risk-versus-benefit ratio of such medications. Although the use of dopamine agonists to treat neuroleptic-induced hyperprolactinemia is often effective by stimulating D_2 dopamine receptor activity, it can theoretically precipitate worsening of psychiatric disease. Although some reports have been reassuring, this approach cannot be recommended for all patients until larger trials in different patient subgroups have been shown to be effective and safe.

Prospective studies are necessary to determine the effects of several newer neuroleptics and antidepressant medications on bone metabolism. In addition, future studies to determine therapeutic strategies for low bone density associated with psychiatric disorders are essential.

Drug names: aripiprazole (Abilify), cabergoline (Dostinex), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Thorazine, Sonazine, and others), citalopram (Celexa), clomipramine (Anafranil and others), clozapine (Fazaclo, Clozaril, and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lithium (Lithobid, Eskalith, and others), loxapine (Loxitane and others), mirtazapine (Remeron and others), molindone (Moban), olanzapine (Zyprexa), paroxetine (Paxil and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), trifluoperazine (Stelazine and others), trimipramine (Surmontil), valproic acid (Depakene and others), ziprasidone (Geodon).

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