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Review Article

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Review of the Selective Serotonin Reuptake Inhibitors Effects on Precipitating Secondary Osteoporosis and Bone Fractures

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ABSTRACT

The Selective serotonin reuptake inhibitors (SSRIs) are currently being approved for the treatment of several psychiatric conditions. Given the relatively decreased incidence of irreversible adverse effects from this class of psychopharmacological agents, the SSRIs are frequently chosen as first choice intervention by many clinicians. There is an emerging body of studies identifying the subtle and often unrecognized effects of the SSRIs on the development of osteoporosis. These studies suggest a possible correlation between SSRIs and a decrease in bone mineral density and an increased incidence of bone fractures. This review would summarize common causes of primary and secondary osteoporosis with special emphasis on the possible role of SSRIs in precipitating secondary osteoporosis and leading to bone fractures.

Keywords: SSRIs, Osteoporosis, Bones, Mineral Density, Treatment, Serotonin

Preamble- Osteoporosis

Primary osteoporosis develops as a result of aging or menopause-related bone demineralization. Secondary osteoporosis is due to pathological conditions and medications other than aging and menopause that lead to decreased bone mass and elevated fracture risk.

Similar to other body organs, bones are living, and growing tissues. Throughout the life cycle bones are regenerating and continuously rebuilt. Bones homeostasis or balance in achieved by regenerating more than losing bone tissues [1]. Approximately around the age of 35, this balance is reversed, with bone loss occurring at a slightly faster rate than it can be rebuilt and as a result bone density gradually decreases leading to an increased risk of primary osteoporosis [2]. A common complication of primary osteoporosis is bone fractures. The most vulnerable bones to fracture are those of the wrist, spine and hip. Hip fractures are the most serious as they can lead to hospitalization, loss of mobility, permanent disability and mortality. Primary osteoporosis is considered a worldwide serious public health disease affecting over 200 million people with an approximate 1.7 million annual incidence of hip fracture [3].

Secondary osteoporosis could arise as a complication of medical conditions and medications that lead to decreased bone mass and an increased risk of bones fracture. Endocrine disorders, gastrointestinal diseases, hematological and oncological disorders, miscellaneous organ diseases, genetic disorders, nuitritional disorders,and various organ transplantations could cause secondary osteoporosis [4]. Medications-induced osteoporosis is considered a significant health hazard and may skip the attention of clinicians prescribing medications for many medical, neurological and psychiatric conditions. Aside from the selective serotonin receptor inhibitors (SSRIs), glucocorticoids, proton pump inhibitors, thiazolidinediones, anticonvulsants, medroxyprogesterone acetate, aromatase inhibitors, androgen deprivation therapy, heparin, calcineurin inhibitors, and some cancer treatment chemotherapies could precipitate secondary osteoporosis [5]. Many patients are also frequently treated with

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combinations of these medications, possibly increasing the risk of secondary osteoporosis. A list of medical conditions that could precipitate secondary osteoporosis are summarized in Table 1 [4].

Table 1: Medical Causes of Secondary Osteoporosis

Endocrine disorders	Acromegaly Addison disease Cushing syndrome Primary or secondary Gonadal insufficiency Endometriosis Hyperparathyroidism Hyperprolactinemia Hyperthyroidism Hypogonadism Type 1 diabetes mellitus Hormones replacement therapies
Gastrointestinal diseases	Alcohol liver diseases Celiac disease Chronic hepatitis Chronic cholestatic diseases Gastrectomy Inflammatory bowel disease Malabsorption syndromes Pancreatic insufficiency Primary biliary cirrhosis Chronic liver disease Bariatric surgery for weight reduction
Hematological and Oncological Disorders	Myloidosis Hemochromatosis Hemophilia Leukemia Lymphoma Mastocytosis Multiple myeloma Pernicious anemia Sarcoidosis Sickle cell anemia Thalassemia Congenital porphyria Hemophilia Tumor secretion of parathyroid hormone-related peptides
Miscellaneous Organ Diseases	Ankylosing spondylitis Chronic obstructive pulmonary disease Congenital porphyria Epidermolysis bullosa Idiopathic hypercalciuria Idiopathic scoliosis Multiple sclerosis Rheumatoid arthritis Serious kidney failure
Genetic disorders	Hypophosphatasia Osteogenesis imperfecta
Nutritional disorders	Nutritional/Vitamin deficiencies Parenteral nutrition Eating disorders
Organs Transplants	Bone marrow Heart Kidney Liver Lung

SSRIs -Overview and Clinical Guidelines

The SSRIs are a class of psychopharmacological agents most commonly prescribed to treat depression. They are often used as first-line pharmacotherapy for depression and numerous other psychiatric disorders due to their relative safety, efficacy, and tolerability. They are also approved for use in both the adult and pediatric populations.

