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Antidepressant medications and bone loss: An insight for researchers and clinicians

Abdulrahman S. ALAnazi

Department of Clinical Pharmacy, Unaizah College of Pharmacy, Qassim University, Kingdom of Saudi Arabia

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ABSTRACT

Depression is one of the mental health disordersleads to major public health problems worldwide.The association between depression and reduced bone mineral density (BMD) has been reported inconsistently.However the role of depression as a risk factor for low bone mineral density (BMD) and osteoporosis is not fully understood, mainly because the relevant literature is inconsistent and because information on the mechanisms mediating brain-to-bone signals is rather scanty. Selective serotonin reuptake inhibitors (SSRIs), the first-line antidepressants, increase extracellular 5-hydroxytryptamine (5-HT) levels but have deleterious skeletal effects. The skeletal serotonergic system consists of 5-HT receptors and the 5-HT transporter (5-HTT) in osteoblasts and osteocytes. 5-HTT is a transmembrane protein targeted by SSRIs. 5-HT restrains osteoblastic activity, thus leading to bone loss.This review provides an extensive literature on markers of osteoporosis, and updated information on association between depression, antidepressants and bone loss. Furthermorethis review highlights the probable mechanisms of antidepressant drug-induced bone disease with emphasis on the side effect profile of these medications on bone metabolism thus prompting clinicians to screen patients at high risk of osteoporosis onantidepressant drugs, to help reduce the incidence of potentially avoidable fractures.

Key words: Depression, antidepressants, Osteoporosis, and bone mineral density

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INTRODUCTION

The bony adverse consequences of drugs for mental illness, particularly in patients withdepression and psychosis have been relatively neglected by both researchers and clinicians. Among the various mental illnesses; anxiety, depression and psychotic disorders are the most common that often require chronic treatment. In addition to this, major depressive disorder was ranked first as a cause of years of life lived with disability (YLDs) in 1990, 2005, and 2010 in Saudi Arabian population [1].In the past three decades, the association between depression, antidepressant drugs and osteoporosis has been the subject of a growing body of research, implicating major depressive disorder (MDD) as a risk factor for bone loss and osteoporosis [2]. Like osteoporosis, MDD is a prevalent disease, considered the second leading global cause of years of life lived with disability [3]. Both depression and osteoporosis are approximately three fold more common in women than in men [4]. With the advances in our understanding of the impact of depressive illness on medical health, until recently a largely neglected area, and the introduction of medications that have limited side effects,attention has largely been focused on altered behaviour and neuroendocrine problems associated with depression[5,6].Some reports have suggested that not only depressionbut also antidepressants may lead to osteoporosis/reduced bone mineral density and increased fracture incidence[7,8].

Serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE) and dopamine are the main neurotransmitters implicated in the pathophysiology of depressive illness [9,10]. The serotonin transporters are the main target of

selective serotonin reuptake inhibitors (SSRIs) often used to treat depression in adults [11], as well as children and adolescents [12]. SSRIs are often preferentially prescribed because of the reduced potential for adverse effects [13,14] butserious questions have been raised regarding the influence of SSRIs on bone tissue.Moreover,the functional serotonergic pathway in bone has been demonstrated to regulate bone metabolism [15,16] and preliminary clinical evidence demonstrating detrimental effects of SSRIs on the skeleton [17]. In addition to this, impaired bone mineral accrual was demonstrated in growing mice treated with SSRI (fluoxetine) [18]. Furthermore, 5-HTT null mutant mice had a consistent skeletal phenotype of reduced mass, altered architecture, and inferior mechanical properties [19].

This review focuses on the recent updates on the association between depression, antidepressants and bone abnormalities. Moreover, the review provides an understanding of the underlying pathophysiological mechanisms that can aid clinicians in identifying and monitoring vulnerable patients and in defining the optimal therapy for all affected patients.

1. Osteoporosis

Osteoporosis is a disease characterised by low bone mass and deterioration of the bone architecture leading to increased fragility and fracture. A fragility fracture is defined as one that results from no identifiable trauma or minimal trauma, such as fall from standing height or less. Osteoporotic fractures-particularly of the femoral neck and of the vertebral bodies-impair the quality of life [20,21] and increase mortality [22]. They account for most of the burden of disease in patients with osteoporosis. Fractures also lead to greater utilization of medical services, with the associated high costs [23]. Although a fragility fracture can occur in any bone, fracture of the hip, spine, and wrist are particularly common in individuals with osteoporosis. *Primary osteoporosi*s refers to a reduction in bone mass related to aging and menopause, whereas *secondary osteoporosis* results from specific diseases or drugs.

