Does the Intake of Selective Serotonin Reuptake Inhibitors Negatively Affect Dental Implant Osseointegration? A Retrospective Study

Mehmet Ali Altay, DDS, PhD[1]*
Alper Sindel, DDS, PhD[1]
Öznur Özalp, DDS[1]
Nelli Yildirimyan, DDS[1]
Dinçer Kader, DDS[1]
Uğur Bilge, MD, PhD[2]
Dale A. Baur, DDS, MD[3]

The success of osseointegration is influenced by several factors that affect bone metabolism and by certain systemic medications. Selective serotonin reuptake inhibitors (SSRIs) have been previously suggested to be among these medications. This study aims to investigate the association between systemic intake of SSRIs and failure of osseointegration in patients rehabilitated with dental implants. A retrospective cohort study was conducted, including a total of 2055 osseointegrated dental implants in 631 patients (109 implants in 36 SSRI \users and 1946 in 595 nonusers). Predictor and outcome variables were SSRI intake and osseointegration failure, respectively. The data were analyzed with Mann–Whitney test or Fisher exact test accordingly. Both patient-level and implant-level models were implemented to evaluate the effect of SSRI exposure on the success of osseointegration of dental implants. Median duration of follow-up was 21.5 months (range = 4–56 months) for SSRI users and 23 months (range –60 months) for nonusers ($P = .158$). Two of 36 SSRI users had 1 failed implant each; thus, the failure rate was 5.6%. Eleven nonusers also had 1 failed implant each; thus, the failure rate was 1.85%. The difference between the 2 groups failed to reach statistical significance at patient and implant levels ($P = .166$, $P = .149$, respectively). The odds of implant failure were 3.123 times greater for SSRI users compared with nonusers. Patients using SSRIs were found to be 3.005 times more likely to experience early implant failure than nonusers. The results of this study suggest that SSRIs may lead to increase in the rate of osseointegration failure, although not reaching statistical significance.

Key Words: dental implant, implant failure, osseointegration, risk factors, selective serotonin reuptake inhibitors

INTRODUCTION

Replacement of missing teeth in partially and totally edentulous patients with osseointegrated dental implants is extensively practiced worldwide with high success rates and predictability.[1] Despite a success rate of up to 92%,[2] dental implant failures still occur and remain a significant concern for both the patients and clinicians.[3] Several factors, including the quality and quantity of the residual bone, primary stability at the time of implant placement, and formation of direct bone to implant contact, may influence the overall success and survival of implants.[4] Among these factors, osseointegration is accepted to be the key factor for implant success.[5]

Osseointegration is a well-documented process that is based on the migration of osteoprogenitor cells to the bone-implant interface and apposition of bone in close contact with the implant surface.[6] Therefore, the success of osseointegration is directly related to bone formation and remodeling.[7] It is influenced by several factors that affect bone metabolism; such as age, sex, radiotherapy, smoking habits, implant dimension, surgical conditions, and certain systemic medications.[7,8] A number of researchers have investigated the effects of pharmacologic agents on the osseointegration process[9–13] and suggested that systemic intake of certain medications may either enhance or impair the osseointegration process.[5] Among these, proton pump inhibitors and anticoagulants have been previously found to be associated with increased risk of implant failure due to their negative effects on bone metabolism.[5,14] Recently, a small number of studies appeared in the literature, suggesting that selective serotonin reuptake inhibitors (SSRIs) may also affect the success of dental implants.[10,13]

[1] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Akdeniz University, Antalya, Turkey.
[2] Department of Biostatistics and Medical Informatics, Faculty of Medicine, Akdeniz University, Antalya, Turkey.
[3] Department of Oral and Maxillofacial Surgery, Case Western Reserve University, School of Dental Medicine, Cleveland, Ohio.
* *Corresponding author,* e-mail: malialtay@hotmail.com
DOI: 10.1563/aaid-joi-D-17-00240

Downloaded from http://meridian.allenpress.com/joi/article-pdf/44/4/260/2035350/aaid-joi-d-17-00240.pdf by guest on 20 September 2021

SSRIs are the most commonly prescribed antidepressant drugs that increase the levels of serotonin within the synapse by blocking its reabsorption.[15] Furthermore, serotonin receptors have been shown to be present in peripheral tissues, including the digestive tract; blood platelets; as well as osteoblasts and osteoclasts.[10] In bone metabolism, blockage of the reuptake of serotonin causes increased osteoclast differentiation and decreased osteoblast proliferation, which eventually results in decreased bone mass and bone mineral density.[16,17] Given the negative effects of SSRIs on bone metabolism, it is conceivable that they may affect osseointegration by the same mechanism. Nevertheless, there is only limited information in the current literature on the effects of SSRIs on osseointegration. This study aims to investigate the association between systemic intake of SSRIs and failure of osseointegration in patients rehabilitated with dental implants.

