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Marc De Hert, Johan Detraux & Brendon Stubbs

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# Review

# Relationship between antipsychotic medication, serum prolactin levels and osteoporosis/osteoporotic fractures in patients with schizophrenia: a critical literature review

De Hert Marc[1], Detraux Johan[1], Stubbs Brendon[2,3].

1 KU Leuven - University Psychiatric Centre, Department of Neurosciences, B-3070 Kortenberg Belgium.
2 Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom.
3 Health Service and Population Research Department, Institute of Psychiatry, King's College London, De Crespigny Park, London, Box SE5 8AF, United Kingdom.

**Corresponding author:** Marc De Hert, psychiatrist, KU Leuven - University Psychiatric Centre - campus Kortenberg, Leuvensesteenweg 517, 3070 Kortenberg, Belgium, marc.dehert@upckuleuven.be





## Abstract

### Introduction

Using an antipsychotic medication can increase prolactin (PRL) levels, causing hyperprolactinemia (HPRL). Although the occurrence of osteoporosis within the population of patients with schizophrenia has been recognized, the precise nature of the association between antipsychotic treatment, PRL, osteoporosis, and the disease itself seems to be elusive.

### Areas covered

The aim of this review is to critically review the literature regarding the association between osteoporosis and PRL and to summarize the available evidence with respect to the impact of PRL-elevating antipsychotics on bone mineral density (BMD) and fractures in non-elderly patients with schizophrenia.

**Expert opinion**

Although long-standing HPRL can have an impact on the rate of bone metabolism and, when associated with hypogonadism, may lead to decreased bone density in both female and male subjects, the relative contribution of antipsychotic-induced HPRL in bone mineral loss in patients with schizophrenia remains unclear. Methodological shortcomings of existing studies, including the lack of prospective data and the focus on measurements of BMD instead of bone turnover markers, preclude definitive conclusions regarding the relationship between PRL-raising antipsychotics and BMD loss in patients with schizophrenia. Therefore, more well conducted prospective trials of these biomarkers are necessary to establish the precise relationship between antipsychotics, PRL levels and osteoporosis/osteoporotic risk.

**Keywords:** *hyperprolactinemia, schizophrenia, antipsychotic, prolactin, osteoporosis, fracture*





## 1. Introduction

Epidemiologic data have convincingly indicated that bone loss occurs in both women and men as part of the natural aging process, and begins, contrary to previous beliefs, as early as the third decade in both sexes [1-3]. One of the adverse consequences associated with this bone loss is an increased fracture risk [3,4]. Despite the advances in the management of osteoporotic fracture cases, osteoporosis and associated fractures remain a significant public health concern because of related morbidity and mortality [5,6].

People with schizophrenia are known to be at increased risk of experiencing low bone mineral density (BMD) and osteoporosis, compared to the general population [5,7-14]. A recent meta-analysis showed that osteoporosis is over two and a half times more common in

patients with schizophrenia, compared with age- and sex-matched controls. Although these patients were treated with medication, data were inadequate to clearly elucidate the influence of this factor on the observed results [8].

The etiology of BMD loss in these patients is complicated [8,16]. On the one hand, BMD loss seems to be related to the disease itself [17]. On the other hand, a plethora of lifestyle factors (e.g., smoking, reduced physical activity, alcohol abuse, vitamin D and calcium deficiency, polydipsia) [14,18-22], besides the intake of antipsychotic medication and antidepressants, are implicated [7,23].

It has been suggested that raised prolactin (PRL) levels evoked by antipsychotics can accelerate bone loss and increase the risk of osteoporosis [21,23-26]. Antipsychotics have a dopamine D2 receptor-blocking effect and therefore elevate the secretion of PRL, causing hyperprolactinemia (HPRL) (usually defined as fasting levels > 20 ng/ml in men, and > 25 ng/ml in women) [27]. Although all antipsychotics have the propensity to induce HPRL, differences between antipsychotic drugs with respect to PRL elevation are large [27]. The highest rates of HPRL are consistently reported in association with the first generation antipsychotics (FGA) and the second generation antipsychotics (SGA) amisulpride, risperidone and paliperidone, while the SGA aripiprazole and quetiapine have the most favourable profile with respect to this outcome [27]. Although results were mixed, samples and effects were small, and only two studies were prospective, one review [11] showed that 60% of the studies examining the relationship between antipsychotic-induced HPRL and BMD loss found some effects of HPRL. In line of these results, a recent meta-analysis showed that BMD in patients with schizophrenia receiving PRL-raising antipsychotics (FGA, amisulpride, risperidone, paliperidone) was significantly lower than that in patients receiving PRL-sparing antipsychotics (p=0.006) [15]. However, another recent meta-analysis [8] demonstrated that neither the percentage of the patients with HPRL, nor the percentage of

patients taking PRL-raising antipsychotics were found to be related to the prevalence of osteoporosis.

While it is a fact that most antipsychotics have an acute effect on PRL in the first 1-5-hour period after administration [28] (while the degree and duration of PRL elevation depends on the differential binding properties of each antipsychotic on dopamine D2 receptors at the level of the anterior pituitary lactotroph cells) [29], it is not yet clear to what degree and over what time period a given antipsychotic may have an effect on the bone itself [16]. Despite this, several studies suggest that alterations in bone turnover markers can occur very early in the course of treatment [30], over relatively short periods of time [31], or after switching to a PRL-sparing antipsychotic [32].

Thus, although the PRL-elevating propensity of several antipsychotics and the occurrence of osteoporosis within the population of patients with schizophrenia has been recognized, the precise nature of the association between antipsychotic treatment, PRL, osteoporosis, and the disease itself seems to be elusive. Therefore, a critical review of the literature was performed to summarize the available evidence with respect to the PRL-elevating propensity of antipsychotics and the risk of osteoporosis/osteoporotic fractures associated with these compounds in patients with schizophrenia using this medication regularly.

## 2. Definition and assessment

Osteoporosis is a systemic skeletal disease characterized by decreased bone density and microarchitectural alterations of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [3,6,33-36] and has been operationally defined on the basis of BMD assessment [37]. Osteoporosis caused by any factor other than aging or post-menopausal status, such as medication, is called secondary osteoporosis [34].

DXA (dual energy X-ray absorptiometry) is currently considered as the most widely and precise used method for assessing BMD [3,20,33,35,38,39]. The most clinically relevant DXA measurements are those taken at the lumbar spine and proximal femur, because they are the most correlated with spine and hip fractures [13,33]. Nonstandard or less accurate techniques to measure BMD include single-energy X-ray absorptiometry (SXA), peripheral dual-energy X-ray absorptiometry (pDXA), dual-photon absorptiometry (DPA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS) (this last one is equally widely used because of the low cost and lack of ionizing radiation). Other novel assessment tools for osteoporosis diagnosis arise, including reference point indentation (RPI) [40]. Finally, a number of biochemical assessments of fracture risk exist (see further).

Although BMD may be expressed as absolute raw levels ($g/cm^2$), it is clinically more relevant to measure it in relation to two sets of values generated by the DXA scanner [22,27,35,31,41,42]:

- t- scores, comparing the individual's BMD with standardised peak bone mass for gender-specific groups of young healthy adults between 20-30 years;

- z- scores, comparing the individual's BMD with the average for his/her age/gender/ethnic group.

According to the WHO criteria osteoporosis can be operationally defined as a t-score of 2.5 standard deviations (SD) or more below the mean value for peak bone mass in young healthy adults, as determined by DXA. Osteopenia is defined as a BMD of more than 1 SD below this value [33,35,36,38,39] (see Table 1).

