ABSTRACT
Neurologic disorders impede oral hygiene measures and routine clinical follow-up, along with the various drugs used may jeopardise oral health and the peri-implant tissue health. A total of 7 studies were considered eligible for the current systematic review. The overall estimated effect was categorized as significant where \( P < 0.05 \). Funnel plot was used to assess the publication bias within the studies. Difference in means was used as principal summary measure. \( P \) value <0.05 was considered as statistically significant. 1069 implants survived in test group and 4677 implants survived in control group (odds ratio: 2.58, 95% CI: 1.93-3.43) indicating significant success in patient without any disorders or taking medications for these disorders. Subgroup analysis was done to check the implant survival rate in patients taking selective serotonin reuptake inhibitors (SSRI) compared with SSRI non-users. Subgroup analysis showed that SSRI non-users had higher implant survival rate than patients taking SSRI (odds ratio: 2.45, 95% CI: 1.82-3.31). Serotonin significantly inhibits bone mineralization and osteoblast differentiation. The presence of any form of neuropsychiatric or neuromuscular disorders precludes proper oral hygiene and may contribute towards implant failure.

Keywords: Implant survival, implants and neurologic patients, neuropsychiatric disorders

INTRODUCTION
Rationale
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 patients.\(^1,2\) Dental implants are becoming one of the most predictable treatment modalities to combat edentulism.\(^3,4\) The 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 with dementia or milder forms of cognitive impairment. These symptoms can lead to a higher risk of functional decline.\(^5-10\)

In a recent cross-sectional analysis in US individuals, it was found that depression was the most common individual symptom in those with normal cognition (12%), cognitive impairment, not demented (30%), and mild dementia (25%), whereas apathy (42%) and agitation (41%) were most common in those with severe dementia.\(^11\) Cognitive impairment (CI) is one of the natural outcomes of the progression of Alzheimer’s disease (AD) and other NDs. Studies based on clinical data report showed an increase in the prevalence of AD and other NDs leading to dementia.\(^12\)

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. Prosthodontic rehabilitation in patients with neurological disorders needs a specific approach because these patients belong to a class with special needs. Progression of the neurological disease and the side effects of the neurological 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. The implant survival rate is dependent on the maintenance of oral hygiene in patients having dental implants and plaque index and other periodontal indices. Serotonin (5-hydroxytryptamine) is a monoamine neurotransmitter that modulates well-being and happiness in any individual. Depression can be caused by lower levels of serotonin and blockage in its circulatory pathway. 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 boost its levels to treat depression. Deranged metabolism of peri-implant bone in healing period is one of the reasons of implant failures. Various pharmacological therapies either directly or indirectly modulate bone metabolism.

Objectives
The purpose of this present systematic review (SR) is to evaluate how implant survival rate changes in patients suffering from neuropsychiatric or NDs or any medications used in these disorders.

METHODS

Protocol
The current SR has been prepared according to the equator guidelines (https://www.equator-network.org) and Prisma Statement (http://prisma-statement.org/). The study is registered with Prospero (https://www.crd.york.ac.uk/PROSPERO/) ID: CRD42020201520.

Eligibility criteria
The Patient, Intervention, Comparison, Outcome, and Study Questionnaire has been used to assess the eligibility of the studies.

Focus question: What is the effect of neurodegenerative, neurocognitive, and neuromuscular disorders on survival of dental implants?

Inclusion criteria
1. Studies evaluating the dental implant survival in patients with neurodegenerative, neurocognitive, neuromuscular disorders and patients on antidepressant drugs
2. Human studies
3. Randomized and nonrandomized clinical trials and observational studies.

Exclusion criteria
1. Isolated case reports
2. Animal studies
3. Inadequate follow-up.

Information sources
Electronic database: MEDLINE (PubMed), https://www.ncbi.nlm.nih.gov/pubmed; EMBASE, https://www.embase.com; and Cochrane database http://www.cochranelibrary.com.

Search terms
Population: # (Adults) or (elderly) or (edentulous) or (antidepressants) or (SSRIs) or (Parkinson) or (Alzheimer) or (psychiatric) or (neurocognitive) or (neurodegenerative) or (neuromuscular).

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

Comparator: # (healthy adults) or (normal adults) or (healthy individuals).

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

Study Design: # (Randomized clinical trial) or (nonrandomized trials) or (prospective) or (retrospective).

Filters
- Language – Not applied
- Species – Human
- Ages – middle aged, young, aged, and older
- Journal categories – Dental, oral surgery, implant dentistry, and dentistry
- Search dates – 1986–June 2020.