Materials and Methods

A retrospective cohort study was designed and implemented to investigate the association between the intake of SSRIs and the risk of osseointegration failure of dental implants. This study followed the Declaration of Helsinki on medical protocol and was approved by the regional Ethical Review Board. The study comprised all patients rehabilitated with dental implants between May 2012 and March 2017.

All patients enrolled in the study had undergone periodontal therapy—either phase I or both phases (I and II) —following their examination by the same specialist at the periodontology department. All patients were regular attendees of their recall sessions for which the intervals were set by their periodontologist. None of the patients included in this study showed clinical signs of active periodontal disease and were judged to be clinically healthy with regard to their periodontal conditions at the time of implant placement. Individuals with clinical signs of active periodontal disease at the intended time of surgery and patients who refused to undergo periodontal therapy before implant surgery were not included.

All implants were placed following a delayed protocol corresponding to type 3 or type 4 placement.[18] All patients were provided with solid-screw type implants with titanium plasma sprayed or sand-blasted acid-etched surfaces, which were placed according to the classic 2-stage protocol by 2 experienced surgeons (M.A.A. and A.S.) under local anesthesia.[19]

Patients were included in the study if they were presenting with no systemic conditions and not taking any medications other than SSRIs for psychiatric disorders. Only the patients with a complete set of information available for the investigated variables were included. Patients were excluded if they reported having a medical disorder known to impair bone metabolism, such as hyperthyroidism, hypothyroidism, hyperparathyroidism, vitamin D deficiency, osteomalacia, osteoporosis, Paget disease, diabetes or an oncologic condition, or a severe systemic condition corresponding to a physical status classification of American Society of Anesthesiologists (III or IV). Other exclusion criteria were history of radiotherapy to the head and neck region, pregnancy, alcoholism, and smoking. In addition, patients taking antihypertensive, immunosuppressive, antithrombotic, antiepileptic medication, corticosteroids, proton pump inhibitors, bisphosphonates or medications for asthma or high cholesterol levels were also not included in this study.

Patient's SSRI status was selected as the predictor variable for this study. An SSRI user was defined as a patient who reported taking any type of SSRI medication perioperatively. These medications comprised all verified types of SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) currently being prescribed in Turkey.

The outcome variable was osseointegration failure, which was defined as the condition leading to early implant removal before prosthetic loading due to implant mobility and advanced peri-implant bone loss. Other investigated variables included sex (female or male), age ($<$30, 30–60 or $>$60 years), and implant location (anterior, premolar or posterior—maxilla or mandible).

Patient records were collected and studied according to the inclusion/exclusion criteria. The statistical analysis was carried out using IBM-SPSS version 20.0 (IBM Corp, Armonk, NY). A P value $<$ .05 was used to assess the significance of all statistical analyses. Continuous variables that are normal distributed were presented with their mean $\pm$ standard deviation; other continuous variables were presented with their median (minimum-maximum), and categorical variables counts and percentages. The Student t test was used to determine the difference between the 2 independent groups when the parametric test assumptions were valid, and the Mann-Whitney U test was used as the nonparametric alternative to this test when the parametric test assumptions were not present. The χ^2 test was used to determine whether there was a statistically significant difference between the categorical variables, and the Fisher exact test was used when more than 20% of the boxes in crosstab had expected counts less than 5.

Both patient-level and implant level models were designed and implemented to assess the effects of SSRI intake on the success of osseointegration. The intake of SSRIs was selected as the exposure variable. To verify multicollinearity, a correlation matrix of predictor variables with a significant odds ratio (P value cut-off point of .5) was scanned to determine whether there was any correlation among the predictors.

Results

According to the eligibility criteria, a total of 2055 implants, 13 of whom failed before prosthetic loading, were included in the study. Implants were placed in 631 patients, 339 of which were women (53.7%) and 292 were men (46.3%) patients with median ages of 51 (18–84) and 50–57 ($\pm$14.18 years, range: 17–87 years), respectively. Of these 2055 implants 962 were placed in male patients and the remaining 1093 were placed in female patients.

