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Abstract

This paper brings attention to a case report of osteoporosis diagnosed in a 67-year-old female due to a low trauma fracture. The individual was deemed high fracture risk, and unestablished in primary care. The drug class of Selective Serotonin Reuptake Inhibitors (SSRIs) and their recently identified risk of decreasing bone mass density, increasing osteoporosis, and ultimately doubling fracture incidence will be explored. Current osteoporosis screening guidelines are examined and criticized in relation to the presented evidence. Evidence based articles and up to date practice recommendations were reviewed. The results of multiple meta-analyses concluded that SSRIs have a significant negative impact on bone metabolism, increasing fracture risk. The high rates of unscreened osteoporosis, the current prevalence of the disease, and the lack of inclusion of SSRI use in the current fracture risk assessment prove significant clinical relevance of the results found.

The Increased Risk of Osteoporosis with Selective Serotonin Reuptake Inhibitor Use and The Need for Adjusted Screening Methods

Osteoporosis is defined as a "chronic skeletal disease marked by microarchitectural deterioration of the bone matrix and depletion of bone mineral density (BMD), with a consequent increased risk for fragility fracture" (Fernandes, Hodge, Pasco, Berk & Williams, 2016). An article by Gillespie and Morin (2017) discusses the current disparities in osteoporosis screening for women. A retrospective six-year study of over 1.6 million women over the age of 50 revealed that osteoporosis screening was low overall. Only 21.2% of women ages 50-64, 26.5% ages 65-79, and 12.8% ages 80 and above were appropriately screened (Gillespie & Morin, 2017). This represents a clear discrepancy in osteoporosis screening.

Osteoporotic fractures in post-menopausal women currently have a higher incidence rate than stroke, myocardial infarction, and breast cancer combined. Fractures occurring in the osteoporotic population represent a financial public health issue as they increase disability and mortality risk (Watts & Manson, 2017). The commonality of osteoporosis along with the current disparities in screening creates an outrageous health care concern.

Current osteoporosis screening guidelines from the United States Preventative Services Task Force (USPSTF) recommend screening women aged 65 years and older or in younger women with an equivalent fracture risk. Up to Date (2017) advises to perform a fracture risk assessment in all adults, post-menopausal women, men over 60, or any patient with a history of a low trauma fracture. The fracture risk assessment was introduced in 2008 by the World Health Organization (WHO), termed as the Fracture Risk Assessment Tool (FRAX). The FRAX estimates the 10-year risk of a major osteoporotic fracture for an untreated patient using the sum of clinical risk factors.

Over the past two years, meta-analysis reviews have revealed that the use of SSRIs at therapeutic levels for depression and anxiety have a negative effect on bone structure, decreasing bone mineral density and increasing fracture risk (Bruyere & Reginster, 2015) (Fernandes, Hodge, Pasco, Berk & Williams, 2016). Currently, the FRAX does not consider SSRI use in calculating one's fracture risk. This paper gives its readers the evidence to include SSRI use into the fracture risk assessment, along with the importance of adjusted screening methods for the SSRI population.

Background

A 67-year-old female presents for an 8-week post-operative follow up appointment for a right hip replacement due to a total right hip fracture. She has little primary care history. She displays high fracture risk qualities of post-menopausal age, current 1.5 ppd smoker with a 75-pack year history, low body weight, and does not participate in weight bearing exercise. Per patient report of the low trauma injury causing her fracture and additive risk factors, a dual-energy x-ray absorptiometry (DXA) scan was ordered, and revealed the diagnosis of osteoporosis. The current screening guidelines previously stated by the USPSTF are in place with a rationale that half of all post-menopausal women will experience an osteoporotic-related fracture in their life (Gillespie & Morin, 2017). The previously stated screening disparities may rise from the ill-defined wording and ambiguity of the current guidelines.

