

Selective Serotonin Reuptake Inhibitors and their Impact on Bone Health: A Case Report and Literature Review

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Abstract

Selective serotonin reuptake inhibitors (SSRIs) are the commonest class of drug prescribed in the management of anxiety and depression. The array of co-morbidities that occur in the elderly population can lead to difficulties in prescribing for depression. Here we present a case report and brief review of the current evidence surrounding SSRIs and their impact on bone health. On the basis of this paper, we suggest caution when prescribing SSRIs in those with osteoporosis, or in those that are at high risk of falls, due to an increased fracture risk in SSRI users compared to non-users.

Abbreviations: SSRIs - selective serotonin reuptake inhibitors; BMD - bone mineral density; DEXA - dual energy X-ray absorptiometry

Background

Depression and osteoporosis are two extremely common comorbidities in geriatric patients. Each have their associated mental and physical impacts on the patient, and economically on the wider healthcare system. Staggeringly, up to 39% of frail patients suffer with depression.¹ Selective serotonin reuptake inhibitors (SSRIs) have long since been used in the management of depression and anxiety states and are one of the fastest-growing classes of drugs prescribed. Their use is not without the potential for negative effects; their side effect profile includes nausea, anxiety, insomnia, sexual dysfunction and gastro-intestinal upset, with the impact on bone mineral density (BMD) being controversial.

Statistics from the International Osteoporosis Foundation (IOF) reveal that in 2015, 6.8% of men and 21.8% of women over the age of 50 had osteoporosis. The estimated lifetime risk of hip fractures for women over 50 is 17.2%, with fracture-related costs at 5.3 billion pounds in 2017.² Osteoporosis is a progressive, systemic skeletal disorder characterised by loss of bone tissue and disruption of bone microarchitecture, that leads to increased bone fragility and consequently an increased risk of fracture. As well as increasing age and female sex, other well documented risk factors for reduced BMD include early menopause, alcohol use, corticosteroid use, smoking, sedentary lifestyle, low body weight, impaired eyesight, and recurrent falls. What is more, depression itself cannot be overlooked as a risk factor for osteoporosis.

The mechanism by which depression leads to lower BMD is by that of alternation of the hypothalamic-pituitary-axis system, resulting in hypercortisolism. Cortisol is a well-known factor in bone loss. Proinflammatory cytokines have been implicated in depressive disorders, and they may directly stimulate osteoclastic activity.³ What must also be considered is the impact that depression has on certain lifestyle choices such as

the potential for increased alcohol and nicotine consumption, inadequate nutrition and low physical activity.

The presence of serotonin receptors, neurotransmitters, and transporters has been found within osteoclasts and osteoblasts.⁴ 95% of serotonin is synthesised in the gut and cannot cross the heteroencephalic barrier. Gut derived serotonin reduces osteoblast proliferation, thereby leading to bone loss. Brain derived serotonin signals to the ventromedial hypothalamic neurones leading to decreased sympathetic output and therefore favours bone formation by action on the beta-2 adrenergic receptors on the osteoblasts. It appears that with shorter duration of use, decreased bone resorption predominates, and with longer term use, bone loss outweighs.⁴

The impact of SSRIs on bone health has long since been the subject of research, with a possible link with both increased risk of fractures, and reduced bone mineral density being identified. In response to emerging evidence, the MHRA issued advise to healthcare practitioners, stating that we “should be aware of epidemiological data showing a small increased risk of fractures associated with the use of TCAs and SSRIs, and should take this risk into account in discussions with patients and in prescribing decisions”, yet this has not yet filtered down to prescribing guidelines.⁵ The National Institute for Health and Care Excellence (NICE) guidelines state that on choosing the antidepressant to prescribe, healthcare practitioners must consider that there is currently no evidence to support using specific antidepressants for specific physical health problems.⁶

We therefore present a case of recurrent depressive disorder in a patient with a background of osteoporosis. We also include a review of the most up-to-date literature, with the aim of increasing awareness of the impact of SSRIs on bone health for fellow prescribers. We aim to highlight the difficulties we face as clinicians whilst there are no formal recommendations regarding the use of SSRIs in high risk populations.

