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Brains, Bones, and Aging: Psychotropic medications and bone health among older adults

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Abstract

Psychotropic drugs are a crucial element of treatment for psychiatric disorders; however there is an established association between many classes of psychotropic medications and fracture risk among older adults, and growing evidence that some classes of medications may also impact bone mineral density (BMD). In this paper we review recent epidemiologic research on the association between psychotropic medications and osteoporosis, and discuss current controversies and unresolved issues surrounding this relationship. Key areas in need of focused inquiry include resolving whether the apparent association between psychotropic medications and BMD is due to confounding by indication, whether this relationship differs for men and women, and whether the implications of these medications for bone health vary over the life course. Clinical research to delineate the risk/benefit ratio of psychotropic medications for older adults, particularly those who are at high risk for fracture, is also needed to facilitate prescribing decisions between patients and physicians.

Keywords

Epidemiology; aging; psychiatry; polypharmacy; medications; osteoporosis

Introduction

Osteoporosis affects approximately one in two women and one in four men over age 50 [1]. In 2005, the direct medical costs of osteoporosis were estimated to be between \$13.7 billion and \$20.3 billion [2], and annual fracture-related expenditures have been projected to reach \$25.3 billion by 2025 [1]. Psychotropic drugs are a crucial element of mental health treatment [3]; however there is growing evidence that some classes of psychotropic medications may adversely impact bone mineral density (BMD) and osteoporosis risk. The use of psychotropic medications, particularly among older adults, has increased exponentially in the past 10 years [4] pointing to a need to better understand whether and how such medications influence risk of osteoporosis, falls, and fractures.

In this article we review recent epidemiologic research on the association between psychotropic medications and osteoporosis, and discuss potential mediating pathways linking these drugs to bone health (see Figure 1). We focus on medications used to treat mood disorders, including major depression and bipolar disorder, because these are the most

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commonly prescribed psychotropic drugs – and among the most commonly prescribed medications overall in the US population. The primary medications used to treat major depression are selective serotonin reuptake inhibitors (SSRIs) such as citalopram, paroxetine, and sertraline; serotonin and norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine; tricyclic antidepressants (TCAs) such as amitriptyline, doxepin and imipramine; monoamine oxidase inhibitors (MAOIs) such as phenelzine and isocarboxazid; and other agents such as bupropion. The primary medications used to treat bipolar disorder are antidepressants; lithium; antiepileptic drugs (AEDs), including both cytochrome P450-inducing agents such as phenytoin, carbamazepine, as well as non-inducing agents such as lamotrigine and gabapentin; and neuroleptics such as chlorpromazine and haloperidol. We discuss potential biological mechanisms underlying this relationship, and highlight unresolved issues and current debates regarding the relationships between mental health and osteoporosis risk in later life.

Psychotropic medication use in the United States

Every year, approximately 20% of US adults experience a psychiatric or substance use disorder, and psychotropic medications are often integral to mental health treatment [3]. Over the past 30 years, psychotropic medications have become increasingly popular as a component of mental health treatment [4, 5]. Among US adults, the prevalence of psychotropic medication increased approximately 82% from 1988 – 1994 to 1999 – 2002 [6]. Per capita spending on psychotropic drugs increased from \$22 million in 1996 to \$52 million in 2001 [5].

Antidepressants are the most commonly prescribed psychotropic medication. In 2001, data on drug spending suggested that the largest increase among all medication classes was for antidepressants [7]. These trends are also seen in other developed countries; in the United Kingdom the number of antidepressant prescriptions increased two-fold from 1975 to 1998 [8]. Among antidepressants, there has been a dramatic increase in the availability and use of SSRIs over the past 20 years; these medications are considered first-line treatments for major depression [9, 10]. SSRI use has increased for all age groups, but this rise has been most notable among older (age 55+ years) women [8]. Analyses of the Medical Expenditure Panel Survey in 1996 and 2005 showed a 40% increase in antidepressant prescriptions among patients aged 65 years and older, with over 1 in 10 persons in this age group prescribed an antidepressant in 2005 [4].

