

# Effect of Selective Serotonin Reuptake Inhibitors on Dental Implant Survival Rate in Patients with Neurological Disorders: A Systematic Review and Meta-analysis

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## ABSTRACT

**Aim and objective:** The aim and objective of the review was to evaluate how implant survival rate changes with the intake of selective serotonin reuptake inhibitors (SSRIs) in patients with neurological disorders.

**Materials and methods:** A systematic literature search was done in an electronic database (PubMed). In addition to this manual search of the references and gray literature was also done. Case reports, animal studies, literature reviews, and articles in non-English languages were not included. The Newcastle–Ottawa Scale was followed to assess the quality of the included studies. The meta-analysis was performed using statistical software Review Manager 5.03 and the outcome mean was measured by bivariate differential mean statistic with an intergroup estimate with a 95% confidence interval.

**Results:** A total of 344 articles were found in the PubMed database ( $n = 344$ ) during the literature search. Five studies were included in the qualitative and quantitative analysis after removing duplicates and screening of titles and abstracts. Two studies were excluded by using eligibility criteria for the review. A total of 988 implants survived in the test group and 4,585 implants survived in the control group among all the studies (odds ratio: 0.41, 95% CI: 0.30–0.55).  $p < 0.00001$  value from the analysis indicated a significant implant success rate in patients who were not taking any SSRI group of medications.

**Conclusion:** After evaluating the data from included studies, it can be concluded that patients taking the SSRI group of drugs for any neurological disorders had a higher chance of implant failures compared to the control group of patients.

**Keywords:** Dental implants, Neurological disorders, Selective serotonin reuptake inhibitors, Systematic review.

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## INTRODUCTION

Tooth loss has a major influence on oral health in geriatric patients. Inability to masticate food adequately due to tooth loss can lead to decreased nutrition and affect general health in edentulous subjects.<sup>1,2</sup> Dental implants are becoming one of the most predictable treatment approaches to combat edentulism.<sup>3,4</sup> Prevalence rate of neuropsychiatric and neurocognitive disorders (NDs) among individuals is increasing in recent times. Various neuropsychiatric symptoms, such as agitation, depression, apathy, delusions, and hallucinations, are highly prevalent in older adults associated with dementia or milder forms of cognitive impairment (CI). These symptoms can lead to a higher risk of functional decline.<sup>5–10</sup> In a recent cross-sectional analysis in US individuals, depression was considered to be the most common individual symptom in those with normal cognition (12%), chronic immunological and neurological diseases (30%), and mild dementia (25%), whereas apathy (42%) and agitation (41%) were prevalent with severe dementia.<sup>11</sup> Cognitive impairment is one of the natural outcomes due to the progression of Alzheimer's disease (AD) and other NDs. Studies based on clinical data report stated that dementia is directly related to the prevalence rate of AD and other NDs.<sup>12</sup> The Alzheimer's Association recently reported that there is an overall increased number of NDs in the last 25 years despite a decrease in the last 3–4 years.<sup>13</sup> Prosthodontic rehabilitation in patients suffering from neurological disorders needs specific approaches because these patients belong to a class with special needs. Progression of the neurological disease, the side-effects of the neurological

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medication on the oral cavity can modulate maintenance of oral hygiene and professional care during the recall system (follow-up) for this group of patients.<sup>14</sup> Implant survival rate is dependent upon the maintenance of oral hygiene in patients having dental implants and plaque index and other periodontal indices. Serotonin [5-hydroxytryptamine (5-HT)] is a monoamine neurotransmitter having a role in the well-being and happiness of any individual. Depression can be caused by lower levels of serotonin and blockage in its circulatory pathway.<sup>15</sup> Selective serotonin reuptake inhibitors (SSRIs)—such as Celexa, Paxil, Lexapro, Prozac, and Zoloft, have

become widely used antidepressants by inhibiting the reuptake of serotonin and increasing its level to treat depression.<sup>16</sup> Deranged metabolism of peri-implant bone in the healing period is one of the reasons for implant failures.<sup>17–19</sup> Various pharmacological therapies either directly or indirectly modulate bone metabolism.<sup>20</sup> The systematic review was aimed to evaluate how implant survival rate changes with the intake of SSRIs in patients suffering from neurological disorders.

## MATERIALS AND METHODS

The current systematic review has been prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.

Population, intervention, comparison, outcome, study design (PICOS) strategy of the review.

P: Patients with neurological disorders rehabilitated with dental implants.