1.1. Epidemiology

Osteoporosis is considered as a serious public health concern due to its worldwide prevalence. Currently it is estimated that over 200 million people suffer from this disease worldwide [24]. Approximately 30 % of all postmenopausal women have osteoporosis in the United States and in Europe. At least 40% of these women [25] and 15-30% of men [26] will sustain one or more fragility fractures in their remaining lifetimes. Ageing of populations worldwide will be responsible for major increase in the incidence of osteoporosis in postmenopausal women [27]. Osteoporosis is common in Saudi Arabian population and the burden of management in an aging population will increase in coming decades. Greer et al., estimated the prevalence of osteoporosis among Saudi Arabian women aged 50-70 years to be approximately 23% [28,29].

1.2. Risk Factors

The various risk factors associated with osteoporosis includenutrition, Sodium, Caffeine, Race, Asiatic/Caucasoid ethnicity, Body weight, Thinners/Low Peak bone mass; Life Style, Alcohol abuse, Cigarette smoking, Lack of exercise; Genetics, personal and family history, Female gender; Disease, Cushing's syndrome, Hypertension and Hyperparathyroidism. Further some medications have also been reported to induce bone loss such as selective serotonin reuptake inhibitors, glucocorticoides, antiepileptic drugs, heparin, diuretic medication, aromatase inhibitors and thyroxine[30].

Severalexperimental and clinical studies demonstrated the multifactorial pathogenic mechanisms of bone loss associated with excessive alcohol consumption suchas ethanol-induced hypocalcaemia [31], increased renal calcium and magnesium excretion/calcium[32] and magnesium[33] deficiency due to liver disease, malabsorption of calcium due to alcohol-induced structural alterations of the enterocyte, [34] defective vitamin D metabolism,[35] ethanol-induced depression of plasma testosterone levels, [36] secondary hyperparathyroidism[37], elevation of free plasma cortisol levels[38], defective bone collagen synthesis[39] and metabolic acidosis [40].

The direct toxic effects of cigarette smoking on bone has been demonstrated in animal studies, reported impaired new bone formation on exposure to nicotine [41]. However the exact physiological consequence of cigarette smoking on bone is not clear. It has been reported that smoking is positively associated with higher serum concentrations of gonadotrophins and lower serum parathyroid hormone leading to reduced circulating estrogen level causing secondary increase in bone resorption [42]. Moreover, smoking reduces absorption of calcium [43] and transient rise in cortisol level [44], reduces the bone mineral density. Recently, it has been reported vitamin D3 deficiencies in patients with chronic rhinosinusitis after exposure to cigarette smoke [45]. Moreover the depressed subjects contained a higher proportion of smokers [46].In addition to this nutritional deficiencies such as dietary protein deficiency[47], very low calcium intake[48]also contribute to bone loss.

1.3. Diagnosis

1.3.1.DEXA Scan

The diagnosis of osteoporosis is primarily based on the measurement of BMD, but a clinical diagnosis can be made in someone with several risk factors experiencing a fragility fracture. Methods for measuring BMD include central DEXA, peripheral DEXA, quantitative computed tomography, and quantitative ultrasound densitometry. Although all of these can predict the risk of fragility fractures, evidence supports the use of DEXA as the most accurate method, with the best positive predictive value, to estimate fracture risk in postmenopausal women and men older than 50[49].

The World Health Organization (WHO) has recommended the classification of bone health based on T-score determined by DEXA scan (Box 1). Inspite of the measurement of BMD by DEXA scan as gold standard diagnostic test, some other biochemical markers of bone turnover such as bone resorption markers and bone formation markers are also used forthe diagnosis of osteoporosis.