**INSERT TABLE 1**

If the results of a BMD test show osteopenia or osteoporosis, it does not automatically mean that one will have a fracture [38]. Although a decreased BMD does increase an individual's susceptibility for a fracture, there is no clear threshold of BMD below which fractures actually occur [13]. Nevertheless, osteoporosis is a clinically significant predictor of fractures, and it is for this reason that BMD measurements are of great interest. Despite the fact that the WHO criteria for the diagnosis of osteoporosis are based on Caucasian women data (while it is well documented that there is significant variation in BMD between ethnic groups [43]), available evidence suggests that the cut-off value for osteoporosis in Caucasian women, i.e. 2.5 SD or more below the average, can be used for the diagnosis of osteoporosis in men and women of all ethnic groups [44].

## 3. Bone physiology

### 3.1. General

Throughout life bone tissue is continually being formed and removed, a process called bone remodeling [11,33], involving osteoclasts (break down components of bone) and osteoblasts (components stimulating new bone formation) [4,13]. Osteoblasts are under the control of over 15 different factors – cytokines, hormones and growth factors. Osteoclasts are also stimulated or inhibited by most of these factors, as well as by other factors such as vitamin A [19, 45,46]. Regardless of etiology, in all cases of osteoporosis an imbalance exists between bone resorption and formation [33,35,36,38,39,47].

Sex steroid hormones, estrogens and testosterones, play key roles in the development and maintenance of the skeleton in both men and women [4]. Estrogen inhibits osteoclastic bone resorption, plays an important role in determining the life span of bone cells through controlling the rate of apoptosis, and increases the production of growth factors and

procollagen synthesis in osteoblasts, resulting in a major net effect of bone formation and a decrease in resorption [3,7,13,45]. When there is an estrogen deficit, the life span of osteoblasts is thought to be shortened and that of osteoclasts lengthened [22]. Therefore, any process that leads to hypoestrogenism might increase a person's vulnerability to and probability of osteoporosis [13]. Testosterone deficiency, due to its effect on osteoblastic activity, equally has been shown to be associated with profound osteoporosis and with a substantially increased risk of fractures [4,13]. However, as estrogens are also important to the male skeleton, estrogen deficiency is a major cause of bone loss and fracture, not only in women, but also in men.

Other important parameters for bone metabolism are parathyroid hormone (PTH), vitamin D and its metabolites, dehydroepiandrosterone (DHEA), insulin-like growth factors (IGF)-I and IGF-II, transforming growth factor-β 1, 2 and 3, platelet-derived growth factor, acidic and basic fibroblast growth factor (α-FGF and β-FGF), prostaglandins and at least several bone morphogenetic proteins. PTH stimulates bone resorption and inhibits bone formation. Vitamin D, in particular its metabolite 25-hydroxyvitamin D (25-OH-D), has an important impact on bone resorption [45,48,49] (see Table 2).

**INSERT TABLE 2**

### 3.2. Hyperprolactinemia and osteoporosis: putative mechanisms

Two potential mechanisms have been proposed by which HPRL may result in BMD reductions – a direct one (in the absence of hypogonadism), and an indirect one (in the presence of hypogonadism) mediated via the hypothalamic-pituitary-gonadal axis through suppression of gonadal hormone levels [23,24,50,51] (see **Figure 1**). To date, most credence has been attributed to the latter mechanism. Prolonged antipsychotic-induced HPRL may

inhibit the pulsatile release of the gonadotropin-releasing hormone (GnRH) from the hypothalamus and reduce pituitary sensitivity to GnRH, which in turn inhibits release of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. This then causes suppression of ovarian and testicular function and reduced sex steroid production. Low production of gonadal hormones (testosterone and estrogen, identified as hypoandrogenism and hypoestrogenism, respectively) or hypogonadism in both sexes favours abnormal bone metabolism and osteoporosis similar to that associated with postmenopausal osteoporosis, as estrogen and testosterone withdrawal leads to an increase in osteoclast activity not compensated by a concomitant increase in osteoblast activity [11,16,23-25,31,39,45,52,53]. However, suppression of the hypothalamo-pituitary-gonadal axis is not the only possible mechanism as PRL might also have direct effects on bone that are independent of circulating sex steroid hormones [19,24]. There is increasing evidence on the molecular level that PRL receptors exists on human osteoblasts and PRL has been shown to decrease osteoblast cell numbers due to reduced proliferation [54-56], thus providing a direct effect mechanism explaining BMD reduction.





## 4. Risk factors of osteoporosis

The pathogenesis of osteoporosis is multifactorial, including genetic and hormonal mechanisms, lifestyle choices (dietary habits and physical inactivity) and environmental factors (the most important role being reserved for genetic factors). Advancing age (> 50 years), (excessively) low bodyweight, lack of exercise, and use of medicines (especially corticosteroids) are important risk factors for the development of osteoporosis [57-59]. Certain conditions and circumstances (for example, diabetes mellitus), hormonal anomalies, early menopause, insufficient calcium and decreased exposure to sunlight resulting in

vitamine D deficiency also play a role [3,7,11,19,22,33-35,38,60,61]. Table 3 presents an overview of the identified risk factors.

**INSERT TABLE 3**

As in the general population, the aetiology of low bone mass in schizophrenia is multifactorial [14, 19]. Nonetheless, people with schizophrenia have an elevated prevalence of various risk factors that might increase the risk of low BMD. For instance, people with schizophrenia have poor lifestyle factors which greatly influences bone density [14,22]. Typically, these people are very sedentary [62] and engage in very little physical activity [63]. Only 25.7% of these patients meet the minimum U.S. public health recommendation of 150 min a week of at least moderate-intensity physical activity [64,65]. The high prevalence of smoking and alcohol consumption in these patients increases further the risk of osteoporosis [14,18,20,23,66]. It is well known that many patients with schizophrenia smoke. A meta-analysis of worldwide studies demonstrated that patients with schizophrenia, compared with the general population, have a higher prevalence of ever smoking, heavy smoking and high nicotine dependence, as well as of risk factors that make them more vulnerable to start smoking [67]. Smoking is associated with reduced BMD and increased fracture risk at all skeletal sites [47,68]. One meta-analysis found current smoking was associated with a 25% increased risk of any fracture, compared to non-smokers (RR=1.25; 95% CI: 1.15 to 1.36) [69]. Several pathophysiologic mechanisms predispose smokers to bone loss, including direct toxic effects of active as well as passive cigarette smoking on osteoblasts/osteoclasts activity, and indirect actions on sex, calciotropic and adrenocortical hormones, vitamin D, intestinal calcium absorption, and the vascular system and oxygen supply [47, 70-72]. Excessive

alcohol consumption is also common in schizophrenia [11,66]. Alcohol may have a direct, as well as indirect adverse effects on osteoblasts [11,20,73-75]. Polydipsia, which occurs in 6-20% of patients with schizophrenia [14,76,77], can also contribute to bone loss. Excessive calcium loss through the urinary tract is putatively the mechanism that underlies this pathology [14,78]. Malnutrition or inappropriate amounts or composition of food intake is another factor that can lower BMD [11]. Several studies reported profound 25-hydroxyvitamin D deficiency in patients with schizophrenia [46,61,79-81]. Finally, people with schizophrenia are at increased risk of diabetes mellitus, another key risk factor for poor bone health and osteoporosis [82-84].





## 5. Methods

Given the lack of clarity regarding the relationship between antipsychotic-induced HPRL and bone health outcomes, a literature search (1950 until December 2015), using the MEDLINE database, was conducted for reviews, meta-analyses and clinical trials of SGA and FGA. The following key words were used: “antipsychotic”, “neuroleptic”, “clozapine”, “olanzapine”, “quetiapine”, “amisulpride”, “sertindole”, “ziprasidone”, “aripiprazole”, “risperidone”, “paliperidone (extended-release and palmitate)”, “asenapine”, “iloperidone”, “lurasidone”, “schizophrenia”, “prolactin”, “hyperprolactinemia” and “osteoporosis” or “fracture”. The review is based upon studies carried out with non-elderly adults (< 65 years old) having been diagnosed with schizophrenia. We attempted to identify additional studies

through searches of reference lists of identified studies and reviews. This literature review, however, summarized the most recent evidence concerning this topic.