As formerly discussed, to calculate fracture risk, current practice guidelines listed in Up To Date (2017) recommend using the FRAX assessment tool. The FRAX tool is meant to allow providers the ability to assess fracture risk with or without bone mineral density information. Clinical information used to assess risk include; age, gender, weight, height, previous fracture, parent fractured hip, current smoking status, current glucocorticoid use or a history of more than

a 3-month dose of prednisone 5mg/day, rheumatoid arthritis, secondary osteoporosis, alcohol use of 3 or more units/day, and can consider femoral neck BMD. Secondary osteoporosis is present when a patient has a disease strongly associated with osteoporosis. Stated on the FRAX calculator, this includes "type I diabetes, osteogenesis imperfecta in adults, untreated long standing hyperthyroidism, hypogonadism or premature menopause (<45 years of age), chronic malnutrition, or malabsorption and chronic liver disease." (Fracture Risk Assessment Tool, http://www.shef.ac.uk/FRAX/index.aspx). SSRI use is not taken into account in any area of the FRAX screening tool.

Recent reviews have looked at longitudinal, cross-sectional, prospective cohort, and randomized controlled trials and have unanimously stated that SSRI use independently decreases bone health, leading to increased developments of osteoporosis. Additionally, SSRIs independently doubled the occurrence of fragility fractures associated with osteoporosis (Fernandes et al, 2016). SSRIs are the first line therapy worldwide for treatment of depression, mood, and anxiety disorders, especially in the older adult population due to the favorable adverse effect profile (Bruyere & Reginster, 2015). With the evidence presented here and the high prevalence of SSRI use, the absence of its inclusion in the Fracture Risk Assessment Tool (FRAX) needs to be addressed.

The purpose of this report is to relate the defined terms and guidelines of osteoporosis to recently studied SSRI effects on bone mass, and further, to identify current disparities in fracture risk assessments and improve screening efforts related to osteoporosis.

Case Report

A 67-year-old female presents for an 8-week post-operative appointment for a right hip replacement due to a total right hip fracture. The total right hip fracture occurred from a fall in

the bath tub. The patient states she is feeling O.K. today, and denies any concerns or complaints. She has little primary care history, and inconsistent health care visits. She would like to discuss establishing care at this clinic. Patient is Caucasian. Past medical history of hypertension, depression, and breast cancer of the right breast. Denies any history of fractures. Denies any drug allergies. She is widowed with three grown children. Currently smoking 1.5 ppd for 50 years (75 pack years). Rarely uses alcohol and does not exercise. She is retired, and states she is relatively inactive. She denies being up to date on any of her screenings besides a mammogram in 2016 that was unremarkable. Current medications are Lisinopril 10mg po daily and arimidex 1mg po daily. Today's vital signs are: BP: 132/70, HR: 78, RR:16, O2: 96%, Weight: 121lbs.

She denies any pain today. She does occasionally experience mild pain at home, mostly in the mornings, and takes 650mg of Tylenol every 6 hours as needed. She states she graduated from her assigned physical therapy post-surgery. She denies any fevers, chills, redness, drainage, or swelling at the surgical site.

In an in-depth review of systems, she further denies headache, changes in vision, recent illness, shortness of breath, chest pain, heart palpitations, muscle weakness, numbness or tingling, nausea, vomiting, diarrhea, dysuria, polyuria, or any other pain unrelated to her hip. She denied any issues with her mood now, but does have a history of taking sertraline (Zoloft) for depression symptoms in the past.

Physical exam is unremarkable. Patient is good spirits, and happy with the results of her recovery. She is moving all extremities equally, and transferring well onto exam table. No grimacing or guarding noted. Surgical site is well approximated, and healing appropriately. No redness, drainage, bruising or swelling noted to surgical site. She is alert and cooperative throughout exam. No signs of distress. Non-diaphoretic. Head is normocephalic and

atraumatic. No adenopathy. Normal S1, S2 heart sounds with regular rate and rhythm. Radial and distal pulses +2. Capillary refill less than 3 seconds. No peripheral edema or swelling noted. Breath sounds auscultated are clear and equal throughout all lung fields. Good air exchange noted throughout.