2.3.2.Biochemical markers of bone turnover

Bone metabolism is characterised by two opposing activities coupled in time and space at the level of a basic multicellular unit (BMU). Bone resorption consists of the dissolution of bone mineral and catabolism of the bone matrix constituents by osteoclasts, leading to formation of a resorptive cavity and release of bone matrix components. During bone formation, osteoblasts synthesise bone matrix, which fills up the resorption cavity and undergoes rapid primary mineralisation followed by the slow long-term secondary mineralisation[50]. Bone formation markers are direct or indirect products of active osteoblasts expressed during different phases of osteoblast function and bone formation. The molecular markers of bone formation and resorption are shown in table 1. Except for tartrate-resistant acid phosphatase, majority of bone resorption markers are degradation products of bone collagen. Only recently have non-collagenous proteins such as bone sialoproteinandosteopontin been investigated as markers of bone turnover. Until recently, most assays for bone resorption markers were confined to urine, but newer assays are now available also for serum measurements [51]. The molecular markers of bone resorption are shown in below (Table 1).

2. Depression and bone mineral density

Like osteoporosis, major depression is a prevalent disorder, considered the second leading global cause of years of life lived with disability [3]. In the past three decades, the association between depression and osteoporosis has been the subject of a growing body of research, implicating major depressive disorder (MDD) as one of the most important medical conditions that contribute to reduced BMD and increased incidence of osteoporosis. The association between depression and osteoporosis has not been officially acknowledged possibly because the literature on the relationship between these conditions is insufficiently conclusive and contradictory. It has been reported in some clinical studies that patients with MDD suffer up to 6-15% reductionin BMD, whereas others, particularly large-scale population-based studies, show a weak or no relationship between the two conditions [2]. Further, the correlation between MDD and low bone mass, which is stronger in women than in men and in pre- than postmenopausal women has been explored in this meta-analysis study. In addition to this, a case-control study suggested an inverse association between MDD and lumbar bone mineral density (BMD) [52]. However, not only does the pharmacological modification of serotonergic system but also depression itself affected the bone health. Apart from antidepressant medication many other factors which contribute to bone loss and increased risk of fracture have been well documented. Further, some studies reported that the association between depression and bone mineral density (BMD) appears to be independent of the deleterious effects of antidepressants on the skeleton [53]. In addition to this, Bab et al. (2010) reported reduced BMD in depressed patients than non-depressed patient.

The association between depression and BMD is stronger in women than men, and in premenopausal than postmenopausal women. Only women psychiatrically diagnosed for major depression display significantly low BMD. The association of depression with lower bone mass was significant for the spine (vertebrae), hip (proximal femur), and distal radius. A prospective study showed increased risk of nonvertebral fracture (adjusted hazard ratio [HR], 1.30, p=0.008) and vertebral fracture (adjusted odds ratio [OR], 2.10, P<0.001) in 7414 elderly white depressed women[54].Indeed, the greater the severity of depression, the lower the BMD [55].Consistently, a metaanalysis investigated the association between the depressive symptoms and bone stiffness in young adult wherein they reported that the depressive symptoms were significantly associated with lower SI in men, but not in women in Asian population [56]. This increased fracture risk in depressed patients appears to be partly explained by disease associated falls and partly by a decrease in BMD [57,55, 6, 58].

These findings are further supported by a recent meta-analysis of 23 studies on the relationship between depression and osteoporosis,which found that depressed patients had lower BMD at all sites (spine, femoral neck, and total femur)versus controls, which is likely to increase fracture risk [59].More recently,a systematic review and meta-

analyses of epidemiologic studies [60]demonstrated that MDD was associated with lower BMD. These studies have shown that the presence of current depression was associated with a significant reduction in age-sex-height-race-specific bone mineral density (BMD) and content (BMC) of total body less head and lumbar spine [60,61]. In this context, some studies reported that the association between depression and bone mineral density (BMD) appears to be independent of the deleterious effects of antidepressants on the skeleton [53].

There are a various range of risk factors in depressed patient that could be associated with the reduction in BMD and increased rate of fracture[62].These risk factors could be i) Behavioural: indeed most of the behavioural factors that contribute to reduced bone mass are also known to be risk factors for osteoporosis which includeincreased rates of smoking and alcohol use; poor nutrition; weight loss and lower body mass index; immobilization or reduced physical activity leading to muscle weakness and increased risk for falls; and a sedentary lifestyle with less exposure to sunlight and lower vitamin D levels[63]. Moreover, depression has been recognized as an important risk factor for falls [54]. It predicts functional decline and the onset of excess disability, such as poor physical function [64-67], falls [68-72], and low bone density [73,74], all of which increase susceptibility to osteoporotic and traumatic fractures [75,76]. ii) Biological: Hyperprolactinemia**,** hypercortisolemia, inflammation, increased catecholamines, reduced gonadal steroids and iii) a series of potentially confounding factors [77], including comorbid conditions which are known to increase the risk for depression and osteoporotic fracture, such as cardiovascular disease, Crohn's disease, and diabetes, the concomitant use of medications such as glucocorticoids, estrogen, and loop diuretics that reduce bone mass [78] as well as antidepressants. Chronic disease may also be associated with depression induced by the disability stemming from the chronic disease in question.