## 6. Osteoporosis, prolactin and antipsychotic medication

### 6.1. General results concerning the relationship between antipsychotic-induced hyperprolactinemia and BMD loss in patients with schizophrenia

The hypothesis that antipsychotic-induced HPRL lowers BMD is derived from observations in patients with usually severe HPRL due to medical reasons, such as PRL-secreting pituitary tumors, which are associated with significant bone loss (osteopenia or osteoporosis) at one or more sites [85-90]. Although somewhat more than half of the studies (13/24 or 54%) in patients with schizophrenia treated with antipsychotic medication found high PRL levels to be associated with low BMD values [25,31,41,42,52,91-98], the other half (11/24 or 46%) [45,46,51, 99-107] do not support the role of HPRL in low BMD in these antipsychotic-treated patients. For an overview and details of the studies that investigated PRL effects of antipsychotic medication on BMD in patients with schizophrenia, we refer the reader to table 4.

**INSERT TABLE 4**

### 6.2. Duration of antipsychotic-induced hyperprolactinemia and BMD loss in patients with schizophrenia

As higher PRL levels over a longer period may be necessary to lead to BMD loss [100], particularly results of the longitudinal studies are relevant. Until now, five longitudinal studies [31,51,92,95,106], examining BMD alterations in relation to PRL-raising antipsychotics,

exist, which sometimes have their own artefacts (e.g., see 51,95). Of these studies, only two [31,92] indicated significant BMD loss in patients using PRL-raising antipsychotics, compared to patients taking PRL-sparing antipsychotics. The largest of these studies [92], investigating the association of PRL with BMD loss in 163 patients with first-episode schizophrenia, has found that the BMD value of patients taking PRL-raising FGA (chlorpromazine, sulpiride and perphenazine) decreased significantly after 12 months of treatment, and that this was negatively correlated with PRL levels, whereas no statistical significant change was found in patients treated with PRL-sparing SGA (clozapine, quetiapine and aripiprazole). However, an important limitation of the study is the lack of clinical assessment of more risk factors for osteoporosis than age, gender and BMI (body mass index). In the study of Meaney & O'Keane [31] women on PRL-raising antipsychotics showed a decrease in lumbar BMD, compared to women taking a PRL-sparing antipsychotic. However, no differences in femoral BMD were found between both antipsychotic groups. The study with the longest duration [95], which followed patients (N=164) up to 5 years, equally indicated a negative impact of PRL-raising antipsychotics on BMD. A significant time versus group interaction was demonstrated, suggesting there was a difference in the time course of BMD between the PRL-raising and PRL-sparing groups. Despite this interaction effect, the BMD of the PRL-raising and PRL-sparing group failed to reach any statistically significant difference at each individual time point. Once again, besides age, gender and BMI, no other risk factors for osteoporosis were assessed. Moreover, as changes of BMD z-scores over time for both groups were less than one below what's normally expected for someone of their age, sex, and ethnic or racial origin, these results do not suggest that something else than aging is causing abnormal bone loss [108,109], although the International Society for Clinical Densitometry does however stress that z-scores above -2 do not preclude the possibility of skeletal fragility [110]. Another one-year study [106] also provided no convincing evidence

for the hypothesis that high PRL levels induced by certain antipsychotic medications reduce BMD. In this study, Abraham et al. [106] found that HPRL accelerated bone metabolism without resulting in BMD loss. Finally, a recent three year follow-up study did not find significant changes in BMD despite the common use of PRL-raising antipsychotics [51].

### 6.3. Gender differences in the relationship between antipsychotic-induced hyperprolactinemia and BMD loss in patients with schizophrenia

Several studies [42,52,91,93,106] have found important gender differences in the prevalence of low BMD. It is repeatedly found that PRL responses to antipsychotic medication are greater in females than in males. This difference can be explained by the ability of estrogens to elevate serum PRL levels and enhance responsiveness to PRL-releasing stimuli. Moreover, estrogens increase the number of lactotrophic cells of the anterior pituitary and act on the hypothalamus to decrease dopamine content [27]. However, despite the higher prevalence and severity of HPRL in women and contrary to the general trend in which women are at a higher risk of osteoporosis, compared to men [111], certain studies on the relationship of PRL levels and BMD reveal that HPRL with associated hypogonadism may have a more profound impact on BMD in male, compared to female, patients [42,52,112]. Interestingly, research has shown that the combination of both low sex steroid hormone with low 25-OH-D (an important risk factor in patients with schizophrenia) is associated with a 4-fold risk of a major osteoporotic fracture in older men [113]. In women protecting factors (such as estrogen) that inhibit bone resorption and enhances bone formation may be not or much less affected despite higher levels of HPRL. A direct effect of PRL on bone formation markers may be more applicable in female patients with schizophrenia, although this pathway to low BMD is important in male patients as well (see also Figure 1) [52].

## 7. Osteoporotic fracture, prolactin and antipsychotic medication

Although the diagnosis of osteoporosis relies on the quantitative assessment of BMD, the clinical significance of osteoporosis lies in the fractures that arise. Fractures are an important public health issue that leads to substantial morbidity and mortality and consequently reduces quality of life and increases health care costs [114]. It is well known that the relative risk of a fracture is at least quadrupled in individuals with DXA-verified osteoporosis, compared to those with normal BMD [115]. BMD of the hip is a stronger predictor of future fracture risk than spine BMD [35].

Studies examining the association between osteoporotic fractures and the use of antipsychotic medication in patients with schizophrenia are limited (3 of the 20 identified studies included patients with schizophrenia, of which only 2 considered non-elderly patients). A recent 10-year population-based case-control study [114] in patients with schizophrenia (N=3,433) did not find a positive association between the current use of the PRL-elevating SGA compounds risperidone (adjOR=1.15, 95%CI: 0.87 to 1.51), amisulpride (adjOR=1.06, 95%CI: 0.56 to 1.99) or sulpiride (adjOR=1.30, 95%CI: 0.95 to 1.79) and the occurrence of hip fracture. Another nationwide study in patients with schizophrenia (N=15,431) showed that both PRL-increasing (Incidence Rate Ratio, IRR=1.12; 95%CI: 1.04 to 1.21) and non-PRL-increasing (IRR=1.15; 95%CI: 1.05 to 1.25) antipsychotics contributed to the demonstrated relationship of hip fracture and lifetime antipsychotics consumption. Exposure to the PRL-elevating compound risperidone, however, was found not to be related to the risk of hip fracture in patients with schizophrenia (adjIRR=1.06, 95%CI: 0.66 to 1.72) [117].

## 8. Conclusion

Although it has been suggested that raised PRL levels provoked by antipsychotic medication in patients with schizophrenia can lead to an increased risk of osteoporosis/osteoporotic fracture, to date, clinical data implicating antipsychotic-induced HPRL as a possible risk factor for bone loss are limited and inconsistent and preclude a definitive connection between HPRL, antipsychotics and osteoporosis. Thus, on the basis of available studies, one is forced to conclude that the results do not provide sufficient evidence for the claim that antipsychotic-induced raised PRL levels, in the absence of hypogonadism, constitute an independent risk factor for the development of osteoporosis in patients with schizophrenia. Possibly this lack of evidence concerning the possibility of a relationship between PRL-raising antipsychotics and bone loss explains why the World Federation of Societies of Biological Psychiatry (WFSBP) states that although osteoporosis should be considered as an important long-term consequence of HPRL [118], the association between antipsychotic-induced PRL elevation and osteoporosis remain to be established [119]. Moreover, the possible involvement of antipsychotic-induced HPRL in BMD loss in patients with schizophrenia probably is only one amid others, which probably are more important contributors to the multi-factorial processes accounting for the variance in BMD. According to a recent symposium on osteoporosis, the main ways to prevent osteoporotic fractures have not changed in nearly 25 years: stop smoking, be active and eat well [115], all known to be highly problematic in patients with schizophrenia [62,120].