Following the physical exam, we discussed future screenings and interventions that she should have at a follow up appointment to establish primary care. These included a colonoscopy, follow up mammogram, a low dose CT scan given her smoking history, up to date immunizations, a complete metabolic panel, CBC, lipid profile, and TSH. It was explained to the patient that a dual energy x-ray absorptiometry (DEXA scan) should be complete today. This is needed imaging to evaluate her bone density. Given the nature of her fracture, and osteoporosis risk factors, it is suspected that she has osteoporotic changes in her bones.

The DEXA scan resulted with a T score of -4.1 of the lumbar spine, and of -2.1 in the femoral neck. These scores are significant, and the conclusion is a diagnosis of osteoporosis with a high fracture risk. These results were reviewed with the patient. We discussed associated risk factors of smoking, post-menopausal age, low body weight, taking an aromatase inhibitor, and her sedentary lifestyle. A treatment plan was created with the patient and includes a smoking cessation plan, weight bearing exercises for 30 minutes 3 times a week, begin taking 1000mg of a calcium supplement and 800 units of vitamin daily, and to take alendronate (Fosamax) 70mg PO once a week. Education was provided on adverse drug reactions and the importance of taking Fosamax with a large glass of water, 30 minutes before the first meal or medication of the day. Additionally, avoid laying down for 30 minutes after taking. Instructed patient to follow up with dentist annually. The patient verbalized understanding, and agreed with

plan of care. She denied any further questions or concerns. She will follow up in two weeks for an annual physical and to schedule additional primary care screenings.

Literature Review

The above case report presents a high-risk osteoporosis patient. Due to her lack of regular visits with a provider, she did not have the opportunity to be appropriately screened prior to fracture occurrence. As previously stated, a 2017 study revealed that only 21.2% of women ages 50-64, 26.5% ages 65-79, and 12.8% ages 80 and above were appropriately screened for osteoporosis (Gillespie & Morin, 2017). This data shows that even post-menopausal women visiting their provider regularly, are not being appropriately screened for osteoporosis. Had this patient been established in primary care, or had regular clinic visits, she may have had a "26.5%" chance of being appropriately screened. Gillespie and Morin (2017) show a clear gap in preventative care related to osteoporosis. Additionally, recent studies reveal a strong relationship between depression, SSRI use, decreased bone density, and increased fracture occurrence. This additional information would put this patient in an even higher baseline risk category for osteoporosis. A literature review was conducted on the current evidence available on osteoporosis screening, and the relationship between SSRIs and bone density. By implementing appropriate and early screening methods, high risk osteoporosis patients have the opportunity for early interventions and lifestyle management. Early interventions may decrease fracture occurrence, ultimately improving patient quality of life, and driving down health care costs.

Current Screening and Management Recommendations

Screening for osteoporosis is mildly unclear, and autonomy is given to the provider to assess risk factors on an individual basis. This may account for the low screening numbers in postmenopausal women. Kleerekoper (2015), writes for the Up To Date practice guidelines

stating, “Screening for osteoporosis involves fracture risk assessment and measurement of bone mineral density (BMD). We recommend assessing risk factors for fracture in all adults, especially postmenopausal women, men over 60 years, and in any individual who experiences a fragility or low-trauma fracture.” Here the author’s recommendations differ from the USPSTF recommendations for screenings for all adults versus adults over 65 years of age. Risk factors are listed as: advanced age, previous fracture, long term use of glucocorticoid therapy, low body weight (less than 127lb), family history of hip fracture, cigarette smoking, and excess alcohol intake. It is recommended to use clinical information to assess fracture risk using the FRAX tool previously discussed. USPSTF recommends screening women aged 65 years and older or in younger women with an equivalent fracture risk. As more findings arise showing adverse effects on bone health from a variety of risk factors, risk assessments should be completed in all adults.

USPSTF and Up to Date (2015), suggest bone mineral density (BMD) testing using a DEXA scan in women 65 years of age and older, and in younger postmenopausal women with clinical risk factors for fracture. BMD testing in men is only suggested if they present with clinical risk factors of low bone mass and fracture.