2.1. Causal Relationship between depression and bone loss

Depression is currently believed to result from environmental (stress) and genetically induced alterations in neurotransmission in one or more of the central monoaminergic pathways (noradrenergic, serotonergic, and dopaminergic) mediated by a complex mesh of factors including corticotropin-releasing factor, hypothalamic–pituitary– adrenal hormones, and cytokines [79-81]. These biological changes during depressive episode have been implicated in the pathogenesis of depression induced bone loss. It has been demonstrated that chronic mild stress (CMS), an established model for depression in rodents [82], leads to bone loss. Moreover, CMS selectively inhibits bone formation and that this inhibition is mediated by activation of the sympathetic nervous system (SNS) [83]. Furthermore, the CMS-induced bone loss, but not the depressive-like state, could be prevented using the β-adrenergic antagonist, propranolol, portraying bone sympathetic innervation as a brain-to-bone pathway communicating depressive signals to the skeleton.

Studies have confirmed the role of persistent elevation of plasma cortisol due to stress during the depressive episode in depression induced reduction in bone mass and increased risk of fracture [84]. Furthermore, there is decrease in gonadal steroids [85] in depressed patients which further contribute to the reduced bone loss and increased risk of fracture. In addition, proinflammatory cytokines such as Il-6 and TNF-alpha, appear to mediate resorption [86,87] and are upregulated in depression [88-90].

2.2. Role of serotonergic system and bone turnover

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine neurotransmitter known best for its role in the CNS, gastrointestinal (GI) tract, and cardiovascular system. Biogenic amine transporters are important regulators, controlling the synaptic and extracellular concentrations of these amines in the CNS by their high-affinity reuptake from the extra- to the intracellular milieu. They are also major targets for many antidepressant drugs that inhibit their activity, thereby potentiating the effect of the biogenic amines.

The role of antidepressants in the bone, specifically the selective serotonin reuptake inhibitors (SSRIs), actingas targetsfor serotonin transporters has recently attracted substantial interest because of its potential impact on osteoporosis and resultant fractures. Serotonin transporters (5-HTT) as well as functional 5-HT receptors are well known for their expression in osteoblasts, osteocytes, and osteoclasts[18]. 5-HT receptor agonists influence cell proliferation, modulation of cellular response to mechanical stimuli, potentiation of parathyroid hormone induced increase in activator protein-1 activity and increased cAMP and prostaglandin E2 level in osteocytes[91]. However, in osteoclasts, 5-HT and 5-HTT have been shown to affect differentiation, but not activity [18].Moreover,disruption of the 5-HTT gene or pharmacologic inhibition of 5-HTT by SSRIs leads to a low bone mass phenotype in growing mice [19]. These apparently paradoxical findings may suggest that 5-HT has different effects on done. Interestingly, it has been suggested recently that the peripheral and central 5-HT signaling have opposite effects on bone. Peripherally, 5-HT directly activates osteoblastic 5-HTR(s) to inhibit bone formation, whereas centrally it inhibits the sympathetic nervous system, thus alleviating the negative adrenergic tone on osteoblasts [92].These findings in rodents are consistent with the limited data in humans that suggest an important role for serotonin in regulating bone metabolism [93].

SSRIs exert their effect by inhibiting the serotonin (5-HT) transporter (5-HTT), resulting in blocked reuptake of 5-HT from the extracellular space [11]. In the short term, administration results in elevated systemic 5-HT levels, but in the longer term, levels are reduced by about 50% [94]. Any systemic effects of SSRIs may result from changes in levels of systemic 5-HT, local blockade of 5-HTT, a combination of both, or effects on other pathways.The role of circulating serotonin in regulating bone mass has been demonstrated by recent preclinical studies. In addition to this, patients treated with selective serotonin reuptake inhibitors (SSRIs) have reduced areal bone mineral density (aBMD).