## 9. Expert opinion

Most studies investigating antipsychotic-induced PRL effects on BMD in patients with schizophrenia used a cross-sectional design. This is an important remark as, naturally, cross-sectional analyses cannot identify causal relationships. Besides this, many of these studies suffer from other methodological shortcomings, such as the presence of confounding factors (e.g., low physical activity, high rate of smoking) and the absence of control groups, which equally may contribute to the inconsistent pattern of results. Therefore, more well designed, prospective studies are urgently needed.

For accurate assessments of the time period needed for osteopenia or osteoporosis to develop due to the use of antipsychotic medication, bone turnover markers may be more useful in evaluating this risk than BMD itself. In humans, bone is continuously replaced through remodeling, resulting from the coupled actions of osteoblasts and osteoclasts. In healthy adults, the rates of bone formation and resorption are equal, and therefore, net bone mineral balance is near zero. The ability to rapidly detect changes or disruptions in this balance would be of great value in the evaluation of the effects of antipsychotic medication on BMD. Many studies, examining the relationship between antipsychotic-induced HPRL and BMD loss in patients with schizophrenia, assessed the risk of BMD loss by using radiologic examination (in most cases a DXA scan). These measurements are hampered by the need to wait months to years for altered bone mineral balance to produce changes in BMD large enough to be resolved by radiologic examination such as DXA [121]. Bone turnover markers, that show physiological fluctuations over a time period of weeks to months, therefore are conceivably better indicators of osteoporosis than BMD, particularly for psychiatric patients with numerous confounding factors in addition to antipsychotic treatment [16].

Many widely used medications have now been shown to have harmful effects on bone homeostasis (see Table 3), possibly leading to decreases in BMD and increases in fractures. The most common form of medication-induced osteoporosis in humans is glucocorticoid-

induced osteoporosis [122-124]. As in the case with schizophrenia, a key point is that the underlying inflammatory disease, one of the diseases for which glucocorticoids are used, also has a role in bone fragility. Despite this, evidence shows that the effect of glucocorticoids on the bone is a direct one, independent of the inflammation effect [125]. The predominant effect of glucocorticoids on bone is the impairment in bone formation, although bone resorption is also rapidly increased. The increase in fracture risk is immediate, as early as 3 months after the initiation of therapy, and reverses sharply after discontinuation of glucocorticoids [123,126,127]. It is a fact that antipsychotic-induced pathological elevations of PRL and associated dysfunction of the hypothalamo-pituitary-gonadal axis results in diminished concentrations of oestrogen and testosterone or hypogonadism and that PRL has been shown to directly decrease osteoblast cell numbers. It is by these mechanisms that antipsychotics affect bone metabolism. However, more, particularly *in vivo*, studies are needed to determine the extent to which PRL exerts its effect on osteoblast and osteoclast activity. At the moment, it is difficult to make definitive conclusions on the degree and time period a given antipsychotic may have an effect on the bone itself, as studies are mainly cross-sectional, and therefore open to inherent selection biases and other confounders, and most of the these studies use radiologic examinations. Therefore, more well conducted prospective trials of bone mineral markers are necessary to establish the precise relationship between antipsychotics, PRL levels and osteoporosis.

Until now, available data suggest that although sustained HPRL has been found to have an impact on the rate of bone metabolism (that bone turnover is accelerated), the use of PRL-induced antipsychotics over longer time periods seems not induce profound changes in BMD (probably because PRL-levels are not as high as in cases of HPRL due to medical reasons, such as PRL-secreting pituitary tumors). However, the effects of antipsychotic-induced HPRL

on bone metabolism may be more powerful in men than women. Hypogonadism is a well-established risk factor for the development of osteoporosis and increased fracture risk and available data seem to indicate that HPRL and associated hypogonadism may be a risk factor, leading to BMD loss, particularly in men [52]. This is reflected in the US label for risperidone and paliperidone, which both state that long-standing HPRL when associated with hypogonadism may lead to decreased BMD in both female and male subjects [128,129]. The possible impact of antipsychotic medication on bone metabolism would be most concerning in children and adolescents. The use of antipsychotic medication in this population is widespread and many pediatric psychiatric conditions often require long-term treatment. Antipsychotics may prevent children and adolescents from optimizing their peak bone mass and this suboptimal bone accrual during development may lead to increased fracture risk later in life [48]. However, little research has been conducted to directly explore skeletal health in children and adolescents receiving antipsychotic medication.

Prospective studies designed to discriminate between etiological mechanisms and secondary effects of disease and treatment have not been conducted [51]. This is important as decreased BMD and osteoporosis are multifactorial processes, including not only treatment, but also genetic and disease-related factors. Although schizophrenia is, compared to the general population, associated with reduced BMD, the relative contributions of these other factors remain unclear. Moreover, considering treatment-related factors, antipsychotic medication may affect bone health independently of their effect on PRL, with or without hypogonadism. These include the modulation of serotoninergic and adrenergic signaling, sympathetic nervous system activity, and perhaps muscular function as well [48]. Antipsychotic drugs may in the short term, and possibly through histaminergic (sedation, somnolence, dizziness), α-1 noradrenergic (orthostatic hypotension), producing psychomotor

impairment, or dopaminergic (extrapyramidal side effects that may reduce gait stability) antagonistic effects increase potentially the risk of falls and osteoporotic fractures [130].

## Declaration of interests

M De Hert declares that he has been a consultant for, received grant and/or research support and honoraria from, and has been on the speakers' bureaus and/or advisory boards of the following companies: Janssen-Cilag, Lundbeck and Takeda. J Detraux declares that his work for the Belgian Discussion Board on Antipsychotic Treatment, established by Janssen and consisting of Belgian psychiatrists discussing relevant topics on antipsychotic treatment, has been partially supported by the Janssen Academy. No sources of funding were used to prepare the review. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

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## Article highlights

- A low to moderate increased risk of osteoporosis and osteoporotic fractures compared with the general population is reported in patients with schizophrenia treated with antipsychotic medication. However, the question that antipsychotic medications are a *causal factor* in falls and fractures remains to be elucidated.
- Although antipsychotic-induced hyperprolactinemia has been suggested as one of the mechanisms of low bone mineral density in schizophrenia, results are mixed and firm

conclusions cannot be drawn at this point, due to a inconsistent pattern of results and methodological shortcomings.

- More well designed, prospective studies, particularly of bone turnover markers, are needed, in order to better examine the relationship between antipsychotics, osteoporosis and osteoporotic fractures.
- Unhealthy lifestyle behaviors, such as little or no exercise, alcoholism, smoking, undernutrition, and unhealthy diet with deficiencies of calcium and vitamin D, neurochemical and functional abnormalities due to the disease probably contribute more to low bone mineral density and elevated fracture risk in schizophrenia.

Figure 1Hypothetic med1aniS1ns whereby antipsychotic (AP)-induced HPRL may lead to osteoporosis.

GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone;FSH: follicle-stirrrulating hormone.

Figure 1: Hypothetic mechanisms whereby antipsychotic (AP)-induced HPRL may lead to osteoporosis.