I: Selective serotonin reuptake inhibitor group of drugs were used as a medication in this group of patients.

C: Patients not taking any SSRI group of medications for neurological disorders.

O: The implant survival rate.

S: Randomized controlled clinical trials, prospective studies, retrospective studies.

### Focused Question

"Do selective serotonin reuptake inhibitors show less implant survival rate in patients with neurological disorders compared to controlled patients who are not taking this type of medications?"

### Eligibility Criteria

#### Inclusion Criteria

- Studies evaluating the dental implant survival rate in patients with neurological disorders.
- Selective serotonin reuptake inhibitors must be used in patients as a medication for the disorders.
- Published articles in English languages.
- Randomized controlled clinical trials, prospective studies, retrospective studies.
- *In vivo* studies.

#### Exclusion Criteria

- Animal studies, *in vitro* studies, literature reviews.
- Case reports and case series.
- Articles in non-English languages.
- Studies with incomplete data.

### Search Methodology

A comprehensive search was done with no publication year limits by two independent reviewers (BB and RB). Following electronic database was searched for published studies—PubMed. In addition to this manual search of the references mentioned in the included studies and a manual search of gray literature was done. Following keywords were used during the literature search:

Population: # (edentulism) (Selective serotonin reuptake inhibitors) (SSRIs) (neurological disorders).

Intervention: # (dental implants) (implants) (prosthesis).

Outcome: # (implant failure) (survival rate) (marginal bone loss) (complications).

Boolean operators OR and AND were used with these above-mentioned keywords to conduct the literature search.

### Data Extraction

Two reviewers independently extracted data from the included studies. Disagreements were resolved through discussion. The inter-rater reliability was assessed using Cohen's kappa; values  $\leq 0$  indicated no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as perfect agreement. From each study, the following data were obtained—study design, publication year, country, sample size, sample gender, sample age, intervention, follow-up period, implant characteristics, and loading protocol.

### Quality of the Studies

The Newcastle–Ottawa Scale was followed to assess the quality of retrospective studies.<sup>21</sup> The methodological quality was based on selection, comparability, and outcome. The studies were classified according to the following criteria –

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

The level of evidence of our selected studies was also evaluated according to The Oxford 2011 Levels of Evidence.<sup>22</sup>

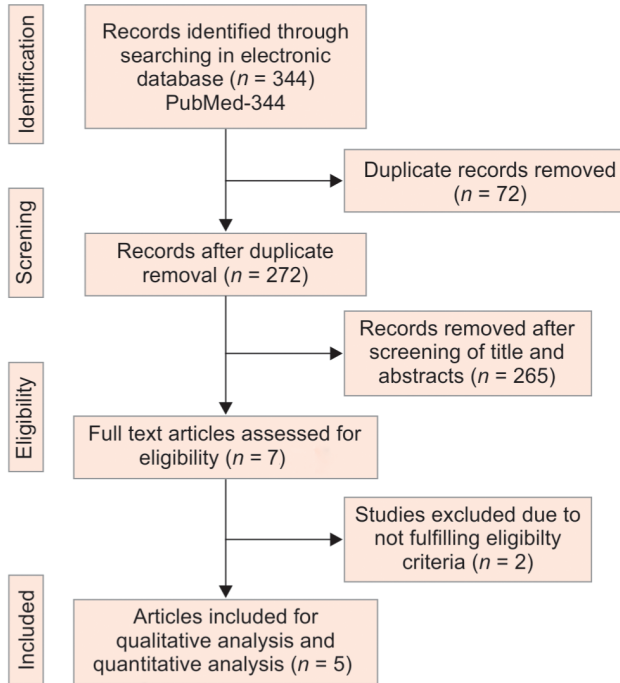
### Data Analysis

Software review manager 5.03 (RevMan, Nordic Cochrane Center, Copenhagen, Denmark) was used to assess the outcome variable implant survival rate. The outcome mean was measured by a bivariate differential mean statistic with an intergroup estimate with a 95% confidence interval. A fixed-effect model in accordance with Mantel–Haenszel statistics were used during the analysis.  $I^2$  test statistics were applied to evaluate the heterogeneity in-between the studies.  $p$  value  $< 0.05$  was considered statistically significant. Forest plots were generated for the outcome variables with a 95% confidence interval and effects of treatment with a significance level of 0.05.