Antidepressant drugs and bone

SSRIs as the first-line widely used group of antidepressants (ADs), could also be a confounding variable affecting the present meta-analysis, as most studies report that it is associated with low BMD and increased fracture risk, particularly of the hip and vertebrae [55,57, 58,95] which is presumably by increasing extracellular 5-HT levels in the brain. Moreover, the use of SSRIs has been shown to be associated with lower bone mineral density (BMD) in postmenopausal women [62] and men [55,57,96], increased rates of bone loss in older women [6], and an increased risk of fracture [7,55,97,98]. With regard to the adverse effects of SSRIs in bones, several studies demonstrate a skeletal serotonergic system consisting of 5-HTRs in osteoblasts and osteocytes as well as the 5-HTT, the main transmembrane protein as targetsfor SSRIs. Increased 5-HTR activation restrains osteoblastic activity, thus leading to a negative bone remodelling balance. Active 5-HT receptors and the transporter 5-HTT have been detected in chicken, mouse, and rat bone cells, indicating a role for 5-HT in bone biology, possessing the capability to both manufacture and respond to 5-HT via receptor signaling [15,16,99]. The role of 5-HT on bone remains contentious, however, with some reports showing 5-HT decreases osteoblast (OB) proliferation and formation [100,101], while others refute a direct role [102]. It appears that the negative skeletal effects of the peripheral SSRI-induced increase in 5-HT outweigh the skeletal benefits resulting from the enhanced central 5-HT antidepressant and sympatholytic activity.

Further, research has shown that osteoblasts have serotonin receptors, and inhibition of the serotonin transporter system may lead to osteopenia in animal models [19,103]. This could signal a reduction in BMD in humans following the use of SSRIs with the attendant increase in fracture risk.Interestingly, human studies have added to this concern, showing a reduction in BMD in a cross-sectional study [57] and an increased loss rate for BMD in a longitudinal study [58]. Regarding fracture risk, several studies [7,98,104]have shown an increase in the risk of fractures, in particular within the first 14 days of use of SSRIs.In support of these observations, both in vitro and in vivo evidence provide further support to the human clinical findings [105] where SSRIs alone were shown to have deleterious effects in vivo on mouse bone macroarchitecture and microarchitecture, as well as mechanical properties, suggesting an inhibition of bone growth [106]. Furthermore, administration of 5-HT has been shown to increase BMD in rats [107] and inhibition of the 5-HTT decreases BMD and bone quality[105,107] and reduces bone mineral accrual [19]. This reduction in bone quality is however not clearly seen with dual reuptake inhibitors [106]. More recently, all SSRIs except (citalopram) inhibitedalkaline phosphatase (ALP)activity and bonemineralization by osteoblast but only at higher concentration (30 μmol/L)*in vitro* on human osteoclast and osteoblast and thereby modify their formation and function [108]. This finding may explain the mechanisms of bone loss with chronic use of these therapeutic agents.

It is worth noting that not only SSRIs but also tricyclic antidepressants (TCA) have beenreported to exertadverse skeletal effects. Until recently only two studies investigated the impact of tricyclic and SSRIs on the hip fracture risk [7,104]. However, it remains unclear if differences exist between the various types of TCAs and SSRIs, i.e., if drugs with, e.g., higher sedative potential carry a higher risk of fractures than other types of antidepressants. It may thus be that both TCAs and SSRIs share a common risk of falls, whereas the SSRIs carry an additional risk of decreasing BMD through effects on the bone cells. A further point is that some of the TCAs may also affect serotonin reuptake in the same way as SSRI but to a lesser extent [8]. There was an increased risk of any fracture at low doses for amitriptyline but not for imipramine and nortriptyline. The TCAs and SSRIs may thus, besides effects related to falls, also share effects on bone turnover and BMD. One study of institutionalised elderly patients has suggested that patients using SSRIs were at higher risk of falling than those using TCAs [109]. Some antidepressants, especially the MAO-B inhibitors and the norepinephrine modulators such as mirtazapine and mianserin, do not affect the serotonin reuptake system, whereas others such as venlafaxine and reboxetine, do [8]. One study indicated that the MAO B inhibitors and norepinephrine reuptake inhibitors, were not associated with an increased risk of fractures, in contrast to TCAs and SSRIs [104].

Table 2 summarizes the studies evaluating the association between depression, antidepressant and bone mineral density or fracture risk. The type of antidepressant drug used, study design, number of samples and the major conclusion drawn from each study are listed. It provides as insight into the upto date studies conducted to assess the bony impact of antidepressant drugs.