All implants were placed with open-flap surgery; 564 (27.4%) implants were placed in the anterior region, 633 (30.8%) in the premolar region, and 858 (41.8%) in the molar region. Furthermore, 1016 (49.4%) implants were placed in the maxilla and the remaining 1039 (50.6%) implants were placed in the mandible. The number of implants per patient ranged from 1 to 14, with a median of 2 (range: 1–14). Median follow-

Downloaded from http://meridian.allenpress.com/joi/article-pdf/44/4/260/2035350/aaid-joi-d-17-00240.pdf by guest on 20 September 2021

Table 1

Cross-tabulation of selective serotonin reuptake inhibitor (SSRI) status vs failed cases at the patient level

	SSRI Status		
	SSRI User	No SSRI	Total
Failed			
Count	2	11	13
% within fail	15.4%	84.6%	100.0%
% within SSRI status	5.6%	1.8%	2.1%
Survived			
Count	34	584	618
% within fail	5.5%	94.5%	100.0%
% within SSRI status	94.4%	98.2%	97.9%
Total			
Count	36	595	631
% within fail	5.6%	94.3%	100.0%
% within SSRI status	100.0%	100.0%	100.0%

Table 3

Cross-tabulation of selective serotonin reuptake inhibitor (SSRI) status vs location at the implant level

	Location			
SSRI Status	Anterior	Premolar	Posterior	Total
SSRI user				
Count	26	37	46	109
% within SSRI status	23.9%	33.9%	42.2%	100.0%
% within location	4.6%	5.8%	5.4%	5.3%
Nonuser				
Count	538	596	812	1946
% within SSRI status	27.6%	30.6%	41.7%	100.0%
% within location	95.4%	94.2%	94.6%	94.7%
Total				
Count	564	633	858	2055
% within SSRI status	27.4%	30.8%	41.8%	100.0%
% within location	100.0%	100.0%	100.0%	100.0%

up time was 21.5 months (range: 4–56) for SSRI users and 23 months (range: 3–60) for nonusers ($P = .158$, Mann-Whitney U test).

The 36 SSRI users comprised 29 female and seven male patients. A total of 109 implants were placed in SSRI users and 1946 implants were placed in 595 nonusers. Of 36 SSRI users, 2 patients with a total of 8 implants had 1 failed implant, each; thus, the failure rate was 5.6% (2/36). Eleven nonuser patients, with a total of 60 implants, had 11 failed implants, 1 in each patient; thus, the failure rate for these patients was found to be 1.85% (11/595); although the difference between the 2 groups failed to reach statistical significance at both the patient and implant levels. ($P = .166$, $P = .149$, respectively; Fisher exact test) (Tables 1 and 2).

More implants were placed at a posterior region in both SSRI users and nonusers, but there was no statistically significant difference between the 2 groups in terms of implant location ($P = .633$; χ^2 test). More implants were placed in the mandible in SSRI users, and the difference was found to be statistically significant between the 2 groups ($P = .006$, χ^2 test) (Tables 3 through 5).

Women were 4.2 times more likely to be SSRI users than men, and this difference was found to be statistically significant ($P = .001$). Comparisons between SSRI users and nonusers in terms of age, sex, and fail status are given on Table 6. Patients younger than 60 years were less likely to be taking SSRIs than older patients ($\geq$60 years), but the only statistically significant result was found between middle-aged (30–60 years) and older patients ($\geq$60 years), where middle-aged patients were 61.7% less likely to be SSRI users ($P = .007$) (Table 7).

In terms of osseointegration failure, the odds of osseointegration failure were 3.123 times greater for SSRI users, compared with nonusers. Patients on SSRI medications were 3.005 times more likely to experience early implant

Table 2

Cross-tabulation of selective serotonin reuptake inhibitor (SSRI) status vs failed cases at the implant level

	SSRI Status		
	SSRI User	No SSRI	Total
Failed			
Count	2	11	13
% within fail	15.4%	84.6%	100.0%
% within SSRI status	1.8%	0.6%	0.6%
Survived			
Count	107	1935	2042
% within fail	5.2%	94.8%	100%
% within SSRI status	98.2%	99.4%	99.4%
Total			
Count	109	1946	2055
% within fail	5.3%	94.8%	100%
% within SSRI status	100%	100%	100%

Table 4

Cross-tabulation of selective serotonin reuptake inhibitor (SSRI) status vs jaw location at the implant level