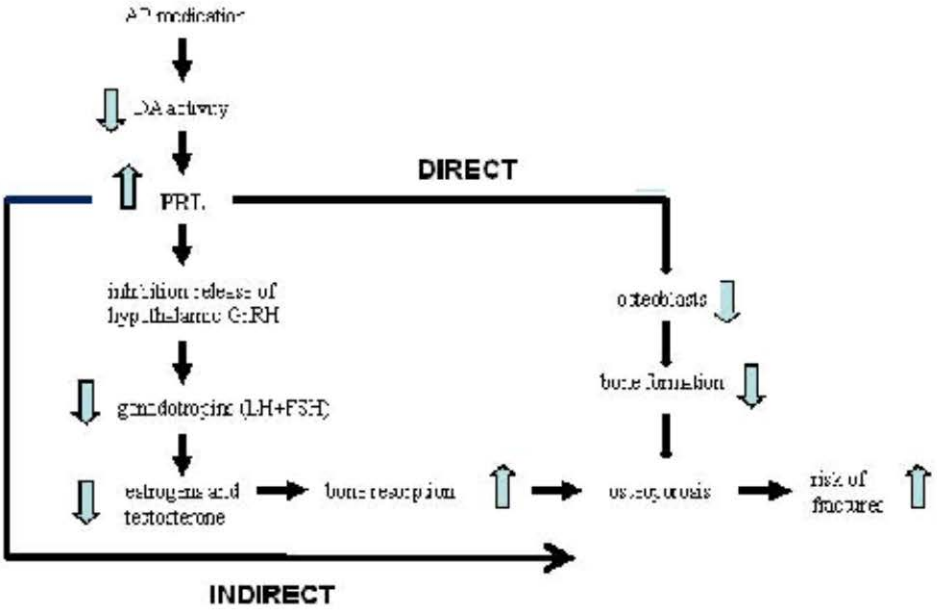

**Table 1 : Criteria for osteoporosis in women, based on measurements by DXA**

**[33,35,36,38,39]**

| | |
|---|---|
| **Normal** | A value of BMD within 1 SD of the young adult reference mean (t-score ≥ -1) |
| **Osteopenia** | A value of BMD more than 1 SD below the young adult mean, but less than 2,5 SD below the value (t-score < -1 and > -2,5) |
| **Osteoporosis** | A value of BMD 2,5 SD or more below the young adult mean (t-score ≤ -2,5) |
| **Severe or established osteoporosis** | A value of BMD 2,5 SD or more below the young adult mean in the presence of one or more fragility fractures |

BMD = bone mineral density; SD = standard deviation

**Table 2 : Factors affecting bone physiology [49]**

**Bone formation markers**

- serum and urinary osteocalcin (s-OC, u-OC)
- serum alkaline phosphatase (s-ALP)
- serum bone-specific alkaline phosphatase (s-BALP)
- procollagen type I C propeptide (s-PICP)
- procollagen type I N propeptide (s-PINP)

**Bone resorption markers**

- urinary and serum amino-terminal cross-linking telopeptide of type I collagen (u-NTX, s-NTX)
- urinary and serum carboxy-terminal cross-linking telopeptide of type I collagen (u-CTX, s-CTX)
- carboxy-terminal cross-linking telopeptide of type I collagen (s-ICTP or CTX-MMP)
- urinary deoxypyridinoline (u-DPD)
- urinary pyridinoline (u-PYD)
- serum tartrate-resistant acid phosphatase (s-TRACP)

**Table 3: Risk Factors for Osteoporosis [3,7,11,19,22,33-35,38,60,61]**

**Genetic Factors:**
- Age (> 50 years)
- Gender (women > men)
- Race/ethnicity (Caucasian or Asiatic)
- Early menopause (last menstruation at 45 years or younger)
- Menopause
- Family history of osteoporosis (osteoporotic bone fracture in the family, broken hip or collapsed vertebrae)

**Physical factors:**
- Slight body build
- Low body weight / body mass index (BMI)

**Lifestyle:**
- Smoking
- Excessive use of alcohol (> 2 drinks per day)
- Excessive consumption of caffeine
- Sedentary life (no or little exercise)
- Vitamin D deficiency
- Calcium deficiency
- Marked consumption of salt

**Miscellaneous:**
- Anorexia nervosa or boulimia
- Chronic neurological disease (e.g., Parkinson disease, multiple sclerosis)
- Hematologic/oncologic diseases (e.g., multiple myeloma, systemic mastocytosis)
- Infectious disease (Human Immunodeficiency Virus, HIV)
- Pulmonary disease (Chronic Obstructive Lung Disease, COPD)
- Hyperphosphatasemia
- Cadmium poisoning
- Ovarectomy
- Deficient sex hormone levels in men or women (e.g., congenital anomalies, impotence, long period without menstruation)

**Endocrine conditions:**
- Hyperthyroidism
- Hyperparathyroidism
- Hypercortisolism
- Diabetes mellitus
- Hypogonadism
- Growth hormone deficiency
- Acromegaly

**Gastrointestinal conditions:**
- Inflammatory bowel disease
- Intestinal malabsorption conditions
- Bariatric surgery
- Celiac disease

**Bone marrow diseases:**
- Leukemia
- Lymphoma
- Systemic mastocytosis
- Anemia
- Plasma cell dyscrasia

**Connective tissue diseases:**
- Osteogenesis imperfecta

Ehlers-Danlos
Marfan's syndrome

**Rhematologic & inflammatory diseases:**

Systemic lupus erythematosus
Rheumatoid arthritis
Ankylosing spondylitis

**Medication:**

Prolonged use of corticosteroids (prednisone and prednisone-like substances)
Long-term glucocorticoid therapy
Certain immunosuppressant (calmodulin/calcineurine phosphatase inhibitors)
High-dose heparin
Aromatase inhibitors
Thiazolidinediones
Benzodiazepines
Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs)
Antiepileptic drugs
Anticoagulants
Antihypertensives
Thyroid hormones
Methrotrexate
Depot medroxyprogesterone acetate (DMPA)
Acid-suppressive medications
Gonadotrophin-releasing (Gn-RH) analogs
Proton pump inhibitors

**Table 4: Studies investigating prolactin effects on bone mineral loss in patients with schizophrenia [25,31,41,42,45,46,51,52,91-107]**

| Reference | Population and treatment data | BMD-PRL measurement and bone structure measured | PRL-BMD results | Conclusion |
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| [51]<br><br>van der Leeuw et al. (2015)<br><br>*Follow-up study of van der Leeuw et al. (2013)* | 30 patients with a psychotic disorder (mean age at scan: 32) using PRL-raising AP (FGA, RIS, AMI, PALI) or PRL-sparing SGA (all but RIS, PALI or AMI)<br><br>44 non-psychotic siblings of patients with a psychotic disorder (mean age at scan: 32.3)<br><br>27 healthy controls (mean age at scan: 35.2) | DXA (lumbar spine L2-L4 and proximal left femur)<br><br>BMD expressed in g/cm$^2$, t-scores and z-scores<br><br>Osteopenia = t-score between -1 SD and -2.5 SD<br><br>Osteoporosis = t-score < -2.5 SD<br><br>Several other potential risk factors, such as physical activity and sunlight exposure, for osteoporosis were assessed | PRL results<br><br>PRL levels were not assessed<br><br>BMD results<br><br>Measures were not significantly different in patients who used a PRL-raising AP compared to those who used a PRL-sparing AP or were AP-free (both at the time of DXA acquisition and during the entire three follow-up period). Cumulative three year or lifetime exposure to PRL-raising AP neither had a main effect on BMD change | Current or past use of PRL-raising AP was not associated with BMD changes |
| [91]<br><br>Lin et al. (2015) | 80 men (mean age: 43.3) and 115 women (mean age: 42.4) with chronic schizophrenia<br><br>PRL-raising AP (n=56) (FGA, RIS, PALI, AMI, ZIPRA)<br><br>PRL-raising + PRL-sparing AP (n=38)<br><br>PRL-sparing AP (n=101) (CLZ, OLZ, QUE, ARIPI) | DXA (lumbar spine L2-L4)<br><br>Low BMD (including osteopenia and osteoporosis) = t-score < -1 SD<br><br>Bone mineral loss with causes other than ageing = z-score < -1 SD<br><br>HPRL (>17 ng/ml in men and >25 ng/ml in women)<br><br>Some other potential risk factors, such as physical activity, for osteoporosis were assessed. It was not easy to control diet and exercise rigorously | PRL results<br><br>PRL-raising AP (72.5 ± 61.6 ng/ml) > PRL-raising + PRL-sparing AP (47.8 ± 57.4 ng/ml) > PRL-sparing AP (17.9 ± 18 ng/ml) ($p<0.001$)<br><br>BMD results<br><br>HPRL was associated with DXA t-score in men ($p=0.009$) but not women | HPRL associated with DXA t-score in men but not women. In men, the BMD in the PRL-sparing AP subgroup was higher than that in the PRL-raising AP subgroup ($p=0.073$). |
| [92] | 163 male and female patients with first-episode schizophrenia | DXA (postero-anterior spine | PRL results | PRL levels negatively correlated with BMD value in PRL-raising FGA group. |