The first SSRI's Fluoxetine (Prozac) was approved by the United States Drug Administration (FDA) in 1987. This approval marked a significant turning point in the treatment of depression, ushering in what is often referred to as the antidepressant era.

The latest SSRIs Vilazodone (Viibryd) was approved by the FDA in 2011.

In Table 2 the SSRIs are listed in the chronological order of their approval by the FDA. Various SSRIs have been FDA approved for the treatment of the following conditions [6].

Major depressive disorder
Generalized anxiety disorder
Bulimia nervosa
Bipolar depression
Obsessive-compulsive disorder
Panic disorder
Premenstrual dysphoric disorder
Post-traumatic stress disorder
Social anxiety disorder (Social phobia)

Clinicians have also prescribed SSRIs for non-FDA approved conditions to treat binge eating disorder, body dysmorphic disorder, premature ejaculation in men, frigidity in women, fibromyalgia, paraphilias, autism spectrum disorder, Raynaud disease, migraine prophylaxis and post menopause associated vasomotor symptoms [7].

Table 2: List of SSRI's generic and brand names

Generic name	Brand name(s)
Fluoxetine	Prozac, Sarafem also found in Symbyax
Sertraline	Zoloft
Paroxetine	Paxil, Paxil CR, Pexeva
Fluvoxamine	Luvox, Luvox CR
Citalopram	Celexa
Escitalopram	Lexapro
Vilazodone	Viibryd

SSRIs -Mechanism of Action

The SSRIs act by selectively blocking the serotonin (5-hydroxytryptamine-5-HT) transporter, leading to increased levels of this neurotransmitter in the somatodendritic and the presynapsis end of neurons [8]. Compared to all other SSRIs,

Vilazadone has a putative mechanism of action whereby it enhances the release of serotonin across the brain's serotonergic pathways specifically by inhibiting the serotonin transporter, similar to other SSRIs, but additionally and simultaneously via partial agonism stimulating serotonin-1a receptors, This combined mechanism of action of vilazodone have led some clinicians to unofficially label it as being a serotonin partial agonist and reuptake inhibitor or (SPARI) [9]. Unlike other classes of antidepressants, SSRIs have little effect on other neurotransmitters, such as dopaminergic, adrenergic, cholinergic, and histaminergic neurotransmitters, and receptors.

SSRIs- Safety profile

SSRIs have relatively lower side effects than the tricyclic antidepressants (TCAs) and the mono amino oxidase inhibitors (MAOIs) due to their lack of pharmacological actions on dopaminergic, adrenergic, cholinergic, and histaminergic neurotransmitters, and receptors. Although originally designed to treat depression, they gradually progressed to becme the most prescribed psychotropic agents, for their FDA- approved indications and their off-label applications [7, 10]. This trend of comfortably prescribing SSRIs by mental health and primary care providers alike resulted from the perceived notion of their relative fewer side effects and overall safer adverse effects profile. This common perception of categorizing SSRIs as safer and well-tolerated agents should be balanced and corrected due to their many reported side effects, ranging from gastrointestinal effects such as nausea, loose stool, constipation, headaches, sexual dysfunctions, tremors, dry mouth, restlessness, sleep disturbances, weight changes, anxiety, dizziness, xerostomia, hyponatremia, hepatoxicity, sedation, urinary retention, and cognitive impairments [7,11], and in the context of this review secondary osteoporosis [5].

SSRIs- FDA and other Warnings

In 2004, the FDA issued a black box warning for SSRIs and other antidepressant medications as precipitating a possible increased risk of suicide among the pediatric and the young adult populations, up to age 25 .This warning was accompanied by a directive to clinicians to carefully assessing and weighing the risk and benefits of initiating SSRIs treatment in acutely suicidal patients since depression by itself carries a high risk factor for suicide and could requires prompt treatment with antidepressants.

Some SSRIs could lead to QTc intervals prolongation, which could precipitate fatal arrhythmias, Torsade de la pointes. Although several case reports linked all SSRIs to QTc prolongation. Many other meta-analysis studies only pointed to Citalopram, Escitalopram and Sertraline as potential causes of QTc intervals prolongation. The increase in QTc intervals prolongation by Sertraline is not considered clinically significant, while several episodes of torsade de la pointes, were linked to Citalopram which led the FDA to impose limits on its daily dosing to not exceed 40 mg [12].

Clinicians are behooved to monitor for QTc prolongation when using high doses of Citalopram or Escitalopram and to avoid using these 2 agents in patients with identifiable risk factors heart diseases such as congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure and in patients who are receiving other medications that could lead to QTc intervals prolongation [12,13].