3. Pathophysiology of antidepressant-induced bone loss

Despite the growing evidence of the link between depression and osteoporosis, the underlying mechanisms are not well understood but may include effects of depression and effects of medications used to treat depressive symptoms on bone metabolism. However, several potential mechanisms have been postulated for a direct effect of depression on bone metabolism. Ample evidence exist to support that depression may be a risk factor for osteoporosis with alteration in the adrenergic axis and the hypothalamic-pituitary-adrenal axis [53,77]. Elevated plasma cortisol levels have been observed in depressed subjects and have been attributed to an impaired hypothalamic–pituitary–adrenal system in depression [110]; these elevations in plasma cortisol levels have been postulated to lead to accelerated bone loss [74]. Upregulation of proinflammatory cytokines, such as IL-6 and TNF-alpha, appear to mediate resorption [86,87] and are upregulated in depression [88-90].Although the physiological processes mediating bone loss are complex, the most common cause of bone loss is sex hormone deficiency [111,](Figure 1).

Box 1: WHO classification of bone health based on T-score determined by DEXA scan.

Box.1: WHO classification of bone health based on T-score determined by DEXA scan in postmenopausal women and men older than 50 years	
Classification	T-Score (SD)
Normal	>-1.0
Osteopenia	-1.0 to -2.5
Osteoporosis	< - 2.5
Severe osteoporosis	< -2.5 plus one more fragility fracture