## RESULTS

### Study Selection

Three hundred and forty-four articles were found in the PubMed database ( $n = 344$ ) through a literature search. In addition to this, a hand search of references mentioned in articles and gray literatures was done. Initial evaluation of titles and abstracts was performed by two independent reviewers (RB and BB) following the removal of duplicates. Seven articles were selected for full-text reading, two studies<sup>23,24</sup> were excluded and five studies<sup>25–29</sup> were included for qualitative and quantitative analysis (Flowchart 1). Excluded studies and the reason for exclusion have been elaborated in Table 1. Any disagreements between reviewers during the study selection process were solved by discussion and kappa statistics were used to assess inter-rater reliability.

**Flowchart 1:** Study selection process

**Table 1:** List of excluded studies

Excluded study	Reason for exclusion
1. Packer et al. (2008) <sup>23</sup>	Implant placement was done in patients suffering from Parkinson's disease, SSRI group of drugs were not used
2. Ekfeldt et al. (2013) <sup>24</sup>	Patients with various neurological disabilities were included in this study and rehabilitated with dental implants. No specific group of drugs was not given

### Quality Analysis

The quality of the included studies was determined by the Newcastle–Ottawa scale. Among the included studies all five studies obtained three stars in the selection domain, two stars in the comparability domain.<sup>25–29</sup> All the studies got three stars in the outcome domain except one study. Three stars in the selection domain were given as the intervention cohort was somewhat representative of accountable care organizations, the selection of non-intervention cohort was from the same community, and ascertainment of the intervention was from a secure record. Two stars were given in the comparability domain for three of the included studies as the study cohort was comparable to controls such as age, gender, and additional factors. Three stars in the outcome domain were given to four studies for the assessment using record linkage and for enough follow-up duration. Deepa et al.<sup>28</sup> did not mention the duration of follow-up in the study (2 stars in outcome/exposure domain). Qualities of the included studies are shown in Table 2. The level of evidence of our selected studies were of III and IV categories according to The Oxford 2011 Levels of Evidence.<sup>22</sup>

### Characteristics of the Included Studies

Characteristics of the included studies have been shown in Table 3. The common baseline characteristics of the included studies were study, study design, country, sample description, intervention,

**Table 2:** Newcastle-Ottawa scale for quality rating of included studies

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcome to occur	Adequacy of follow-up of cohorts
Wu et al. (2014) <sup>25</sup>	1 star	1 star	1 star	–	2 star	1 star	1 star	1 star
Chrcanovic et al. (2017) <sup>26</sup>	1 star	1 star	1 star	–	2 star	1 star	1 star	1 star
Altay et al. (2018) <sup>27</sup>	1 star	1 star	1 star	–	2 star	1 star	1 star	1 star
Deepa et al. (2018) <sup>28</sup>	1 star	1 star	1 star	–	2 star	1 star	–	1 star
Carr et al. (2019) <sup>29</sup>	1 star	1 star	1 star	–	2 star	1 star	1 star	1 star