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| Wang et al. (2014) | PRL-raising FGA (n=81) (CPZ, n=26, PERPH, n=27, SULP, n=28) (mean age: 35.9)<br><br>PRL-sparing SGA (n=82) (CLZ, n=26, QUE, n=28, ARIPI, n=28) (mean age: 33.1)<br><br>90 healthy controls (mean age: 34.2) | L1-L4)<br><br>Osteoporosis = t-score < -2.5 SD<br><br>Lack of clinical assessment of more potential risk factors for osteoporosis than age, gender and BMI | PRL-raising FGA (before treatment 31.73 ± 22.18 ng/ml, after treatment 53.05 ± 30.25 ng/ml) > PRL-sparing SGA (before treatment 29.79 ± 16.03 ng/ml, after treatment 32.81 ± 17.42 ng/ml)<br><br>BMD results<br><br>BMD value of the PRL-raising FGA group was statistically significantly ($p<0.05$) lower than that of the control group at 12 months after treatment, whereas there was no difference between the PRL-sparing SGA group and the control group. | No significant correlation between PRL and BMD in PRL-sparing SGA group |
| [95]<br><br>Takahashi et al. (2013) | 164 male and female patients with schizophrenia (mean age at scan: 58.5) using PRL-raising FGA, RIS or blonanserine (n=141) or PRL-sparing ARIPI, OLZ, QUE or perospirone (n=23) | DXA (at the distal one-third portion of the radius of the arm contralateral to the dominant arm of the subject)<br><br>BMD expressed in t-scores and z-scores<br><br>Osteoporosis = t-score < -2.5 SD<br><br>No other potential risk factors for osteoporosis were assessed | PRL results<br><br>PRL levels were scarcely measured, precluding inclusion of this value in the analyses. Therefore, the authors could not examine whether there was a relationship between the degree of HPRL and the extent of BMD reduction.<br><br>BMD results<br><br>During a mean follow-up period of 3.4±1.6 years, there was a difference in the time course on BMD between the PRL-raising and PRL-sparing groups, indicated by a significant time versus group interaction ($p=0.011$). However, the BMD z-scores at each time point were not significantly different between the two groups. | Although a significant antipsychotic-class versus time interaction was found ($p=0.011$), indicating a negative impact of PRL-raising AP on BMD, the BMD difference did not reach statistical significance between the PRL-raising and PRL-sparing group at each individual time point over the mean follow-up period of 3.4±1.6 years |
| [99]<br><br>van der Leeuw et al. (2013) | 62 patients with a psychotic disorder (mean age at scan: 27.4) using PRL-raising AP (FGA, RIS, AMI) or PRL-sparing SGA (all but RIS or AMI)<br><br>67 non-psychotic siblings of patients with a psychotic disorder (mean age at scan: 28.2)<br><br>48 healthy controls (mean age at scan: 31.2) | DXA (lumbar spine L2-L4 and proximal left femur)<br><br>BMD expressed in g/cm$^2$, t-scores and z-scores<br><br>Osteopenia = t-score between -1 SD and -2.5 SD<br><br>Osteoporosis = t-score < -2.5 SD<br><br>Several other potential risk | PRL results<br><br>PRL levels were not assessed<br><br>BMD results<br><br>In women, but not in men, the current use of PRL-raising AP was negatively associated with BMD measures of the lumbar spine, but not the femur, when compared to AP-free patients. However, these results were not upheld after correction. | After correction PRL levels were not associated with bone mass for either gender |

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| | | factors, such as physical activity and sunlight exposure, for osteoporosis were assessed | | |
| [52]<br><br>Kinon et al. (2013) | 402 male (mean age: 40.8) and female (mean age: 44.5) patients with schizophrenia using PRL-raising FGA (n=275) or RIS (n=126) for at least 3 months prior to study entry (average duration of treatment with all drugs was ≥8 years) | QUS (calcaneus)<br><br>BMD expressed in g/cm$^2$ and t-scores<br><br>Osteopenia = t-score between -1 SD and -2.5 SD<br><br>Osteoporosis = t-score < -2.5 SD<br><br>HPRL (>18.8 ng/ml in men and >24.2 ng/ml in women) | PRL results<br><br>43% of male patients (n=248) had HPRL (mean 20.2±14.6 ng/ml). 61% of female patients (n=142) had HPRL (mean 44.1±36.0 ng/ml).<br><br>BMD results<br><br>31% of male and 23% of female patients with HPRL had low BMD. Negative correlation between t-score and PRL levels was found in male patients after controlling for age (p=0.05), but not in female patients. | An association between BMD and PRL increase was observed in male patients only. |
| [96]<br><br>Lin et al. (2012) | 48 women with chronic schizophrenia (mean age: 41.8)<br><br>CLZ (n=24) versus PRL-raising AP (n=24) [CPZ n=3, FLU n=2, HAL n=5, RIS n=8, PALI n=1, SULP n=5] | DXA (lumbar spine L2-L4)<br><br>Low BMD (including osteopenia and osteoporosis) = t-score < -1 SD<br><br>Bone mineral loss with causes other than ageing = z-score < -1 SD<br><br>HPRL (>25 ng/ml)<br><br>Some other potential risk factors, such as physical activity, for osteoporosis were assessed. It was not easy to control diet and exercise rigorously | PRL results<br><br>PRL-raising AP (109.01 ± 65.63 ng/ml) > CLZ (19.17 ± 9.96 ng/ml) (p<0.001)<br>HPRL: PRL-raising (95.8%) > CLZ (20.8%)<br><br>BMD results<br><br>Rate of patients with t-score < -1: PRL-raising group (45.8% ) > CLZ (16.7%)<br>Rate of patients with z-score < -1: PRL-raising group (33.3% ) > CLZ (0%)<br><br>OR of low BMD in the PRL-raising AP medication group, compared to the PRL-sparing (CLZ) group, was 28.2 (95% CI: 2.37-336.10, p=0.008).<br><br>However, neither PRL level, nor HPRL was significantly associated with BMD in either treatment group or in the studied subjects as a whole | Use of PRL-raising AP was related to low BMD, compared with PRL-sparing AP. However, neither PRL level, nor HPRL was significantly associated with BMD in either treatment group or in the studied subjects as a whole. This finding does not support the role of HPRL/hypogonadism in low bone density in women receiving AP. |
| [100]<br><br>Sugawara et al. | 114 patients with schizophrenia or schizoaffective disorder (49 men and 65 women) (mean age: | QUS (calcaneus)<br><br>OSI as indicator of BMI | PRL-levels<br><br>male mean: 27.8 ± 25.4 ng/ml<br>female mean: 51.4 ± 45.2 ng/ml | PRL levels were not associated with bone mass for either gender and therefore suggest that PRL levels do not contribute to poor bone mass. |