Study selection
Two reviewers (RNB and BB) screened all identifiable titles and abstracts independently. In addition, the reference lists of the subsequently selected abstracts and the bibliographies of the SRs, human randomized and nonrandomized controlled trials (RCTs), and prospective and retrospective cohort studies were searched manually. For studies appearing to meet the inclusion criteria, or for which insufficient data in the title and abstract were available, the full text was obtained. Disagreements were solved through discussion between the reviewers. The inter-rater reliability was assessed using
Cohen’s kappa; values ≤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. Regarding the translation of studies from other languages, two independent translators blinded to the outcome translated the entire manuscript into English. Disagreements were again sought with discussion, and kappa statistics was used to assess inter-rater reliability. Finally, the full-text evaluation of the remaining publications was done using the above-listed inclusion and exclusion criteria.

Data extraction
Two reviewers (RNB and BB) independently extracted data from the included studies. Disagreements were again resolved through discussion. With respect to the listed question of our SR, data were sought for predictor variables, i.e., dental implants in patients with neurodegenerative, neurocognitive, neuromuscular disorders and patients taking antidepressants. Both reviewers evaluated the primary outcome of the study and the survival of dental implants. The secondary outcomes assessed were implant-related complications.

Quality of the studies
The quality assessment of the selected studies was executed by the Newcastle–Ottawa Scale.

Stars were awarded such that the highest quality studies were awarded up to nine stars. The oxford level of evidence 2011 was used to assess the strength of each study. The levels of evidence of our selected studies were of III and IV categories.

The Oxford 2011 Levels of Evidence

| Level category of evidence | Description |
|-----------------------------|-------------|
| I SR (with homogeneity) of RCT | Individual RCT. |
| II SR (with homogeneity) of cohort studies | Individual cohort study (including low-quality RCT, for example, <80% follow-up) |
| III SR (with homogeneity) of case–control studies | Individual case–control study. |
| IV Case series and poor-quality cohort and case–control studies | |
| V Expert opinion without explicit critical appraisal, or based on physiology, bench research, or first principles. | |

Statistical analysis
Statistical software RevMan (Review Manager [Computer program], version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for meta-analysis. The overall estimated effect was categorized as significant where \( P < 0.05 \). Chi-square test and \( I^2 \) were used to measure heterogeneity among the studies. A value of <25% indicated a lack of heterogeneity. A funnel plot was used to assess the publication bias within the studies. Difference in means was used as a principal summary measure. Z-test was used to measure the statistical significance. \( P < 0.05 \) was considered statistically significant.

RESULTS

Study selection
The literature search yielded a total of 344 articles from PubMed electronic database (n = 344). In addition to this, a hand search of references mentioned in articles was done. After removal of the duplicates (n = 72), initial screening of titles and abstracts was performed by two independent reviewers (RB and BB). Eighteen articles were selected for full-text reading, seven studies were included for qualitative and quantitative analysis, and eleven studies were excluded [Figure 1]. Any disagreements between reviewers during study selection process were solved by discussion. Kappa statistics was used to assess the inter-rater reliability among the reviewers. A coefficient value between 0.61 and 0.80 indicated substantial agreement. Non-English articles were translated by two independent translators, and Cohen’s kappa was used to address the reliability. A kappa value of 1.00 indicated definitive agreement.

Study characteristics
The characteristics of the included studies are shown in Table 1. The common baseline characteristics of the included
| Study | Study design | Country | Sample characteristics | Intervention | Follow-up |
|-------|--------------|---------|------------------------|--------------|-----------|
| Packer et al. (2009)[27] | Prospective | United Kingdom | Sample size - nine individuals<br>Gender - male (9), female (0)<br>Age range - 54-77 years (mean 63 years) | Nine patients who were definitively diagnosed suffering from Parkinson’s disease were included in the study and implant placement was done. “The DIDL assessment” assessed on the 3rd and 12th month after placing provisional final prosthesis. DIDL composed of two components - The OH-QoL inventory and the SROH and functional status. | Third and 12th month after completion of treatment |
| Ekfeldt et al. (2013)[28] | Prospective | Norway | Sample size: Twenty-seven individuals<br>Gender - Male (14), female (13)<br>Age - 19 to 80 years (mean - 46 years) | Patients with various neurological disabilities were included in the study. After completion of implant placement in all the patients, five patients died during observation period. Twelve implant-supported crowns and 17 implant-supported fixed prostheses were fabricated. Implant survival rate, bleeding on probing was measured during 5-10 years follow up. | 5-10 years |
| Wu et al. (2014)[29] | Retrospective | Canada | Sample size - Four hundred and ninety patients<br>Gender - male (198), female (292)<br>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 calculated in both the groups during the follow-up period. | 3-67 months after completion of treatment |
| Chrcanovic et al. (2017)[30] | Retrospective | Sweden | Sample size - Three hundred patients<br>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) | Patients treated with implant supported prostheses in between 1980 and 2014 at one specialist clinic (clinic for prosthodontics, center of dental specialist care, Malmocastle, Sweden) were included in the study. Patients who took SSRI type of medication during the presurgery appointment that was scheduled 1-2 weeks prior to 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. | Within 6 months after the final implant-supported/retained restoration |
| Alty et al. (2018)[31] | Retrospective | Turkey | Sample size - Six hundred and thirty-one patients<br>Gender and age - female (339), 51 years (18-84 years)<br>Male (292), 50.57±14.18 years, range: 17-97 years | Patients who were treated with dental implants between May 2012 and March 2017 were included in the study. 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. Osseointegration failure was the outcome variable in this study, which was considered as the condition leading to early implant removal before prosthetic loading due to implant mobility and advanced peri-implant bone loss. | Median duration of follow-up was 21.5 (4-56) months for SSRI users and 23 (3-60) months for nonusers |
| Deepa et al. (2018)[32] | Retrospective | India | Sample size - Three hundred and fifty-two patients<br>Gender - male (150), female (204)<br>Age - >50 years (95), <50 years (257) | Three hundred and fifty-two 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) was on SSRI users, while Group II (242 patients, 450 dental implants) was non-SSRI users. Implant survival rate defined by analyzing the following factors fracture of implant, prosthesis screw fracture, and loosening of screw, and features of peri-implantitis, such as radiolucency around implant apex and bone loss around implants. | Not mentioned |