Table 3: Characteristics of the included studies

Study	Study design	Country	Sample characteristics	Intervention	Follow-up
Wu et al. (2014) <sup>25</sup>	Retrospective	Canada	Sample size—490 patients Gender—male (198), female (292) Age—17–93 years averaging 56.4 ± 13.7 years	This retrospective cohort study was conducted on patients treated with dental implants from January 2007 to January 2013. A total number of 916 dental implants were placed in the included patients, out of which 94 implants were placed in SSRI users whereas 822 implants were in SSRI nonusers. Implant survival rate was calculated in both the groups during the follow-up period	3–67 months after completion of treatment
Chrcanovic et al. (2017) <sup>26</sup>	Retrospective	Sweden	Sample size—300 patients  Gender and age—145 men (mean age 55.9 ± 18.5, range 15.9–82.6 years), 155 women, mean age 56.0 ± 17.8 years, range 14.9–90.8 years) Sample size—631 patients	Patients treated with implant-supported prostheses between 1980 and 2014 at one specialist clinic (Clinic for Prosthodontics, Centre of Dental Specialist Care, Malmö, Sweden) were included in the study. Patients who took SSRI type of medication during the presurgery appointment that was scheduled 1–2 weeks before implant placement categorized as SSRI users The outcome variable in this study was implant failure. Signs and symptoms which led to implant removal, including lack or loss of osseointegration, implant mobility, continuous pain, advanced marginal bone loss, and refractory infection were considered as implant failure Patients who were treated with dental implants between May 2012 and March 2017 were included in the study	Within 6 months after the final implant-supported/retained restoration
Alltay et al. (2018) <sup>27</sup>	Retrospective	Turkey	Gender and age—female (339), 51 years (18–84 years) Male (292), 50.57 ± 14.18 years, range: 17–87 years	Inclusion criteria were patients with no systemic conditions and not taking any other medications except SSRI for psychiatric disorders. An SSRI-user was defined as a patient who reported taking any type of SSRI medication perioperatively Implant failure was the outcome variable in this study, which was considered as the condition leading to early implant removal before loading of the prosthesis due to implant mobility, and advanced peri-implant bone loss. 352 patients of both genders were included in this retrospective study who were rehabilitated with a total of 680 dental implants. Included patients were divided into two groups Group I (110 patients, 230 dental implants) were on SSRI users, while group II (242 patients, 450 dental implants) were non-SSRI users. Implant survival rate defined by analyzing the following factors fracture of implant, prosthesis screw fracture, and loosening of the screw, and features of peri-implantitis, such as radiolucency around implant apex and bone loss around implants	Median duration of follow-up was 21.5 (4–56) months for SSRI-users and 23 (3–60) months for non-users
Deepa et al. (2018) <sup>28</sup>	Retrospective	India	Sample size—352 patients  Gender—male (150), female (204)  Age—>50 years (95), <50 years (257) Sample size—5,456 patients	Patients who underwent their first implant placement in Mayo Clinic (Rochester, MN) from January 1, 1995, through December 31, 2014, were included in this study. Inclusion of patients was done after assessing their history of SSRI use, active SSRI use, and SSRI use during follow-up with implant failure. Cox proportional hazards regression models were used to check associations between demographic characteristics and SSRI use with implant failure, and outcomes were summarized with hazard ratios (HRs) and 95% confidence intervals (CIs)	Not mentioned
Carr et al. (2019) <sup>29</sup>	Retrospective	USA	Gender—female (3,143) [58%], male (2,313) [42%], Age—median age 53 years (interquartile range 40–64 years)		The median duration of follow-up was 5.3 years (interquartile range, 2.3–10.2 years)

and follow-up. Implant characteristics and prosthesis type used and their loading protocols of different studies have been shown in Table 4.

### Data Synthesis

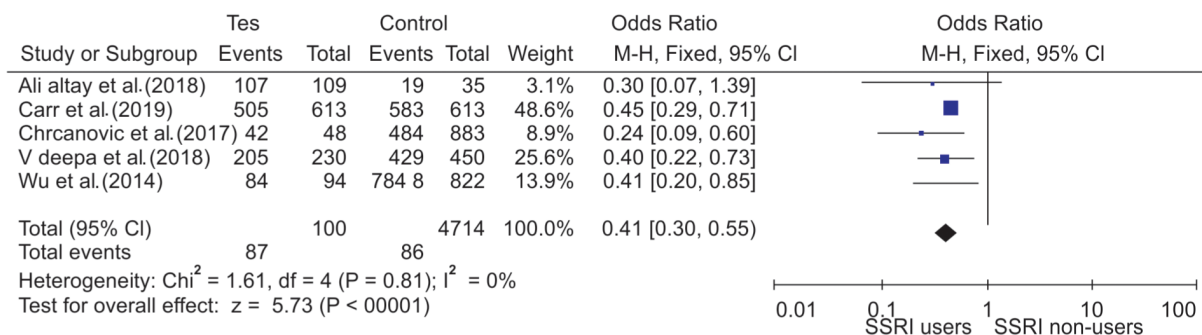
Meta-analysis was done of five included studies using the fixed-effect model. The dichotomous outcome variable of the analysis was implant success and the statistical unit for “implant success” was a dental implant.  $I^2$  test statistics was applied to check the heterogeneity ( $I^2$  value  $< 25\%$ —no heterogeneity,  $I^2$  value  $50\text{--}75\%$ —serious heterogeneity). A total of 1,094 implants were placed in patients suffering from neurological disorders or taking SSRI group of medications for these disorders and a total of 4,714 implants were placed in the control group. Of these 988 implants survived in the test group and 4,585 implants survived in the control group (odds ratio: 0.41, 95% CI: 0.30–0.55) (Fig. 1).  $p < 0.00001$  value from the analysis indicated a significant implant success rate in patients who were not taking any SSRI group of medications.  $I^2$  value was 0% in the analysis and  $\chi^2$  value was less than the degree of freedom. Both of the values signified low heterogeneity in-between the studies. The funnel plot (Fig. 2) showed the inclusion of both positive and negative trials as studies were distributed on both sides of the vertical line.