Epidemiology of psychotropic medications and fracture risk

There is an established association between many classes of psychotropic medications and risk of fracture, particularly among older adults [11, 12]. A recent meta-analysis by Takkouche and colleagues (2007) found that the relative risk of fractures was 1.60 (95% CI: 1.38 – 1.86) for antidepressants (all classes), 1.59 (95% CI: 1.27 – 1.98) for neuroleptics, and 1.54 (95% CI: 1.24 – 1.93) and 2.17 (95% CI: 1.35 – 3.50) for non-barbiturate and barbiturate AEDs, respectively. Among antidepressants, TCAs, SSRIs, and newer medications such as SNRIs and bupropion, have all been associated with 70% to 90% increased risk of fracture [11]. Antidepressants may have a dose-response relationship with fracture, with the relative risk of fracture increasing from 1.15 at <0.15 defined daily dose (DDD)/day to 1.40 for 0.75 DDD/day; SSRIs appear to be associated with higher fracture risk compared to tricyclic antidepressants [13]. One mechanism linking psychotropic medication use and fracture risk is likely due to increased risk of falls as a result of dizziness, a common side effect of these agents. A recent meta-analysis of the impact of nine medication classes showed that sedatives/hypnotics, neuroleptics/antipsychotics, and

antidepressants were all associated with falls on the order of 47%, 59% and 68% increased risk, respectively [14].

The link between other psychotropic drugs and fracture risk is not as clear. There are conflicting results for AEDs [15–19], neuroleptics [20, 21], and lithium [22]. Bolton et al., (2008) found that SSRIs had the highest adjusted odds ratio of osteoporotic fractures compared to other antidepressants; lithium was associated with lower fracture risk; and neuroleptics were not significantly associated with fracture [21]. This study also suggested that higher doses of SSRIs may further increase the risk of osteoporotic fractures, consistent with a potential dose-response relationship [23]. Mezuk and colleagues (2010) found that AEDs were associated with nearly 2.5 times greater risk of fracture for both older adults with and without bipolar disorder [24]; this study also found that persons with bipolar disorder had greater risk of fracture independent of AED use, which highlights a key unresolved question in research on the relationship between these medications and fracture risk, namely whether it is the medications themselves, or the conditions they are prescribed to treat, that drives the association. This issue of *confounding by indication* is discussed more below.

Psychotropic medications and bone mineral density

Many medications used to treat depression and bipolar disorder have been associated with alterations in bone mineral density (BMD) [22, 25]. Many, but not all [26], studies have reported that antidepressants are associated with lower BMD [27], increased rates of bone loss, and increased risk for fracture, even after adjusting for falls [28]. However, results are inconsistent as to whether the relationship between antidepressants and BMD varies by dosage [28]. Vestergaard et al., (2006) reported the relative risk of fractures (any site, as well as at the hip or spine) increased as the DDD increased [13]. However, Zieme and colleagues did not find a linear relationship between SSRIs and fractures [29]. The relationship between medications and lower BMD may also be dependent on duration of medication use, although it is still unknown what the period of highest risk may be; studies of antidepressants have shown increased risk for fracture both early and later in the course of treatment [30, 31]. There is also suggestive evidence that AEDs may increase rate of bone loss, and that this effect may persist for up to two years post-AED exposure [32]. In addition to influencing risk of falls [14], there is suggestive evidence that SSRIs may exert an increase in the risk of fracture independent of any influence on BMD. Wu et al., (2012) showed that although SSRIs were predictive of fracture, use of SSRIs was not significantly associated with bone loss, and adjustment for BMD had no effect on the strength of the association between use of SSRIs and fracture risk [33]. These findings suggest that the mediating mechanisms linking antidepressants and fracture risk do not exclusively involve risk of falling events or alterations in bone mass. Among ambulatory adult patients, AEDs are associated with higher rate of bone turnover and decreased bone mass [34]. Recent studies in both humans and rats have also suggested that neuroleptic medications are associated with lower BMD and increased bone turnover [35, 36].

Potential biological mechanisms

In order to optimize bone health in persons on psychotropic medications, it is crucial to understand the effect of psychotropic medications on BMD and the various metabolic indices of bone and mineral metabolism [37]. Clinical, *in vitro* and animal research has begun to identify the biological mechanisms that link medications used to treat depression and bipolar disorder – both directly and indirectly – to osteoporosis [38–42]. Here we highlight recent findings regarding the biological pathways believed to be involved; we refer

the reader to several recent reviews that discuss in detail the biological correlates of specific medications (see annotated citation list).