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| (2011) | 42.6)<br><br>AP combination therapy (n=46) and AP monotherapy (n=68) [PRL-sparing AP OLZ, QUE and ARIPI, n=19] | | BMD results<br><br>Neither PRL nor duration of AP treatment was associated with OSI for either gender | |
| [101]<br><br>Lee et al. (2010) | 45 male patients with schizophrenia (mean age: 49.5)<br><br>Monotherapy with RIS (n=20), OLZ (n=15) and CLZ (n=10) for at least one year | DXA (lumbar spine L2-L4, femoral neck, trochanteric and intertrochanteric regions of left hip)<br><br>BMD t-score and z-score | PRL-levels<br><br>RIS (33.3 ± 17.1 ng/ml) > OLZ (21.8 ± 17.6 ng/ml) > CLZ (10.5 ± 9.4 ng/ml). PRL concentration RIS versus CLZ group ($p<0.05$). HPRL: RIS (15/20) > OLZ (6/15) > CLZ (1/10).<br><br>BMD results<br><br>BMD z-score: RIS=OLZ=CLZ<br>Osteoporosis: RIS (3/20),<br>Osteopenia: RIS (3/20), OLZ (7/15), CLZ (1/10)<br>No significant difference between all drugs concerning osteopenia or osteoporosis. No significant difference between HPRL and BMD over all subject groups | No significant correlation was found between HPRL and BMD in patients with HPRL over all subject groups |
| [102]<br><br>Renn et al. (2010) | 93 patients with chronic schizophrenia and severely poor adjusted BUA levels [mean age: 46.3 (male, n=48), 48.72 (female, n=45)]<br><br>Patients received their current SGA, FGA or combination for at least 1 year.<br><br>93 age and gender matched patients with normal adjusted BUA levels | QUS-II (heel)<br><br>Reduced bone mass= t-score ≤ -2.5 computed from BUA data of QUS | PRL-levels<br><br>Male: normal (39.70 ± 4.69 ng/ml) > reduced BUA levels (26.91 ± 3.29 ng/ml)<br>Female: reduced BUA levels (62.83 ± 8.62 ng/ml) > normal (55.60 ± 8.01 ng/ml)<br><br>BMD results<br><br>No significant association between BUA levels or type of AP medication (FGA, SGA or combination) and serum PRL | No significant correlation was found between reduced BUA levels and serum PRL |
| [98]<br><br>Rey-Sánchez et al. (2009) | 73 male (mean age: 61.9) and postmenopausal female (mean age: 59.8) patients with chronic schizophrenia | Ultrasound device model measuring the Ad-SoS in the phalanges of the non-dominant hand<br><br>BMD t-score and z-score | PRL-levels<br><br>Female: 19.65 ± 14.98 ng/ml (67.9% of patients PRL values > 9 ng/ml)<br>Male: 7.27± 5.88 ng/ml (30.6% of patients PRL values > 9 ng/ml) | Significant negative correlation between bone mass and PRL levels were observed in female, but not male, patients treated with FGA |

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| | 73 healthy matched controls<br><br>FGA or SGA, but most of the patients showed combined therapies with two or more drugs | | BMD results<br><br>In the group of patients taking FGA a significant negative correlation was found between Ad-SoS and PRL levels (p=0.0005) | |
| [25]<br><br>Kishimoto et al. (2008) | 74 male patients with schizophrenia (mean age: 58.9)<br><br>AP combination therapy (n=48), AP monotherapy (n=26) (of these 19 were receiving SGA monotherapy).<br><br>PRL-sparing AP = OLZ, QUE, ARIPI and perospirone<br><br>PRL-raising AP = FGA and RIS<br><br>Normal PRL group (≤ 12.78 ng/ml) compared with high PRL (> 12.78 ng/ml) to analyse PRL effects on BMD | DXA (radius)<br><br>BMD t-score and z-score | PRL-levels<br><br>PRL-raising AP group (n=64, 30.7 ± 13.47 ng/ml) > PRL-normal AP group (n=10, 8.71 ± 2.89 ng/ml) (p<0.01)<br><br>BMD results<br><br>PRL-raising group generally had lower z-scores, although the difference compared with the PRL normal group was not statistically significant | PRL levels were found to have no significant correlation with z-scores. Among the subjects with high PRL levels, there was a significant negative correlation between the duration of treatment and z-score (p<0.05), whereas there was no correlation between the duration of treatment and z-score in the normal PRL group. |
| [45]<br><br>Bergemann et al. (2008) | 72 premenopausal women with schizophrenia (mean age: 33.8)<br><br>Most patients treated with FGA, some with SGA<br><br>71 age- and sex-matched healthy controls | DXA (lumbar spine L1-L4 and femoral neck) (n= 59)<br><br>BMD absolute values ($g/cm^2$) and t-scores | PRL-levels<br><br>1628 mU/ml ± 1212 mU/ml (total patient group)<br><br>BMD results<br><br>BMD within the normal range [BMD mean t-score -0.22 (1 SD) for femoral neck, -0.11 (1.5 SD) for lumbar spine] | No significant correlation was found between PRL levels and BMD measurements |
| [31]<br><br>Meaney & O'Keane (2007) | 38 premenopausal women with schizophrenia<br><br>Treatment with exclusively either PRL-raising (RIS and FGA) (n=25), or PRL-sparing AP (OLZ) (n=13) | DXA (lumbar spine L1-L4 and 3 areas of left hip)<br><br>BMD t-scores and z-scores<br><br>Efficacy of interventions, such as exercise, nutritional supplements, and HRT), to | PRL-levels<br><br>Follow-up without active intervention: PRL-raising group (1545.4 ± 580.3 IU/l) > PRL-sparing group (399.9 ± 178.5 IU/l)<br><br>Follow-up after active intervention: PRL-raising group (1696.9 ± 1250.2 IU/l) > PRL-sparing group | There was an overall gain in lumbar BMD values in the PRL-sparing subgroup, compared to an overall loss in the PRL-raising subgroup (p=0.02), for the groups that received no specific interventions to improve BMD. No correlation between baseline PRL and rate of change of lumbar and hip BMD over 1 year was found. |

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| | | ameliorate BMD was examined | (333 ± 169.8 IU/l)<br><br>BMD results<br><br>Women in the PRL-raising non-intervention group had a mean reduction in summary lumbar spine BMD values compared to those in the PRL-sparing non-intervention group who had a mean increase (p= 0.017) . However, correlational analysis did not reveal a relationship between baseline PRL and changes in lumbar or hip BMD over 1 year. | |
| [103]<br><br>Jung et al. (2006) | 51 male (n=30) and female (n=21) patients with schizophrenia (mean age: 39.0)<br><br>HAL monotherapy for at least 2 years | DXA (lumbar spine L1-L4, femoral neck, trochanteric and intertrochanteric regions of the proximal right femur)<br><br>BMD loss = t-score < -1<br><br>HPRL (> 20 ng/ml for men, > 24 ng/ml for women) | PRL-levels<br><br>HPRL was evident in 90.5% (19/21) of female patients, while in 40% (12/30) of male patients.<br><br>BMD results<br><br>94.4% (17/18) of the female patients with BMD loss had HPRL of whom 7 showed combined hypoestrogenemia. PRL levels were significantly higher in female patients with BMD loss (low t) as compared to those with normal BMD (normal t) (72.5 ± 49.7 ng/ml versus 42.1 ± 31.2 ng/ml) (p=0.043). Male patients with BMD loss showed no significant differences in PRL levels compared to those patients with normal BMD | PRL levels were not correlated with actual bone density (g/cm$^2$) and t-scores at any of the sites |
| [107]<br><br>Wyszogrodzka-Kucharska & Rabe-Jabłońska (2005) | 60 patients with schizophrenia. Females were all premenopausal.<br><br>Treatment medication: RIS (n=26) or OLZ (n=34). Control group of healthy, non-medicated volunteers | DXA | BMD result<br><br>BMD was decreased in 37.7% of the patients (28.3% osteopenia, 9.4% osteoporosis) receiving antipsychotics and in 15.8% of the controls (13.2% osteopenia, 2.6% osteoporosis). There was no significant statistical difference between BMD in patients treated with RIS or OLZ | No difference in BMD between PRL-raising and PRL-sparing AP |
| [41]<br><br>O'Keane & Meaney (2005) | 38 premenopausal women with schizophrenia (mean age: 31.8)<br><br>Treatment with exclusively either PRL-raising FGA and SGA (n=26), or OLZ (n=12). Mean | DXA (lumbar spine L1-L4, femoral neck, trochanteric, and intertrochanteric regions of the left hip) | PRL-levels<br><br>PRL-raising > OLZ (1692 ± 1109.4 vs. 446.4 mIU/L ± 333.1, p<0.001)<br><br>BMD results | PRL values were predictive of reduced lumbar BMD values only (p = 0.003). No differences in femoral BMD were found between the AP groups. |