### DISCUSSION

Removable prosthesis manipulation demands well neuromuscular coordination from the edentulous patients. There is an important role of neuromuscular coordination in the functioning of dental prostheses. Neuropsychiatric/NDs can create many obstacles during the usage of removable dentures. The tremulous muscle movements and lessened muscle power characterizing Parkinson's disease or other movement disorders make the use of dentures very difficult. Therefore, it is better to rehabilitate these patients with some fixed alternatives. Furthermore, the anticholinergic agents and antidepressants used in these disorders can cause severe xerostomia, burning of dry and emaciated mucosa. Reduced salivation also causes more accumulation of plaque and other debris which can be responsible for postoperative periodontal problems in the case of fixed prosthesis.<sup>30</sup> There is insufficient scientific evidence regarding the use of implant-supported prosthesis in patients suffering from neurological conditions. Previously a report stated that implant-supported prosthesis showed a positive outcome on general health in three edentulous patients with Parkinson's disease.<sup>31</sup> Another study used magnets as an attachment system for an implant-supported overdenture.<sup>32</sup> Implant-retained complete dentures have also been used in patients with cerebral palsy.<sup>33</sup>

**Table 4:** Implant characteristics of the included studies

Study	Implant system	Number of implants placed	Number of subjects	Number of implants survived	Implant success rate	Loading protocol	Prosthesis type
Wu et al. (2014) <sup>25</sup>	Noble Biocare	Test group—94, control group—822	490 subjects	Test group—84, control group—784	Test group—89.36%, control group—95.38%	Conventional	Not mentioned
Chrcanovic et al. (2017) <sup>26</sup>	TiUnite, Nobel Biocare AB	Test group—48, control group—883	300 subjects	Test group—42, control group—854	Test group—87.5%, control group—96.71%	Conventional	Not mentioned
Altay et al. (2018) <sup>27</sup>	Titanium plasma-sprayed (TPS) or sand-blasted acid-etched surfaces	Test group—109, control group—1,946	631 subjects	Test group—107, control group—1,935	Test group—98.16%, control group—99.43%	Delayed	Not mentioned
Deepa et al. (2018) <sup>28</sup>	Noble Biocare	Test group—230, control group—450	352 subjects	Test group—205, control group—429	Test group—89.13%, control group—95.33%	Conventional	Not mentioned
Carr et al. (2019) <sup>29</sup>	Noble Biocare, TiUnite system	613	5,456 subjects	550	89.72%	Not mentioned	Not mentioned