SSRIs

SSRIs may have a direct effect on bone metabolism, however the biochemical nature of serotonergic pathways and their impact on bone metabolism are not yet fully understood [10, 28]. Laboratory investigations have identified that functional serotonin receptors are expressed by osteoblasts, osteoclasts, and osteocytes [38, 43, 44], which indicates that inhibiting the transporter systems may affect bone metabolism [45]. Consistent with this potential direct biological pathway linking SSRIs and bone health, many, but not all, recent studies have reported an independent association between SSRIs and BMD [46]. The influence of SSRIs may be modulated by other factors, including genetic susceptibility. A recent study by Calarge and colleagues showed that variants of the serotonin transporter-linked polymorphic region (5-HTTLPR) moderate the association between SSRIs and BMD [40]; they reported that men on SSRIs with the short allele of the 5-HTTLPR had the greatest reduction in BMD [40]. Such variation in genetic susceptibility to the influence of SSRIs on bone strength may explain the conflicting findings thus far in the SSRI-BMD relationship.

AEDs

There are a number of mechanisms by which AEDs may affect bone density. These include changes in parathyroid hormone, calcitonin, and estrogen [47–49]. However, AEDs can also influence vitamin D turnover and its metabolites, which can result in increased activity in the cytochrome P450 system; activation of this enzyme results in a lower concentration of vitamin D, reduction in the intestinal absorption of calcium, and low serum calcium, secondary hyperparathyroidism, and a reduction in BMD [18]. Research has shown that P450 enzyme-inducing AEDs are more strongly associated with low BMD compared to non-enzyme inducing AEDs [50–52]. However, even AEDs that do not activate cytochrome P450 are associated with lower BMD, suggesting that the biological mechanism linking these medications may be more complex and involve other biochemical and hormonal pathways [47, 49]. The biological consequences of AEDs may be modified by the presence of estrogen [53]. Among premenopausal women, AEDs, specifically topiramate, are associated with lower parathyroid hormone, lower bicarbonate concentrations, hypocalcemia and increased bone turnover [54]. Among post-menopausal women, AEDs, particularly those that induce cytochrome P450, may accelerate age-related bone loss [55].

Neuroleptics

Hyperprolactinemia is an established side-effect of certain atypical neuroleptic medications [32]. Elevated levels of prolactin suppress testosterone in men and progesterone and estradiol in women; this suppression can lead to hypogonadism, a known risk factor for the development of osteoporosis [20, 35, 56, 57]. More specifically, risperidone-induced hyperprolactinemia may cause asymptomatic hypogonadism, and this may cause an increase in C-terminal telopeptide of type 1 collagen, a marker of bone resorption. There is suggestive evidence that risperidone also increases bone resorption via an inhibitory action on brain serotonin [58]. However, many neuroleptic medications also have side-effects that may protect against bone loss; for example, risperidone is known to cause weight gain which may protect BMD [58]. In addition to influencing BMD through changes in gonadal hormones, prolactin may also have direct effects on osteoblasts [58]; osteoblasts express prolactin receptors, and prolactin has been shown to decrease the number of osteoblast cells, thereby directly lowering BMD [20, 59, 60].

Current debates regarding psychotropic medications and osteoporosis

Despite the substantial epidemiologic and clinical research regarding the relationship between psychotropic medications and bone health described above, there are several empirical questions in need of more focused inquiry. The most pressing unresolved issue concerns whether the observed relationship between these medications and osteoporosis and fracture risk is due to confounding by indication; that is, do the medications themselves have an influence on bone health, or are the psychiatric conditions that these medications are used to treat the true causal factor? A second issue concerns whether the relationships between psychotropic medications and bone physiology varies over the life course. It is also unclear whether there are gender differences in the influence of these medications on osteoporosis risk. Finally, the ever-present concern of how to best manage the risks of polypharmacy – particularly among older adults – and the need to quantify the risk-to-benefit ratio of these medications, particularly for older frail adults, are topics in need of additional clinical and public health research.