Up to Date bases these recommendations off a well-designed randomized control trial that concluded that screening is directly related to a reduced fracture risk. The published trial used 4800 postmenopausal women (45-54 years), and randomly placed them in either a BMD screening or no screening group. After an average of nine years, 37-52% of screened women reported using hormone replacement therapy, or other osteoporosis medications compared to 22-45% of unscreened women (Barr, Stewart, Togerson & Reid, 2010). This study showed that screening for osteoporosis increases the percentage of women that initiated anti-osteoporotic medications as an early intervention.

The management guidelines discussed address the microarchitectural disruption that occurs in osteoporosis, as well as lifestyle regimens to prevent, or treat bone loss. Intaking enough calcium and vitamin D daily prevents excessive bone resorption. Supplementation guidelines are based off meta-analysis reports. Combined intake amounts from diet and supplementation should total at 1200mg of calcium, and 800 international units of vitamin D daily. Guidelines further recommend a total intake of 1000mg of calcium, and 600 international units of vitamin D for premenopausal women, or men with osteoporosis (Rosen, 2016, as presented in Up to Date). The U.S. Food and Drug Administration (FDA) currently has four medications approved to improve bone strength. Options include oral bisphosphonates weekly or monthly, or nonoral bisphosphonates administered biannually or annually. Bisphosphonates, supplementation, and lifestyle management to reduce the risk of fracture is the first line treatment regimen for osteoporosis (Watts & Manson, 2017). Early interventions of these management guidelines would benefit patients screened as high fracture risk.

Pathophysiology of Bone Metabolism and the SSRI impact

Osteoblasts, osteoclasts, and osteocytes are the three major cells types that create the bone. Continuous bone remodeling is done as osteoclasts perform bone resorption. This is followed by bone generation of the osteoblasts, which create the osteocytes that interconnect and insert themselves into the bone matrix. This process is how bone mass is preserved, and how it remodels in response to physical stressors (Fernandes et al., 2016). Altering this bone remodeling process is how serotonin disrupts the bone matrix.

Serotonin is commonly known to be produced in the brain, having a centrally inhibitory effect on the sympathetic nervous system. In the treatment of depression and anxiety, SSRIs increase the level of serotonin in the synapse for the post-synaptic cell to uptake. This is done by

inhibiting the reuptake of serotonin of the pre-synaptic cell. Unknown to common belief, serotonin is also produced peripherally. Highest concentrations of peripherally produced serotonin are found in the gastrointestinal tract, but the osteoclasts in the bone microenvironment release peripheral serotonin as well. This peripheral serotonin from osteoclasts has a direct effect on osteoblastic serotonin receptors, inhibiting bone remodeling. In this manner, osteoclast-derived serotonin act as paracrine and autocrine to regulate the process of bone remodeling. In the instance of SSRI use, elevated serotonin levels are induced both centrally and peripherally (Fernandes et al., 2016). These peripheral elevated serotonin levels are increasing the signaling to the osteoblasts to inhibit bone formation, decreasing bone mass, and increasing the risk of osteoporosis and fracture.

Depression and Osteoporosis.

Depression as a disease has been previously associated with bone deterioration, and increased fracture risk. Like osteoporosis, depression is a highly prevalent disease that is lifelong and debilitating. The associated lack of motivation, low energy, and impaired cognitive functioning all impact one's quality of life. Besides their association, the relationship between depression and osteoporosis remains unclear. More recently, there has been strong evidence to support the hypothesis that the chemical imbalance of depression alters bone metabolism, increasingly when SSRI treatment is used. In a review of current studies, even after known risk factors for osteoporosis were eliminated, clinical depression and depressive symptoms were shown to remain negatively associated with decreased bone mass. The evidence supports that negative implications on bone mass occur at the onset of depressive symptoms, not just later in life (Fernandes et al., 2016). A review revealed that people with depression versus without exhibited "lower bone mass at the spine, hip, forearm, with a stronger association observed for

pre-menopausal than for post-menopausal women" (Fernandes et al., 2016, p.23). While studying SSRI use and it's indication on bone health, it is imperative to address the independent association of depression and decreased bone health.