	Jaw Location		
SSRI Status	Maxilla	Mandible	Total
SSRI user			
Count	40	69	109
% within SSRI status	36.7%	63.3%	100.0%
% within location jaw	3.9%	6.6%	5.3%
Nonuser			
Count	976	970	1946
% within SSRI status	50.2%	49.8%	100.0%
% within location jaw	96.1%	93.4%	94.7%
Total			
Count	1016	1039	2055
% within SSRI status	49.4%	50.6%	100.0%
% within location jaw	100.0%	100.0%	100.0%

Downloaded from http://meridian.allenpress.com/joi/article-pdf/44/4/260/2035350/aaid-joi-d-17-00240.pdf by guest on 20 September 2021

Table 5

The χ^2 tests for selective serotonin reuptake inhibitor status vs jaw location

	Value	*df**	Asymptomatic Significance (2-sided)	Exact Significance (2-sided)	Exact Significance (1-sided)	Point Probability
Pearson χ^2	7.478†	1	.006	.008	.004	
Continuity correction‡	6.949	1	.008			
Likelihood ratio	7.570	1	.006	.008	.004	
Fisher exact test				.008	.004	
Linear-by-linear association	7.474§	1	.006	.008	.004	.002
No. of valid cases	2055					

**df* indicates degrees of freedom.

†0 cells (0.0%) have expected count z. The minimum expected count is 53.89.

‡Computed only for a 2 × 2 table

§The standardized statistic is −2.734.

failure than nonusers (Table 8). However, the difference between the 2 groups was not statistically significant.

Discussion

Ther SSRIs are among the most commonly prescribed drugs that are used to treat major depressive disorder and several other psychiatric conditions, including posttraumatic stress disorder; generalized anxiety disorder; panic disorder; premenstrual dysphoric disorder; and some nonpsychiatric conditions, such as chronic pain, fibromyalgia, and postmenopausal vasomotor symptoms.[20] Although they are considered relatively safer than other antidepressant drugs, the effects of SSRIs have recently been subject to numerous studies.[21–23]

The results of studies investigating the effects of SSRI use on bone mineral density support the hypothesis that the serotonin transporters in bone cells have an important role in defining bone mass, structure, and strength.[24] Diem et al[17] reported that SSRI use in women was independently associated with increased rates of hip bone loss compared with nonusers. Similarly, Richards et al[25] found an association between SSRI use and lower bone mineral density that was related to increased clinical fracture risk. Consistent with the findings reported by Richards et al[25] and Diem et al,[17] an observational study conducted by Williams et al [26] demonstrated that SSRIs negatively impact bone mineral density independent of the effect of depression on bone health. Furthermore, results from a large cohort study revealed that the use of SSRIs was associated with a 2.25-fold increase in fracture risk.[27]

Today, the association between the intake of SSRIs and bone metabolism–related conditions remains a subject of interest for further studies. However, a recent review of the current literature fails to offer conclusive information on the effects of SSRIs on osseointegration of dental implants. In 2014, Wu and colleagues[13] conducted a retrospective cohort study to investigate the association between SSRIs and the risk of failures in osseointegrated implants. The study included a total of 916 dental implants in 490 patients (94 implants in 51 patients using SSRIs), and the failure rates were found to be 4.6% for SSRI nonusers and 10.6% for SSRI users. These authors concluded that SSRI intake was associated with an increased failure risk of osseointegrated implants.

In a recent cohort study, Chrcanovic et al[10] retrospectively evaluated the outcome of dental implant therapy in 300 patients (931 implants) and reported 12.5% overall failure rate for SSRI users and 3.3% for nonusers, translating into a statistically significant difference in the cumulative survival rates. However, multivariate analysis of their findings did not reveal a significant difference and suggested that the intake of SSRIs might not be associated with an increased risk of dental implant failure. Similar findings were observed in this study, which failed to identify a statistically significant difference between SSRI users and nonusers, although the intake of SSRIs was found to increase the odds of osseointegration failure of dental implants. It should be noted, however, that aforementioned studies comprised patients who lost implants in the long term, after prosthetic loading of the implants, and therefore comparatively

Table 6

Description of cases (n = 631): selective serotonin reuptake inhibitor (SSRI) users and nonusers