Confounding by indication

The apparent association between antidepressants, AEDs, and neuroleptic medications with osteoporosis begs the question as to whether it is these medications themselves, or the clinical conditions they are prescribed to treat, that is the true causal factor [61]. Many examinations of the link between psychotropic medications and low BMD have been limited by a lack of quality data on the presence of psychiatric conditions (and other clinical indications). This is an important methodological concern, because if psychotropic medication use is measured more accurately than the presence or severity of psychiatric illness (for example, through healthcare utilization records, which accurately document prescription refills but have limited clinical or phenotypic data on patients), it will *appear* that these medications are a stronger predictor of osteoporosis risk than the clinical condition simply because the error in measurement may bias the association between the clinical condition and osteoporosis toward the null [62]. Particularly for psychiatric conditions in which many persons go untreated (e.g., only two-thirds of persons with major depression received any type of psychiatric treatment in the past year) [63], simply being prescribed a medication is likely correlated with both disease severity as well as access to care. Therefore, without valid data as to the clinical severity of the depressive illness, it is possible that any observed association between psychotropic medication use and BMD is due to residual confounding by indication. This is a key concern, because recent research suggests that major depression and bipolar disorder themselves are associated with osteoporosis risk [28, 64]. Most, but not all [26, 33], extant studies report that depression and elevated depressive symptoms are associated with low BMD and greater bone loss over time [27, 65, 66]. Many studies have also reported that persons with bipolar disorder have significantly lower BMD relative to age- and sex-matched controls [25]. Adding to the complex nature of this relationship, Cizza et al., (2010) argued that the link between mood disorders such as depression and bipolar disorder and osteoporosis is likely bidirectional [66].

Another issue concerns general non-comparability of medication users vs. non-users. Persons who are prescribed SSRIs, for example, are different in many ways than persons who are not other than medication use alone, including insurance status, family health history, and presence of other health conditions (for example, some antidepressants are contraindicated for persons with a history of falls) [67], which makes a straightforward comparison of osteoporosis risk between medication users and non-users difficult. In recent decades many statistical methods have been developed to address this issue (e.g., propensity score matching, marginal structural modeling), but such methods generally require large samples with longitudinal follow-up [68, 69], and to date few studies examining psychotropic medications and BMD or fracture risk have utilized such approaches.

Gender differences

There has been insufficient attention to potential gender differences in the relationship between psychotropic medications and osteoporosis and fracture risk. Women are substantially more likely to develop both mood disorders and osteoporosis relative to men, and several studies have suggested that women may be more vulnerable to low BMD associated with depression compared to men [65, 70]. For example, Mezuk and colleagues (2008) reported that antidepressant medications were associated with low BMD among older women but not men, and that there was an additive interaction between history of depression and antidepressant use on BMD for women [27]. Similarly, Rey-Sánchez found that women with schizophrenia who were being treated with neuroleptic medications lost phalangeal bone mass and had increased bone turnover; however, this effect was not seen in men [71]. Hippisley-Cox et al., (2009) found that the use of TCAs was associated with the risk of osteoporotic (including hip, vertebral and distal radius) fracture in men; however, these medications were not significantly associated with risk of hip fracture in women [72]. Other reports suggest that men are at risk of bone loss associated with psychotropic medication use. In one of the few studies to focus on osteoporosis risk among older men, Haney and colleagues (2007) reported that SSRIs, but not other classes of antidepressants, were associated with lower BMD in the Osteoporotic Fractures in Men Study (Mr. OS) [73]. Additional research is needed to identify whether specific psychotropic medications affect bone health differently for men and women, and the biological mechanisms underlying such gender differences, to help inform clinical care for older adults and potentially tailor pharmacologic treatment strategies appropriately.

Variation over the life course

Although it is appreciated that bone strength and bone turnover vary over the life course [39], it is unresolved as to whether the influence of psychotropic medications on BMD and osteoporosis risk differs across developmental periods. While the majority of studies of depression and osteoporosis and fracture risk have focused on older adults, there is evidence that depression is also associated with lower BMD even early in the life course. A recent small study by Cizza and colleagues (2012) reported that among premenopausal women (average age: 35 years), patients with depression had modestly lower BMD and higher levels of intact parathyroid hormone levels relative to comparison women [74]. However, there was no evidence that women with depression lost more bone over the follow-up period. Eskandari et al., (2007) also reported that low BMD was more prevalent in premenopausal women with major depression compared to controls [75]. While depression appears to adversely impact bone health similarly for both older and younger adults, this may not hold for antidepressants. There is suggestive evidence from animal studies that the impact of antidepressants on bone is impacted by the presence of estrogen. For example, in intact mice the SSRI fluoxetine induced an *increase* in trabecular bone formation; however, in ovariectomized animals (which mimics the post-menopausal period for women) fluoxetine did not increase bone mass, indicating that the presence of estrogen is needed for this anabolic effect [76]. Whether these findings translate to humans is unknown. For example, in a small study of adolescent boys SSRI use was associated with lower trabecular BMD at the radius and lumbar spine, consistent with the findings from older adults [39]. Larger studies with sufficiently long follow-up periods are necessary to determine whether the influence of antidepressants and other psychotropic medications on bone health varies over the life course.