Furthermore, a study was completed to study the effects on anxiety disorders and bone health. Anxiety and depression are now commonly thought to be on a continuum. With depression associated with decreased bone health in the past, this study revealed anxiety disorders impact bone metabolism negatively as well. High levels of stress seen in anxiety disorders decrease osteocalcin levels that are naturally increased during bone construction, which decreasing bone density. While studying SSRI use to treat anxiety disorders, the authors concluded a significant negative relationship between duration of SSRI treatment and BMD values (Ak et al., 2015).

Details of SSRI use.

Selective serotonin reuptake inhibitors are the most used antidepressants throughout the world. They make up 60% of all antidepressants prescribed. A Canadian cohort study over 5 years studied 5000 adults over 50, and reveals that daily use of SSRIs doubled the risk of fragility fractures, even after confounding variables were adjusted. Additionally, it found that the fracture risk was dose dependent, but that intermittent users risk was equal to daily users. Further supporting the results, another cohort study of over 7000 adults over age 55, revealed that current SSRI user's risk of vertebral fractures was over double the risk of past SSRI users and tricyclic antidepressants users. This study also clarified that SSRI use was an independent risk factors of depressive symptoms. Additional meta-analysis only potentiates the argument that SSRI use has negative implications on bone metabolism, increasing risk of osteoporotic fractures (as stated in Fernandes et al., 2016).

The peripheral serotonin receptors and transporters in bone cells are directly where changes in serotonin impact bone homeostasis. In a trial on mice, by disrupting the serotonin transporter gene, or by inhibiting the serotonin transporter gene by pharmacologic use, as in SSRIs, resulted in low bone mass. These results were similar in growing and adult mice (Fernandes et al., 2016). The data generated from multiple animal trials presents evidence that serotonin plays a direct role in bone homeostasis, and that the inhibition of the serotonin transporter through SSRI use has a direct anti-anabolic effect on bone metabolism (Fernandes et al., 2016). These animal studies prove the relationship between SSRIs and bone health even in the absence of other human osteoporosis risk factors.

Bruyere and Reginster (2015) looked at fracture outcomes through a review of the literature that further backs the presented data, stating there is a direct relationship with SSRI use and decreased BMD. Their analysis performed a quantitative assessment of the relationship between SSRIs and fracture risk. Results were unanimous and showed that SSRI use was associated with an "increase in fractures of all types, non-vertebral, hip, and spine fractures". (Bruyere & Reginster, 2015, p.66). They discussed that the increased risk of fracture has been supported by "several distinct populations, using various study designs with bone density, bone loss, or fractures as outcomes…these results are consistent after adjustments for confounding variables such a age, body mass index, lifestyle factors, and history of fractures." (p.66). The results of this systematic review present substantial strength in the argument that SSRIs need to be more routinely included in fracture risk assessments.

Additionally, Bruyere and Reginster (2015) found that the strength of the association of SSRIs and decreased BMD differs based on SSRI dose, duration, time, age, or sex. They go on to state a further meta-analysis has been done taking these factors into account and that the

"strength of the association decreased with a longer window of SSRI administration" (Bruyere & Reginster, 2015, p.67). Additional cohort studies presented here support that the highest risk of fracture is found at SSRI initiation-8 months, remaining elevated until 18 months. A 10-year Canadian cohort study revealed that higher doses of SSRIs at base line was associated with high fracture risk. Of equal importance, a Dutch case control study showed a significant association between the discontinuation of SSRI use and the rapid decreased risk of fracture as well (Bruyere & Reginster, 2015). More studies need to be performed to define the details of how SSRI use effect bone health, but there is sufficient evidence of their direct relationship.

The 10-year Canadian cohort study presented in a review by Bruyere and Reginster (2015) was also looked at in depth for this literature review. Interestingly, the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) was also studied. These were found to elevate risk of fracture as well as SSRIs (Moura, Bernatsky, Abrahamowicz, et al, 2014). In relation to osteoporotic changes, this remains a clinically relevant area of study along with SSRIs prescribed for depression. SNRIs are commonly used for depression and vasomotor symptom control in menopausal women, who are already entering a higher fracture risk population.