Case Description

This 78-year-old was referred to our services in late 2019 with low mood and loss of motivation. She lives alone following the death of her husband 3 years ago and sadly has no family. She has a past medical history of depression, hypertension, acute pericarditis, subclinical hypothyroidism, hiatus hernia, cataracts, previous cholecystectomy, and osteoporosis.

She was diagnosed with osteoporosis in 2000. At that time, she had been seeing an osteopath due to back pain, who advised her to see her GP to investigate for arthritis or osteoporosis. She has a family history of osteoporosis on her mothers' side. She was diagnosed by Dual-Energy X-ray Absorptiometry (DEXA) scan, with osteoporosis at the lumbar spine and pelvis, at which time she was started on calcium supplementation.

She was initially started on oral alendronic acid but developed reflux symptoms, so this was discontinued. Over the following years she was tried on various medications for bone protection but sadly developed side effects. Briefly, pamidronate infusion caused iritis, and nausea was reported whilst on sodium ranelate. Later she was to be commenced on sodium risedronate, however did not start this due to concerns she had following reading the information leaflet. Denosumab was discussed as the next suitable option, however she was undergoing dental work including tooth extraction and so this has been delayed due to the risk of avascular necrosis of the jaw.

DEXA scanning in March 2019 showed a T score of -0.8 at the neck of femur, -4.5 at the forearm, -1.3 at the total hip, and -4.2 at the spine. This had, unsurprisingly, worsened from her last DEXA in 2016 (-3.6 at the spine). Her risk of major osteoporotic fracture was last calculated at 21.6%, with the risk of hip fracture 11.5%. She has had no falls or fractures to date since her diagnosis.

Other than Adcal-D3 she is now no longer on bone protection. Her current medications also include levothyroxine, ramipril, bisoprolol, cetirizine, fluticasone nasal spray, and Hypromellose eye drops.

She had initially been started on citalopram by her GP which she had discontinued herself after a period of weeks as she felt it had no positive effect. In December 2019 she scored 92/100 on the Addenbrooke's Cognitive Examination (ACE-III), with no significant deficits in any one category. As well as low mood and loss of motivation, she described frequent tearfulness, anhedonia, lack of energy, difficulty concentrating and poor sleep. There was no clear trigger for her current mental state, and her physical health was otherwise good. She had no suicidal ideation or thoughts of self-harm. There was some evidence of anxiety but no symptoms of psychosis. We could not identify any alcohol or substance use risks. Her mental state examination was unremarkable. She was given the diagnosis of moderate depressive episode, F32.1, and was started on sertraline. However, upon reading the patient information

leaflet, she refused to start this medication due to it mentioning a link with bone disorders.

As a result of this discussion, we accessed the medicines.org patient information leaflet, where an increased risk of bone fractures is mentioned under the heading 'symptoms that can occur when treatment is discontinued'. It also states that following clinical trials in adults, sertraline was found to cause 'bone disorder' in up to 1 in 1,000 people.⁷

Following in-depth discussions, our patient was very hesitant in agreeing to take any medication that may have an impact on her bone density. We were aware of the potential association between SSRIs and BMD but were unable to quantify this risk to our patient.

Discussion

Our case above represents a common situation; a patient that is worried about a side effect, concerning which there are no formal guidelines available to aid decision making. The link between depression, SSRIs and BMD is a complex one, with numerous confounders making analysis and application yet more difficult. We looked at the evidence surrounding SSRIs and their impact on bone health, in order to suitably advise our patient on the most appropriate treatment options.

Impact on BMD

We found several meta-analysis and systematic reviews concerning BMD. The majority showed no significant association between BMD and SSRI use.