Polypharmacy

As discussed above, the use of prescription and over-the-counter medications has increased substantially over the past two decades [77]. Nine out of ten older Americans reported using at least one prescription drug in the past month [78]. Older adults have the highest risk for

experiencing adverse events related to medication use [67], and this demographic is the largest *per capita* consumers of prescription medications [77]. Inappropriate medication use (e.g., taking combinations of medications that may interact, or taking a medication that is contraindicated by a health condition) is also most common among older adults [67, 79]. For example, Qato and colleagues reported that 1 in 25 older adults were at risk for major potential drug interactions [77].

The potential role of polypharmacy, especially among older adults, in the relationship between psychotropic medications and osteoporosis risk needs to be explored in greater depth. Olfson et al., (2009) reported that approximately four in ten persons treated with antidepressants in the US were also taking at least one other psychotropic drug [4]; and other research indicates that a high level of inappropriate prescribing and treatment conflicts among older patients who have been prescribed antidepressants [80]. One potential area for treatment conflict occurs when older patients are simultaneously prescribed drugs for osteoporosis and a mental health condition [80, 81]. Even if taking multiple medications does not directly impact bone health, polypharmacy is associated with risk of falls [82, 83] and fracture [84]. There is also recent evidence suggesting that the risk of polypharmacy on falls may be potentiated by the presence of depression [85]. Polypharmacy also needs to be considered among younger adults [86]; polypharmacy is a common issue for adolescents with chronic psychiatric disorders, and many of these medications that can modulate regulatory systems affecting bone mineralization [40]. It is important to note that the influence of polypharmacy on osteoporosis risk can only be examined using observational data, not in clinical trials, and thus accurate data on medication dosage, duration of use, and adherence are critical to determining what combinations of medications may be most detrimental for bone health.

Quantifying the risk/benefit ratio for psychotropic medication among older adults

Most psychotropic medications are prescribed in primary care, particularly for older adults [87], and in this setting there is the increased potential for a mismatch between physicians' intent and practice in prescribing [88–90]. As discussed above, there is a growing body of evidence linking psychotropic medications to low BMD, as well as falls and fracture risk among older adults [82, 84, 86]. Despite this risk, qualitative research shows that older patients and physicians perceive benefits and express little apprehension about taking and prescribing antidepressants long-term [88]. Some researchers have argued that the use of antidepressants is unlikely to outweigh the associated risk for older adults, and suggest a need to explore other approaches to treatment [91]; at a minimum, there is a need to consider bone health in the evaluation of the risks and benefits of specific psychotropic medications, especially when prescribing to older adults [92]. Information that combines evidence demonstrating clinical efficacy with data quantifying risks is needed for daily clinical practice to facilitate decisions between patients and physicians, including the discussion of alternative effective treatments (e.g., cognitive behavioral therapy) for mental health conditions [93].

Conclusion

The majority of research to date indicates that psychotropic medications are adversely associated with bone health, including risk of osteoporosis, falls, and fracture. However, extant research is limited in several ways. Key unresolved issues include whether these observed associations are due to the medications themselves, or the conditions they are prescribed to treat; whether the impact of psychotropic medications on bone health is similar for men and women; and whether the biological consequences of psychotropic medications on bone physiology vary by age. In particular, more research that specifically addresses the risk/benefit ratio of psychotropic medications among older adults is needed to promote

evidence-based clinical care that reflects an integrative approach to health for the aging population.

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Figure 1. Pathways linking psychotropic medications, bone mineral density, and osteoporosis
 There are several potential factors linking psychotropic medications and osteoporosis (top box). These factors could include mental health disorders for which the psychotropic medication may have been prescribed, including major depressive disorder, bipolar disorder, schizophrenia or neurological illnesses such as epilepsy. Other medical factors, which may be associated with psychotropic medications, include type 2 diabetes (T2D) and COPD (chronic obstructive pulmonary disorder). There are behavioral, biological, and pharmacological mediators of the relationship between psychotropic medications and osteoporosis (middle box). Use of psychotropic medications may influence changes in behavior, such as physical activity and diet. Many medications have side-effects (e.g.,

sedation, changes in absorption of nutrients from diet) that have implications for bone health. Osteoporosis is only one potential consequence of psychotropic medication use for bone health (bottom box). Osteoporosis can also lead to falls and fractures, and fractures can lead to falls.

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