Results and Recommendations the Literature.

With the current presented evidence, The Study of Osteoporotic Fractures have deemed SSRI use an independent risk factor from depressive symptoms for fractures. Their studies concluded this from unexpected findings, and have since stated that treating depression with SSRIs intensifies the original risk of fracture from depressive symptoms. Individuals already at an increased risk of compromised bone density, due to clinical depression, are being put at an even greater risk through SSRI treatment. Final recommendations from the evaluated literature concluded that timely and accurate musculoskeletal evaluations need to be done for patients of

current or potential SSRI use. Further, serial evaluations with DEXA scans, early initiation of anti-osteoporotic medications, and lifestyle management should be implemented in individuals who are at an increased risk at baseline (Fernandes et al., 2016).

Bruyere and Reginster (2015) address the issue that SSRI use is not included in the FRAX assessment scoring. They recommend that osteoporosis management be initiated for the SSRI population. If not to be included in the FRAX scoring, this may be done on an individual level. With the presented evidence, it is apparent that there needs to be a discussion between providers and patients to educated SSRI uses that they may need to be monitored for bone health complications.

Further, Hant and Bolster (2016) conclude in their research that SSRIs on a list of medications that may harm bone. They recommend that health care providers closely monitor the bone density of individuals on any glucocorticoids, proton pump inhibitors, aromatase inhibitors, certain antiepileptic medications, and selective serotonin reuptake inhibitors. By closely monitoring these patients, osteoporotic prevention treatment can be initiated as needed.

Warden and Fuchs (2016), skeptically look at recent meta-analyses on SSRIs and fractures. Their findings were that these studies report a 70% increase in fracture risk when taking an SSRI. Conversely, the authors here feel recent meta-analyses were “observational and limited in their ability to establish causality” (p.211). After using the Bradford Hill criteria to rule out a weak association between SSRI and fractures, they did conclude a strong and consistent relationship between SSRIs and fractures. Warden and Fuchs (2016) demonstrated that although a strong relationship is present, many studies have limitations and confounding variables that remain a concern. Even with limitations preventing them from completely

accepting the results, they do recommend bone density testing and interventions for SSRI users presenting with additional risk factors.

Premenopausal versus postmenopausal women

Premenopausal fracture occurrence is much lower, and not related to BMD as fractures are in postmenopausal women. Because of this, postmenopausal diagnostic criteria and treatment guidelines cannot apply to this population. Screening in this population is up to the provider, and performed on an independent basis. Current best practice guidelines notify providers that it may be appropriate to screen for premenopausal osteoporosis if any of the following occur; a low trauma fracture from standing height or less, causes of estrogen deficiency, drugs including glucocorticoids, anticonvulsants, antidepressants, and high doses of steroids, and similar risk factors to the postmenopausal population (Becker, 2017, as stated in Up to Date). Providers must be proactive in their risk assessment. The responsibility of identifying risk factors in premenopausal women, screening for osteoporosis, and early interventions truly falls on individual providers.

Conclusion and Clinical Practice Proposal

The presented evidence proposes a strong association between SSRI use and osteoporosis, independent of other variables. Although more randomized controlled trials may be needed to strengthen the evidence, and decrease the limitations of the studies, the presence of a negative association is clear through this literature review.

Aside from SSRI implications on bone health, osteoporosis screening numbers need to be improved in primary care. Screening guidelines may need to be altered to become more specific, urging providers of its importance. Including the use of SSRIs in the FRAX calculator or

flagging providers to assess bone health before prescribing an SSRI would be beneficial to patient outcomes.

Learning Points

- Providers should understand the potential implications of SSRIs on bone health
- Assessing bone health risk factors at all ages is a crucial component to preventative care
- High risk osteoporotic fracture patients should have an in-depth bone health assessment completed before starting an SSRI, this may include a DEXA scan and screening before age 65. Early anti-osteoporotic medications should be initiated as needed.

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