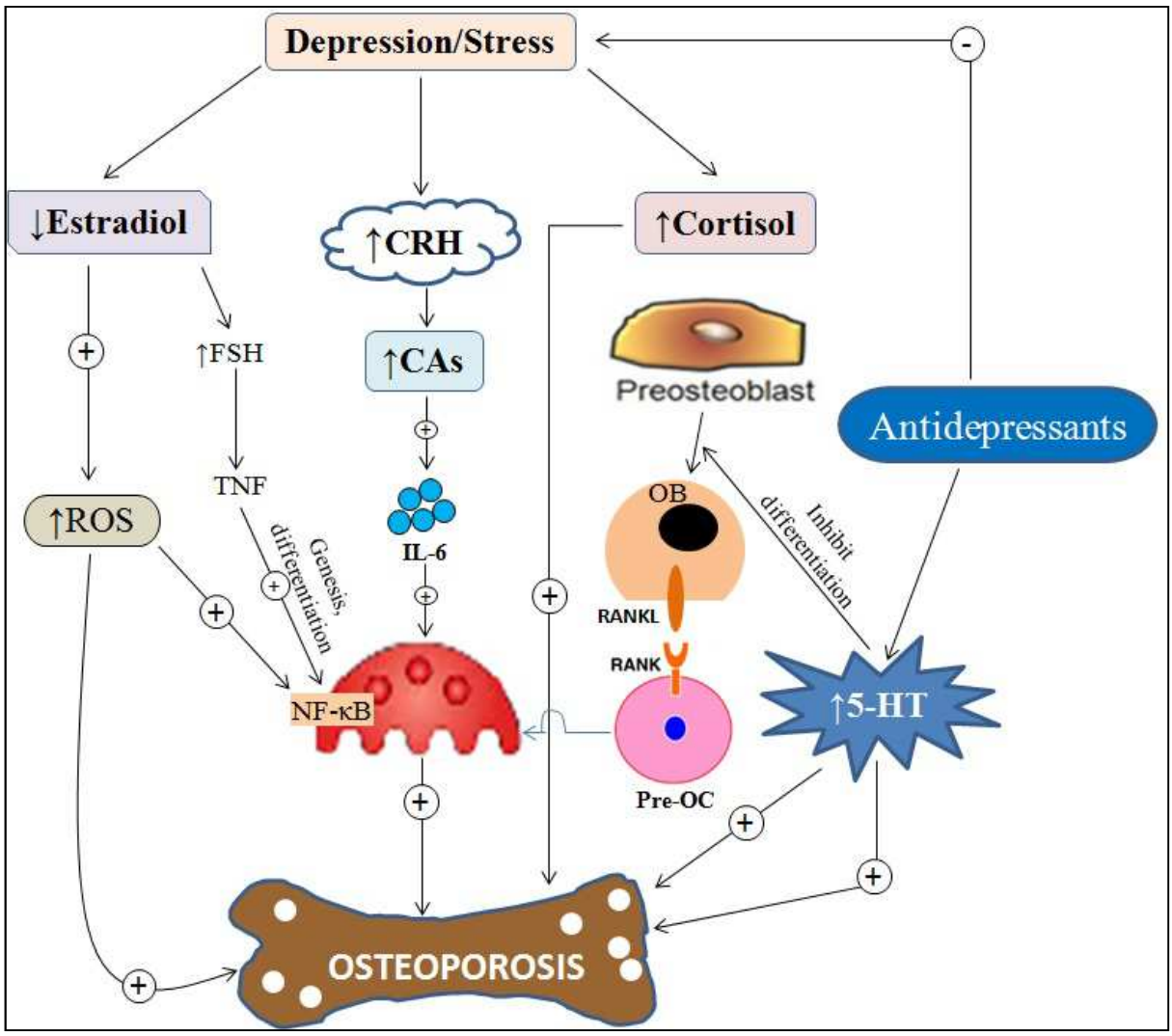

Figure 1: Pathophysiology of bone loss induced by drugs for mental illnesses (antipsychotics and antidepressants). (↑), increase; (↓), decrease; (+), stimulation; (-), inhibition, CRH, Corticotropin-releasing hormone; ROS, Reactive oxygen species; CAs, Catecholamines; OB, osteoblast; RANKL, Receptor activator of nuclear factor kappa-B ligand; Pre-OC, Preosteoclast; 5-HT, 5 Hydroxytryptamine

Table 1: Biochemical markers (bone formation and bone resorption) of bone turnover

Bone resorption		Bone formation	
Markers (Abbreviations)	**Specificity**	**Markers (Abbreviations)**	**Specificity**
Hydroxyproline, total and dialyzable (HxP)	All fibrillar collagens and partly collagenous proteins, including C1q and elastin; present in newly synthesised and mature collagen	Total alkaline phosphatase (total ALP)	Specific for bone formation only in the absence of liver or biliary disease
Pyridinoline (PYD)	Collagens, with highest concentrations in cartilage and bone; absent from skin; present in mature mature collagen only	Bone specific alkaline phosphatise (bALP)	Specific product of osteoblast; some assays show up to 20% cross-reactivity with liver isoenzyme (LALP)
Deoxypyridinoline (DPD)	Collagens, with highest concentration in bone; absent from cartilage or skin; present in mature collagen only	Osteocalcin (OC)	Specific product of osteoblasts; many immunoreactive forms in blood; some may be derived from bone resorption
Carboxy- terminal crosslinking telopeptide of type I collagen (CTX-MMP, formerly ICTP)	Collagen type I, with highest contribution probably from bone; may be derived from newly synthesized collagen	Osteonectin	Bone-specific protein that binds selectively to both hydroxyapatite and collagen
Carboxy- terminal crosslinking telopeptide of type I collagen (α-CTX-I, β-CTX-I)	Collagen type I, with highest contribution probably from bone	Procollagen type I carboxy-terminal propeptide (PICP)	Specific product of proliferating osteoblasts and fibroblasts
Amino-terminal crosslinkedtelopeptide of type I collagen (NTX-I)	Collagen type I, with highest contribution probably from bone	Procollagen type I amino-terminal propeptide (PINP)	Specific product of proliferating osteoblasts and fibroblasts
Hydroxylysine glycosides (Hyl-glycosides: Gal-Hyl, Glc-Gal-hyl)	Collagen and collagenous proteins; Glc-Gal-Hyl in high proportion in collagens of soft tissues, and C1q; Gal-Hyl in high proportion in skeletal collagens	-	-
Bone sialoprotein (BSP)	Synthesised by active osteoclast and laid down in bone extracellular matrix. Appears to reflect osteoclast activity	-	-
Tartrate-resistant acid phosphatase (TRACP)	Osteoclasts (5b), platelets, erythrocytes, other sources (5a)	-	-

Table 2:Studies exploring the relationship between depression, antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants) and bone mineral density (BMD)