**Fig. 1:** Forest plot showing a difference in implant survival rate



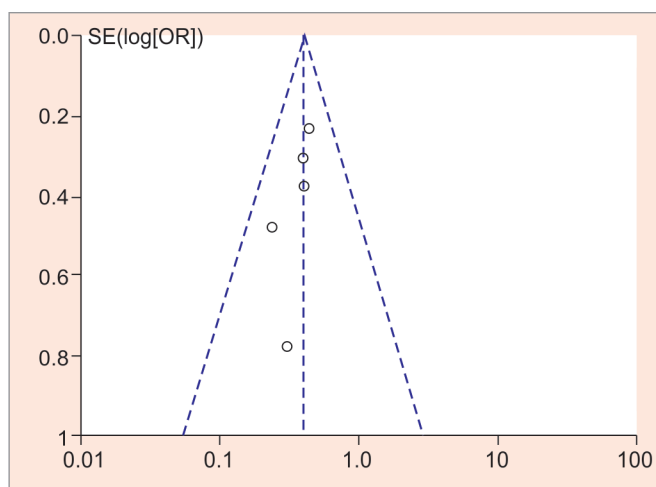


Fig. 2: Funnel plot for assessment of publication of bias

Implant survival rate or postoperative complications in patients with these disorders cannot be predicted depending on these case reports. Packer et al.<sup>23</sup> rehabilitated nine patients suffering from Parkinson's disease (with an age ranging from 54 to 77 years) with either implant-supported removable/fixed prosthesis. The implant survival rate was 85% and 81% in the maxilla and mandible compared to the success rate of 85–90% in the maxilla and 95% in the mandible in normal individuals. Various post-insertion problems were aroused in this study during the follow-up period like fracture of overdentures, difficulty in removing appliances due to dexterity problem, gingival hyperplasia under the attachment systems, etc. Ekfeldt et al.<sup>24</sup> used patients suffering from various neurological disorders like down syndrome, Asperger syndrome, mental retardation, cerebral palsy, etc., as a test group. These patients also showed complications like fracture of porcelain (due to extreme para-functional movements), fracture of an abutment, and implant due to self-destructive behavior. The overall implant failure rate was higher in these patients compared to healthy patients (12 out of 88 implants loosened). Overall, there are very few numbers of prospective and retrospective studies are available which evaluated implant survival rate in patients with neuropsychiatric/NDs. Selective serotonin reuptake inhibitors are one of the commonly used groups of drugs in these neurological disorders in recent times. Nam et al. showed in an animal study that serotonin has a significant role in reducing osteogenic differentiation and mineralization of cells. Serotonin also reduced the expression of osteoblast marker genes including Alpl (alkaline phosphatase), Sp7 (osterix), and Bglap (osteocalcin) and significantly inhibits  $\beta$ -TCP-induced bone regeneration.<sup>34</sup> RANKL-induced osteoclast-like cells generally show increased expression of serotonin receptor (5-HTT). Fluoxetine, an inhibitor of 5-HTT, showed reduced osteoclast differentiation in the result of et al. study. Results from the study showed that there may be a role for serotonin receptor (5-HTT) in osteoclast function and antidepressive agents may affect bone metabolism.<sup>35</sup> Another study demonstrated that SSRIs group of drugs have a detrimental effect on bone mineral density and trabecular microarchitecture.<sup>36</sup> Overall endocrine, autocrine/paracrine, and neuronal pathways are responsible for the effect of SSRIs on bone metabolism. Previous data from *in vitro*, *in vivo* studies, indicate that SSRIs harm the bone at the therapeutic dose levels used for the treatment of neurological disorders.<sup>37</sup>

Wu et al.<sup>25</sup> conducted a retrospective cohort study on patients rehabilitated with dental implants, in which there were two groups. One group of patients were SSRI users and the other group consisted of SSRI non-users. After the follow-up period implants with at least one of the following complications were defined as failures: pain on function; mobility; radiographic bone loss equivalent to one-half of the implant length; uncontrolled exudate; or implant no longer in the mouth. Overall failure rates were 4.6% for SSRI nonusers and 10.6% for SSRI users. The authors concluded that this result supports the anti-anabolic effect of SSRI on bone metabolism. Deepa et al.<sup>28</sup> similarly selected patients with a history of depression and SSRI medication in a retrospective study. Patients with dental implants were divided into two groups depending upon SSRI usage. The SSRI user group showed a greater number of implant failures than the other group. Chrcanovic et al.<sup>26</sup> also showed that the implant failure rate was 12.5% for SSRI users compared to 3.3% for non-users ( $p = 0.007$ ). Implant failure criteria were the same as in previous studies. In another study by Altay et al.,<sup>27</sup> 2 out of 36 SSRI-users had one failed implant each, the failure rate was 5.6%. Eleven non-users out of 595 individuals also had one failed implant each and the failure rate was 1.85% which was lower than the other group. Statistically, the odds of implant failure were 3.123 times greater for SSRI-users, compared to non-users. Overall the patients using SSRIs were found to be 3.005 times more prone to experience implant failure than the patients not using SSRIs. A retrospective review conducted by Carr et al.<sup>29</sup> evaluated the patients who were treated with at least one dental implant. The implant failure rate was assessed with their history of SSRI use, active SSRI use, and SSRI use during follow-up. Six different SSRI medications were assessed with implant failure, only those patients who had a history of sertraline use showed a greater failure rate. Active users of this medication or those patients taking this medication after implant placement did not show any significantly higher failure rate. The authors stated that these results indicate that long-term use of medications may attain a sufficient blood concentration of SSRI that may interfere with the bone healing dynamics. All of the included studies in this review and Flowchart 1 (analysis of studies on SSRI users and non-users) supporting the statement that implant failure rate is significantly higher in the case of patients taking the SSRI medications. No specific correlation was found in any of the included studies regarding the amount of bone loss surrounding implants and the dosage of the SSRI group of drugs. Limitations of the review were the non-availability of randomized controlled clinical trials, a smaller number of included studies that evaluated implant survival rate in patients with neurological disorders. Data from included studies in this review signify the fact that there is always a chance of increased implant failures in patients with neuropsychiatric/NDs or patients taking any medication for these disorders.

## CONCLUSION

Overall after evaluating the included studies it can be concluded that patients taking the SSRI group of drugs for any neurological disorders had a higher chance of implant failures due to its adverse effect on peri-implant bone remodeling and metabolism.

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