	SSRIs (Patients)	
Variables	Users	Nonusers
Age (y)		
≤30	2 (5.6%)	61 (10.3%)
30–60	17 (47.2%)	386 (64.9%)
≥60	17 (47.2%)	148 (24.9%)
Sex		
Female	29 (80.6%)	310 (52.1%)
Male	7 (19.4%)	285 (47.9%)
Fail status (patient)		
Failed	2 (5.6%)	11 (1.8%)
Survived	34 (94.4%)	584 (98.2%)
Fail status (implant)		
Failed	2 (5.6%)	11 (1.8%)
Survived	34 (94.4%)	584 (98.2%)

Downloaded from http://meridian.allenpress.com/joi/article-pdf/44/4/260/2035350/aaid-joi-d-17-00240.pdf by guest on 20 September 2021

Table 7

Odds ratios for study variables*

	B	SE	Wald	*df*	Significance	Exp (B)	95% CI for Exp (B) Lower	95% CI for Exp (B) Upper
SSRI user								
Sex (1)	1.435	.436	10.854	1	.001	4.201	1.789	9.868
Age range (30–60 years)	−1.254	.763	2.701	1	.100	.285	.064	1.273
Age range (>60 years)	−959	.356	7.236	1	.007	.383	.191	.771

*SE indicates standard error; *df*, degrees of freedom; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; Exp (B), exponentiation of the B coefficient; Sex (1), female patients.

investigated the overall outcome of dental implant therapy in SSRI users and nonusers. The authors of the present study believe evaluation of osseointegration success in the presence of SSRI intake could be objectively evaluated by excluding patients who lost implants after prosthetic loading or, in other words, osseointegration that was once successful. As the overall survival and success of implants are dependent on several factors, including oral hygiene and parafunctional habits, only patients who lost implants due to lack of osseointegration were included in this study.

Certain limitations of the present study need to be taken into consideration when interpreting its findings. Several factors that might have influenced the outcome, including the type, dose, and duration of SSRI therapy could not be studied in detail due to limitations inherent to the retrospective nature of the study. However, we believe its findings, obtained from a large sample, may provide a basis for future research investigating the effects of SSRI intake on osseointegration of dental implants. Furthermore, to the best of our knowledge, no study has previously reported on the success of osseointegration of dental implants in patients using SSRIs.

Conclusion

The findings of present study suggest that the perioperative intake of SSRIs leads to increase in the rate of osseointegration failure, although not reaching a statistically significant level. Further prospective, randomized clinical trials taking the type, dose, and duration of SSRI intake into account are required to validate outcomes of this study and better understand the effects of SSRI intake on the osseointegration process.

Table 8

Risk estimate for selective serotonin reuptake inhibitor (SSRI) users

	Value	95% Confidence Interval Lower	95% Confidence Interval Upper
Odds ratio for SSRI status (SSRI user/no SSRI)	3.123	.666	14.652
For cohort fail = failed	3.005	.692	13.051
For cohort fail = survived	.962	.888	1.042
No. of valid cases	631		

Abbreviation

SSRI: selective serotonin reuptake inhibitor

Note

There was no grant support for this study. Dr Baur is a paid consultant of Checkpoint Surgical LLC and Novartis Pharmaceuticals. Dr Altay has provided consultancy for Checkpoint Surgical LLC in 2014. Other authors declare that they have no conflicts of interest relevant to this article.

References

1. Sindel A, Dereci O, Hatipoglu M, et al. The effects of irrigation volume to the heat generation during implant surgery. *Med Oral Patol Oral Cir Bucal*. 2017;22:e506–e511.

2. Ali SA, Karthigeyan S, Deivanai M, Kumar A. Implant rehabilitation for atrophic maxilla: a review. *J Indian Prosthodont Soc*. 2014;14(3):196–207.

3. Chrcanovic BR, Albrektsson T, Wennerberg A. Reasons for failures of oral implants. *J Oral Rehabil*. 2014;41:443–476.

4. Hafezeqoran A, Koodaryan R. Effect of zirconia dental implant surfaces on bone integration: a systematic review and meta-analysis. *Biomed Res Int*. 2017;2017:9246721.

5. Apostu D, Lucaciu O, Lucaciu GD, et al. Systemic drugs that influence titanium implant osseointegration. *Drug Metab Rev*. 2017;49:92–104.

6. Albrektsson T. Direct bone anchorage of dental implants. *J Prosthet Dent*. 1983;50:255–61.

7. Bonsignore LA, Anderson JR, Lee Z, Goldberg VM, Greenfield EM. Adherent lipopolysaccharide inhibits the osseointegration of orthopedic implants by impairing osteoblast differentiation. *Bone*. 2013;52:93–101.