Of note, a 2015 systematic review by Gebara et al, suggested that antidepressant use may well be associated with lower BMD. 4 of the included studies assessed the relationship with BMD, 3 of which highlighted an association with lower BMD. This association was reported with SSRIs but not TCAs. However, they concluded that there was insufficient evidence that SSRIs adversely affect bone health, and therefore a change in current recommendations for the use of antidepressants in older adults was not justified at the present time. They stated that the evidence did not satisfy the Bradford Hill criteria, it is inconsistent, and whilst there is biological plausibility, there are no experimental studies to support a causal relationship.⁸

Yet a 2012 literature review indicated effects on both BMD and fracture risk.⁹ Each and every study included, indicated a risk of reduced BMD, increased fracture risk, or both. Even when controlling for potential confounders this conclusion was drawn. Authors suggested on the basis of this evidence, that caution is advised when considering the use of SSRIs in those with osteoporosis or a history of osteoporotic fractures, despite there being no formal recommendations.

A 5-year longitudinal study involving 1988 women, 319 of which were using antidepressants, measured femoral neck BMD. A dose-response increase in bone mineral loss was evident.¹⁰ An older cohort study also showed that even after

adjustment for potential confounders, mean total hip BMD decreased 0.47% per year in non-users, compared with 0.82% in SSRI users.¹¹ A year later, and a community-based study revealed that after controlling for age, weight, height and smoking history, BMD among SSRI users was 5.6% lower at the femoral neck, 6.2% lower at the trochanter and 4.4% lower at the mid-forearm than nonusers.¹²

Fracture Risk

The evidence surrounding fracture risk is more unanimous. Of the systematic reviews and meta-analyses we found, all highlighted an increased risk of fracture in SSRI users.

Wu et al concluded that the significantly higher risks of fractures observed for patients who received SSRIs compared with patients with no exposure, remained statistically significant in studies that controlled for important risk factors and studies that scored highly in the quality assessment.¹³

Eom et al extrapolated their data, estimating that the increased risk of fractures translates to about one case of fracture for every 42 patients treated with SSRIs.¹⁴ The dose and duration of SSRIs also seems to contribute to fracture risk, with both an early increased risk (under 6 weeks), and a late risk associated with prolonged use.^{14,15}

A notable literature review by Panday et al on medication-induced osteoporosis summarised that treatment decisions concerning SSRIs should be considered on an individual basis for patients with osteopenia, osteoporosis, or fracture risks greater than 3% and 20% for hip and major fractures respectively.¹⁶ Of particular note from this review, a 10-year cohort study revealed that 14.7% of SSRI users suffered at least one fragility fracture over the study period.¹⁷ Whilst those using SSRIs do tend to have more fracture risk factors than the general population; they are more likely to be women, have more comorbidities, use other antidepressants/ anxiolytics, and have a previous history of falls; the significant association remained even after these variables were controlled for. The risk of first fracture specifically was increased by more than 50%, and similar to other studies, a dose–response relationship was evident.¹⁷

Conclusion

The impact of SSRIs on bone health is clearly a topic of contention. Whilst the impact on BMD is unclear, the increased fracture risk is more unanimous. There are plausible biological mechanisms to explain these risks, yet there is also the fact that the risk of falls themselves are higher when taking SSRIs.

Yet why hasn't this filtered down to making formal recommendations in prescribing guidelines? Questions remain as to whether we should be prescribing SSRIs in individual's with osteoporosis at all. Regardless, the relatively high risk of fracture with SSRI use may have a significant clinical impact. These risks must be balanced against the benefits gained by the

treatment for depression; both in terms of mental state and in osteoporosis risk factor modification. What would perhaps be more relevant would be to consider a patient's falls risk independently to their bone health, when deciding whether to prescribe SSRIs. Consideration towards the use of concomitant medications, co-morbidities and other confounders is vital.

It is on this basis that we suggest discussing bone health with your patients (particularly those at high risk), prior to prescribing these medications, and being wary of prescribing SSRIs in those with osteoporosis or more importantly, those at high risk of falls.

Summary

- Impact of SSRIs on bone health is complex with significant confounding factors
- Whilst the impact on BMD is contentious, the increased fracture risk is more significant
- Risk-benefit decision is needed
- Consider the patients falls risk most importantly before prescribing an SSRI

Acknowledgements

None

Competing Interests

None declared

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