The SSRIs are also associated with increased risk of bleeding due to their anticoagulant effects or coagulopathy [14].

SSRIs are associated with a risk of developing serotonin syndrome, especially when prescribed with other serotonergic agents, its development could require medical emergency treatment due to its broad clinical symptoms which may include vital sign abnormalities, autonomic instability, hyperthermia, dilated pupils, akathisia, tremor, deep tendon hyperreflexia, clonus, muscle rigidity, flushed skin, diaphoresis, and altered mental status with possible agitation [15].

SSRIs are metabolized and have pharmacokinetic effects on the cytochrome P450 system. Fluoxetine, paroxetine, sertraline, citalopram, and escitalopram are all inhibitors of CYP2D6. Fluoxetine and fluvoxamine are inhibitors of CYP2C19. Fluvoxamine is an inhibitor of CYP1A2. [16]. These inhibitory effects could lead to fluctuation in the plasma levels of the SSRIs and the co-prescribed other medications thus predisposing to the development of adverse effects and possible loss of therapeutic effectiveness.

SSRIs- Osteoporosis due to fractures

The increased incidence of bones fractures has been associated with the development of secondary osteoporosis. Several studies have documented that the ongoing use of SSRIs is associated with substantially increased risk of fragility fracture [17]. Daily SSRI use was also associated with increased odds of hip fractures that were dose dependent and were similar for those who reported taking SSRIs at baseline and at 5 years' follow-up [18]. Daily SSRI use was associated with increased risk of falling which predispose to fractures especially in the elderly [19]. The use of SSRIs could lead to low bone mineral density (BMD) and thus increasing the risk of fractures and secondary osteoporosis [20].

SSRIs- Serotonin induced bone alterations

In addition to the role of serotonin in bone, the SSRIs have a higher bone marrow concentration than their brain and blood concentrations [21,22]. The bone osteoblast and osteoclast cells contain serotonin neurotransmitters, transporters and receptors [21,23]. The gut and brain generated serotonin exert different metabolic pathways and actions on the bone [21]. The osteoblast proliferation is reduced by the gut derived serotonin resulting in bone loss while the brain derived serotonin decreases sympathetic output and enhances bone formation [24]. The shorter duration of use of SSRIs, and the independent effect of the brain and gut serotonin on the bone predominately lead to decrease in bone resorption [21,25].

The role of serotonin on bone and the differential effects of the gut and brain derived serotonin on the bone is an area that require further research and in-depth investigation prior to establishing a non-refutable link between the long-term use of SSRIs and their effects on bone health and the development of osteoporosis and precipitation of bone fractures [21].

SSRIs- Secondary osteoporosis summary and conclusion

The association between SSRIs and the development of secondary osteoporosis and predisposing to bone fractures is mainly established based on clinical observation and several published studies. There is still a dearth of evidence-based data that are derived from prospective trials and there is insufficient meta-analysis to definitively confirm a causal relationship that link the SSRIs as sole precipitants of secondary osteoporosis [26]. SSRIs appear to contribute to fracture-inducing falls, and addressing any fall risk associated with SSRIs may be an efficient approach to reducing SSRI-related fractures [17-19]. SSRI-induced falls leading to bone fractures also seem to occur more frequently in patients with preexisting poor bone health so clinicians are encouraged to consider bone density testing and prompt medical intervention for those presenting with the various risk factors for osteoporosis [26]. In that context orthopedic care providers may play a critical role in raising the awareness of other health care providers and primary care physicians of the possible side effects of SSRIs and the clinical importance of monitoring of bone health and the institution of therapeutic interventions to prevent the development of secondary osteoporosis and bone fractures.

Conflict of Interests

The materials described in this article are those of the author and do not reflect the views of the Department of Veterans Affairs, the VA Palo Alto Health Care System or the UCSF, Fresno Department of Psychiatry, California.