Authors	Description of Study	Population	Effect on BMD/fracture verses nonusers		Conclusion
			SSRI	TCA	
Robbins et al., 2001 [116]	Population based cross-sectional study	1,566 Medicare enrollees age 65	No association	No association	• Depression was negatively associated with total hip BMD in the full cohort
Kinjo et al. 2005 [115]	Cross-sectional analysis in the NHANES population	14646 adults receiving CNS active agents, including 154 patients on antidepressants	No association	No association	• No relationship between antidepressant use and BMD (but <1% of the NHANES population was using antidepressants)
Diem et al. 2007b [58]	Cohort study (USA)	2722 women, aged ≥65 years 5 years of follow-up	Hip BMD decreased by 0.8% in users versus 0.5% in nonusers(P<0.001)	Hip BMD decreased by 0.5% in users (same as in nonusers)	• SSRI use, but not TCA use, is associated with reduced BMD
Haney et al. 2007 [57]	Cross-sectional analysis (USA)	5995 men, aged ≥65 years	Hip BMD 4% lower (P=0.002) and spine BMD 6% lower in users versus nonusers(P<0.001)	No difference between users and nonusers	• BMD is lower among men reporting current SSRI use
Richards et al. 2007 [55]	Population based Cohort (Canada)	5008 adults, aged ≥50 years 5 years of follow-up	Hip BMD reduced by 4% (significant) and spine BMD by 2% (nonsignificant) versus nonusers	No information	• SSRI use lowers BMD at hip and spine
Vestergaard et al., 2008 [8]	Case-control study	124,655 fracture cases, 373,962 controls	Any fracture: 1.40 (1.35–1.46); Hip: 2.02 (1.85–2.20); Vertebral: 1.56 (1.29–1.88)	Any fracture: 1.27 (1.13–1.42); Hip: 1.35 (0.99–1.84); Vertebral: 1.98 (1.22–3.22)	• Sedating TCAs were associated with higher risk for fracture • Increase in risk may be linked to affinity of SSRI to 5-HTT system
Spangler et al. 2008 [117]	Prospective cohort study (Women's Health Initiative, USA)	6441 women, mean age 64 years, with BMD evaluation 3 years of follow-up	No association	No information	• SSRI use not associated with a change in BMD
Williams et al. 2008 [118]	Cross-sectional Analysis (Australia)	124 women	Reductions in femoral neck BMD (6%), trochanter BMD (6%), and forearm BMD (4%), all P<0.05 versus nonusers	No information	• SSRI use lowers BMD at certain sites
Calarge et al. 2010 [113]	Cross-sectional analysis (USA)	83 adolescent boys treated with risperidone, mean age 12 years 45 out of 83 on risperidone and SSRI	SSRI use associated with lower trabecular BMD at radius (P=0.03) and spine (P<0.05)	No information	• SSRI use reduces BMD in adolescents
Diem et al., 2013 [114]	Prospective cohort study	311 new users of SSRIs, 71 new users of TCAs, and 1590 nonusers	0.63% per year in SSRI users while 0.68% per year in nonusers	0.40% per year in TCA users while 0.68% per year in nonusers	• SSRI or TCA users had an increased rate of bone loss compared with nonusers.
Oh et al., 2013 [56]	Cross-sectional analysis (Korea)	123 men and 133 women	No information	No information	• Depressive symptoms were significantly associated with lower bone stiffness index in men, but not in women
Sommerhage et al., 2013 [119]	Population based study (Estonia)	50 women	No information	No information	• Women with depression have low BMD at the lumbar spine.
Shea et al., 2013 [120]	Prospective study	76 patients using venlafexine aged 60 years and older	12 weeks venlafaxine treatment increased the β-CTX without affecting P1NP	No information	• Serotonergic antidepressants primarily increased the bone resorption.
Calarge et al., 2014 [60]	Cross-sectional analysis	222 adolescents and young adults	No information	No information	• Depressive illness is associated with significantly lower bone mass and reduced cortical thickness in youths

CONCLUSION

This article raises as many issues as it does answers. Closer monitoring of vulnerable groups is suggested to evade long-term bony adverse consequences in patients receiving drugs for mental illnesses (antidepressant and antipsychotics). Although such effects are unavoidable, but the proper selection, close monitoring and supplementation with calcium and vitamin D at the right time can protect the bone from adverse effects of these drugs. Moreover, this article focuses on the pathogenesis of bone loss induced by the aforementioned pharmacological agents. This review also attempted to explore the mechanism of bone loss induced by drugs used for mental illness in experimental models and of bone protective strategies in such conditions to enable chronic therapy with these medications without compromising bone health.

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