8. Sakka S, Baroudi K, Nassani MZ. Factors associated with early and late failure of dental implants. *J Investig Clin Dent*. 2012;3:258–261.

9. Al Subaie A, Emami E, Tamimi I, et al. Systemic administration of omeprazole interferes with bone healing and implant osseointegration: an in vivo study on rat tibiae. *J Clin Periodontol*. 2016;43:193–203.

10. Chrcanovic BR, Kisch J, Albrektsson T, Wennerberg A. Is the intake of selective serotonin reuptake inhibitors associated with an increased risk of dental implant failure? *Int J Oral Maxillofac Surg*. 2017;46:782–788.

11. Kellesarian SV, Abduljabbar T, Vohra F, et al. Role of local alendronate delivery on the osseointegration of implants: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg*. 2017;46:912–921.

12. Wu X, Al-Abedalla K, Eimar H, et al. Antihypertensive medications

Downloaded from http://meridian.allenpress.com/joi/article-pdf/44/4/260/2035350/aaid-joi-d-17-00240.pdf by guest on 20 September 2021

and the survival rate of osseointegrated dental implants: a cohort study. *Clin Implant Dent Relat Res*. 2016;18:1171–1182.

13. Wu X, Al-Abedalla K, Rastikerdar E, et al. Selective serotonin reuptake inhibitors and the risk of osseointegrated implant failure: a cohort study. *J Dent Res*. 2014;93:1054–1061.

14. Wu X, Al-Abedalla K, Abi-Nader S, et al. Proton pump inhibitors and the risk of osseointegrated dental implant failure: a cohort study. *Clin Implant Dent Relat Res*. 2017;19:222–232.

15. Tsapakis EM, Gamie Z, Tran GT, et al. The adverse skeletal effects of selective serotonin reuptake inhibitors. *Eur Psychiatry*. 2012;27:156–169.

16. Battaglino R, Fu J, Spate U, et al. Serotonin regulates osteoclast differentiation through its transporter. *J Bone Miner Res*. 2004;19:1420–1431.

17. Diem SJ, Blackwell TL, Stone KL, et al. Use of antidepressants and rates of hip bone loss in older women: the study of osteoporotic fractures. *Arch Intern Med*. 2007;167:1240–1245.

18. Hammerle CH, Chen ST, Wilson TG Jr. Consensus statements and recommended clinical procedures regarding the placement of implants in extraction sockets. *Int J Oral Maxillofac Implants*. 2004;19(suppl):26–28.

19. Becker W, Becker BE, Ricci A, et al. A prospective multicenter clinical trial comparing one- and two-stage titanium screw-shaped fixtures with one-stage plasma-sprayed solid-screw fixtures. *Clin Implant Dent Relat Res*. 2000;2:159–165.

20. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA*. 2015;314:1818–1831.

21. Chau K, Atkinson SA, Taylor VH. Are selective serotonin reuptake inhibitors a secondary cause of low bone density? *J Osteoporos*. 2012;2012:323061.

22. Gur TL, Kim DR, Epperson CN. Central nervous system effects of prenatal selective serotonin reuptake inhibitors: sensing the signal through the noise. *Psychopharmacology (Berl)*. 2013;227:567–582.

23. Jiang HY, Chen HZ, Hu XJ, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2015;13:42–50.e3.

24. Warden SJ, Hassett SM, Bond JL, et al. Psychotropic drugs have contrasting skeletal effects that are independent of their effects on physical activity levels. *Bone* 2010;46:985–992.

25. Richards JB, Papaioannou A, Adachi JD, et al. Effect of selective serotonin reuptake inhibitors on the risk of fracture. *Arch Intern Med*. 2007;167:188–194.

26. Williams LJ, Henry MJ, Berk M, et al. Selective serotonin reuptake inhibitor use and bone mineral density in women with a history of depression. *Int Clin Psychopharmacol*. 2008;23:84–87.

27. Ziere G, Dieleman JP, van der Cammen TJ, et al. Selective serotonin reuptake inhibiting antidepressants are associated with an increased risk of nonvertebral fractures. *J Clin Psychopharmacol*. 2008;28:411–417.

Downloaded from http://meridian.allenpress.com/joi/article-pdf/44/4/260/2035350/aaid-joi-d-17-00240.pdf by guest on 20 September 2021