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Reference

1. Abdul Alim Al-Bari, Abdullah Al Mamun. Current advances in regulation of bone homeostasis. FASEB BioAdvances. 2020. 2: 668-679.
2. Satoshi Soen. Changes in diagnostic criteria and practice guidelines for primary osteoporosis. Clinical Calcium. 2014. 24: 321.
3. Olof Johnell, John A Kanis. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis International. 2006. 17: 1726-1733.
4. Lorraine A Fitzpatrick. Secondary Causes of Osteoporosis. Mayo Clinic Proceedings. 2002. 77: 453-468.
5. Keshav Panday, Amitha Gona, Mary Beth Humphrey. Medication-induced osteoporosis: screening and treatment strategies. Therapeutic Advances in Musculoskeletal Disease. 2014. 6: 185-202.
6. Hani R Khouzam. Focus on Serotonin Re Uptake Inhibitors Research. In: Focus on Serotonin Uptake Inhibitors Research. Nova Science Publishers. 2006. 1-82.
7. Jannini TB, Lorenzo GD, Bianciardi E, Niolu C, Toscano M, et al. Off-label Uses of Selective Serotonin Reuptake Inhibitors (SSRIs). Current Neuropharmacology. 2022. 20: 693-712.
8. Faquih AE, Memon RI, Hafeez H, Zeshan M. A Review of Novel Antidepressants: A Guide for Clinicians. Cureus. 2019. 11: 4185.
9. Thomas L Schwartz, Umar A Siddiqui, Stephen M Stahl. Vilazodone: a brief pharmacological and clinical review of the novel serotonin partial agonist and reuptake inhibitor. Therapeutic Advances in Psychopharmacology. 2011. 1: 81-87.
10. Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, et al. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. British Medical Journal. 2017. 21: 356.
11. James H Kocsis. Review: SSRIs and TCAs equally effective at treating chronic depression and dysthymia; SSRIs are associated with fewer adverse events than TCAs. Evidence Based Mental Health. 2013. 16: 82.
12. Beach SR, Kostis WJ, Celano CM, Januzzi JL, Ruskin JN, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry. 2014. 75: 441-449.
13. Kylee A Funk, Jolene R Bostwick. A comparison of the risk of QT prolongation among SSRIs. The Annals of pharmacotherapy. 2013. 47: 1330-1341.
14. Laporte S, Chapelle C, Caillet P, Beyens MN, Bellet F, et al.Bleeding risk under selective serotonin reuptake inhibitor (SSRI) antidepressants: A meta-analysis of observational studies. Pharmacological Research. 2017. 118: 19-32.
15. Nicolaj Mikkelsen, Per Damkier, Sidsel Arnspang Pedersen. Serotonin syndrome-A focused review. Basic & clinical pharmacology& toxicology. 2023. 133: 124-129.
16. Bousman CA, Stevenson JM, Ramsey LB, Sangkuhl K, Hicks JK, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6, CYP2C19, CYP2B6, SLC6A4, and HTR2A Genotypes and Serotonin Reuptake Inhibitor Antidepressants. Clinical pharmacology and therapeutics. 2023. 114: 51-68.
17. Richards JB, Papaioannou A, Adachi JD, Joseph L, Whitson HE, et al. Effect of Selective Serotonin Reuptake Inhibitors on the Risk of Fracture. Archives of Internal Medicine. 2007. 167: 188-194.
18. Sebastian Schneeweiss, Philip S Wang. Association between SSRI use and hip fractures and the effect of residual confounding bias in claims database studies. Journal of Clinical Psychopharmacology. 2004. 24: 632-638.
19. Manish Srivastava, Chad Deal. Osteoporosis in elderly: prevention and treatment. Clinics in Geriatric Medicine. 2002. 18: 529-555.
20. Sofie Schwan, Pär Hallberg. SSRIs, bone mineral density, and risk of fractures-a review. European Neuropsychopharmacology. 2009. 19: 683-692.
21. Ravisha Wadhwa, Manoj Kumar, Sushama Talegaonkar, Divya Vohora. Serotonin reuptake inhibitors and bone health: A review of clinical studies and plausible mechanisms. Osteoporos Sarcopenia. 2017. 3: 75-81.
22. Bolo NR, Hodé Y, Macher JP. Long-term sequestration of fluorinated compounds in tissues after fluvoxamine or fluoxetine treatment: a fluorine magnetic resonance spectroscopy study in vivo. MAGMA. 2004. 16: 268-276.
23. Gabriele Jedlitschky, Andreas Greinacher, Heyo K Kroemer. Transporters in human platelets: physiologic function and impact for pharmacotherapy. Blood. 2012. 119: 3394-3402.
24. Patricia Ducy, Gerard Karsenty. The two faces of serotonin in bone biology. The Journal of Cell Biology. 2010. 191: 7-13.

25. Ortuño MJ, Robinson ST, Subramanyam P, Paone R, Huang YY, et al. Serotonin-reuptake inhibitors act centrally to cause bone loss in mice by counteracting a local anti-resorptive effect. Nature Medicine. 2016. 22: 1170-1179.
26. Stuart J Warden, Robyn K Fuchs. Do Selective Serotonin Reuptake Inhibitors (SSRIs) Cause Fractures? Current Osteoporosis Reports. 2016. 14: 211-218.