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| | treatment duration in years: 8.4 (PRL-raising group) and 6.3 (OLZ group). | BMD z-scores<br><br>Osteoporosis (BMD ≤ 2,5 SD below standardized values<br><br>Osteopenia (BMD < 1 SD below standardized values | Significant higher rates of low BMD values (osteoporosis and osteopenia combined) in the PRL-raising group (65%), compared with the OLZ group (17%). HPRL associated with low BMD values: 95% of women with either osteopenia or osteoporosis had HPRL, whereas only 11% of the group with normal PRL levels had abnormal BMD. | |
| [104]<br><br>Howes et al. (2005) | 102 patients taking AP (mean age: 46)<br><br>Treatment with 14 different AP medication (SGA and FGA) (median treatment duration: 3 years). | DXA (lumbar spine and hip)<br><br>BMD z-scores | PRL-levels<br><br>PRL-raising (802 mIU/L ± 1092) > PRL-sparing medications (565 mIU/L ± 688)<br><br>BMD results<br><br>No significant difference in BMD between patients taking PRL-raising or PRL-sparing AP. Mean BMD not significantly reduced. Only black males showed reduced spinal BMD (mean z-score: -0,88, p=0.00001). | PRL levels were not correlated with BMD |
| [46]<br><br>Hummer et al. (2005) | 75 men (mean age: 33.6) and women (mean age: 38.3) with schizophrenia<br><br>Treatment with PRL-raising SGA and FGA (e.g. HAL and RIS) and PRL-sparing SGA (e.g., CLZ, QUE) for at least 1 year | DXA (lumbar spine, L1-L4 and proximal right femur)<br><br>BMD z-score | PRL-levels<br><br>44,4% of women and 22,9% of men had higher than normal levels of PRL<br><br>BMD results<br><br>Exposure time (< 6 months versus ≥ 6 months) to PRL-increasing SGA and FGA was not related to BMD. | Exposure to PRL-increasing AP was not related to BMD |
| [42]<br><br>Meaney et al. (2004) | 55 male (mean age: 43.5) and post-menopausal women with schizophrenia (mean age: 59)<br><br>Treatment with 9 different PRL-raising medication (OLZ, RIS | DXA (lumbar, L1-L4, femoral neck and trochanteric, and intertrochanteric regions of left hip.<br><br>BMD t-scores and z-scores | PRL-levels<br><br>HPRL overall group: 62%. High-dose group (> 300 mg CPZ equivalents) (81%) > low-dose group (45%) (p<0.01) | No statistical relationship between PRL and BMD values |

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| | and FGA) for >10 years (mean treatment duration in years: 16 (men) and 21 (women). | (only z-scores were reported in this study) | BMD results<br><br>Overall, 17% of men and 32% of women had reduced BMD on at least one bone measure.<br><br>Bone loss in the high-dose group (62%) > low-dose group (27%) (p=0.01). High-dose group significantly more severely reduced BMD scores (< 2 SD below normative data) than low-dose group: 35% versus 11.5% (p=0.03). | |
| [93]<br><br>Liu-Seifert et al. (2004) | 402 patients with schizophrenia<br><br>Treatment with PRL-elevating FGA or RIS for a minimum of 3 months prior to study entry | QUS (calcaneus)<br><br>Low BMD= t-score ≤ -1 | BMD results<br><br>Frequency low BMD: females (23.2%, n = 142), males (31%, n = 248) | Elevated PRL-levels significantly associated with low t-scores in males (p=0.05), but not females |
| [105]<br><br>Becker et al. (2003) | 26 premenopausal female patients with schizophrenia (mean age: 38)<br><br>Treatment with RIS (n=12) or OLZ (n=14) for at least 2 years. Mean treatment duration in months: OLZ (35.9 ± 8.2) and RIS (30 ± 6.3)<br><br>HPRL: PRL>25 ng/ml | DXA (lumbar spine and proximal hip) and QUS<br><br>BMD z-score | PRL-levels<br><br>RIS-treated group (123 ± 144 ng/ml) > OLZ-treated group (25.9 ± 25.7 ng/ml) (p<0.05)<br><br>BMD results<br><br>Similar BMD scores for RIS- and OLZ-treated patients were noted at the lumbar spine and femoral neck [z(DEXA): RIS=OLZ]. Bone speed of sound lower in RIS-treated group versus OLZ-treated group when determined at the radius (p<0.05) and phalanx (p<0.05) [z(speed of sound), but not at the tibia. | BMD was similar in the treatment groups. Lack of correlation between PRL levels and bone speed of sound |
| [106]<br><br>Abraham et al. (2003) | 14 female patients with schizophrenia (mean age: 36.3)<br><br>Treatment medication: (n=6), OLZ (n=8) during 12 months.<br><br>PRL-raising group=RIS+one individual on OLZ (n=7)<br><br>PRL-sparing group=all OLZ- | DXA (lumbar spine, L1-L4 and hip)<br><br>BMD absolute values and z-score | PRL-levels<br><br>At baseline: high PRL-group (88.8 ± 34.7 ng/ml) > low PRL-group (21.1 ± 15.7 ng/ml)<br><br>BMD results<br><br>No statistically significant differences between high and low PRL groups on any BMD measures | Elevated PRL levels were not associated with significant changes in vertebral or femur BMD over the 12-month period |

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| | treated individuals, except one (n=7) | | (z-change: high-PRL=low-PRL. | |
| [94]<br><br>Abraham et al. (2002) | 16 patients with schizophrenia (mean age: 43)<br><br>Treatment medication: FGA (n=7), RIS (n=3), CLZ (n=6) for at least 6 months | DXA [lumbar spine, L1-L4 and left hip (femoral neck, trochanter and Ward's triangle)]. | PRL-levels<br><br>Mean: 39.9 ng/ml<br><br>BMD results<br><br>Statistically significant values concerning BMD-PRL correlations were observed for femoral neck ($p<0.01$), trochanter ($p<0.01$), total BMD ($p<0.05$) and Ward's triangle ($p<0.05$). Correlations between the lumbar spine and PRL failed to reach statistical significance. | BMD-PRL correlations inversely related in a consistent pattern across all sites measured. |
| [97]<br><br>Keely et al. (1997) | 16 male patients with schizophrenia (mean age: 41.3)<br><br>FGA medication for at least 1 year | DXA (lumbar spine, right proximal femur at the neck, trochanter and Ward's triangle). | PRL-levels<br><br>Mean: 8.9 ± 1.5 µg/L<br><br>BMD results<br><br>Patients had a significantly lower BMD at the lumbar spine and two of the proximal femur sites (Ward's triangle and trochanter) in comparison with the BMD for the age-matched control subjects. The tendency toward a diminished value at the femoral neck sites did not reach statistical significance | Use of FGA associated with a lower BMD at the lumbar spine and in two of three proximal femoral sites. No correlation was observed between BMD and PRL |

25-OH-D = 25-hydroxyvitamin D; Ad-SoS = amplitude-dependent speed of sound; AP = antipsychotic medication; AMI = amisulpride; ARIPI = aripiprazole; BMD = bone mineral density; BUA = broadband ultrasound attenuation; CLZ = clozapine; CPZ = chlorpromazine; CPZ equivalents = chlorpromazine equivalents; DXA=dual-energy X-ray absorptiometry; FGA = first-generation antipsychotic; FLU = flupentixol; HAL = haloperidol; HPRL = hyperprolactinemia; HRT= hormone replacement therapy; OR = odds Ratio; OLZ = olanzapine; OSI = osteosono-assessment index; PALI = paliperidone; PERH = perphenazine; PRL = prolactine; QUE = quetiapine; QUS = quantitative ultrasound; RIS = risperidone; SD = standard deviation; SGA = second-generation antipsychotic; SULP = sulpiride; QUS = quantitative ultrasound; ZIPRA = ziprasidone