Contd...
Table 1: Contd...

| Study              | Study design | Country | Sample size | Sample characteristics | Intervention                                                                 | Follow-up                              |
|--------------------|--------------|---------|-------------|------------------------|------------------------------------------------------------------------------|----------------------------------------|
| Carr et al., (2019) | Retrospective | USA     | 5456        | Age - median age 53 years (interquartile range 40-64 years)          | Patients who underwent 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 HRs and 95% CIs | The median duration of follow-up was 5.3 years (interquartile range, 2.3-10.2 years) |

DIOL: Dental impact on daily living, OH-QoL: Oral health quality of life, SROH: Self-reported assessment of oral health, BOP: Bleeding on probing, SSRI: Selective serotonin reuptake inhibitor, HRs: Hazard ratios, CIs: Confidence intervals

Table 2: Implant characteristics of the included studies

| Study              | Implant system | Number of implants placed | Number of implants survived | Loading protocol | Prosthesis type                                      |
|--------------------|----------------|---------------------------|----------------------------|------------------|-----------------------------------------------------|
| Packer et al., (2009) | Astra-Tech implants | 28                        | 23                         | Conventional     | Implant-supported/retained fixed prosthesis, single crown, overdentures |
| Ekfeldt et al., (2013) | Nobel Biocare AB | 70                        | 58                         | Conventional     | Implant-supported/retained fixed prosthesis, single crown, overdentures |
| Wu et al., (2014) | Nobel Biocare | Test group - 94, control group - 822 | Test group - 84, control group - 784 | Conventional     | Not mentioned                                        |
| Chrcanovic et al., (2017) | TiUnite, Nobel Biocare AB | Test group - 48, control group - 883 | Test group - 42, control group - 854 | Conventional     | Not mentioned                                        |
| Altay et al., (2018) | TPS or sand-blasted acid-etched surfaces | Test group - 109, control group - 1946 | Test group - 107, control group - 1935 | Delayed          | Not mentioned                                        |
| Deepa et al., (2018) | Nobel Biocare | Test group - 230, control group - 450 | Test group - 205, control group - 429 | Conventional     | Not mentioned                                        |
| Carr et al., (2019) | Nobel Biocare, TiUnite system | 613                        | 550                        | Not mentioned    | Not mentioned                                        |

TPS: Titanium plasma sprayed

studies were study, study design, country, sample description, intervention, and follow-up. Implant characteristics and prosthesis type used in different studies are tabulated in Table 2.

Quality analysis

The quality of the included studies was determined by the Newcastle–Ottawa Scale. Among the included studies, seven studies were of good quality according to predetermined mentioned criteria. All the studies selected the nonexposed cohort from the same source. Deepa et al., (2018) did not mention about the duration of follow-up in the study (two stars in outcome/exposure domain). The qualities of the included studies are shown in Table 3.

Data synthesis

Meta-analysis was done of seven included studies using fixed-effect model. To identify study heterogeneity, $I^2$ test statistics was applied ($I^2 < 25%$ – no heterogeneity, $I^2$ value 50%–75% – serious heterogeneity), and $P < 0.05$ was considered significant statistically. Forest plots were produced for the outcome variables with 95% confidence interval and overall treatment effects and subgroup effects at a significance level of 0.05. Funnel plot asymmetry was checked to report any publication bias. A total of 1192 implants were placed in patients suffering from neuropsychiatric/NDs or taking any medications for these disorders, and a total of 4812 implants were placed in the control group. Of these, 1069 implants survived in the test group and 4677 implants survived in the control group (odds ratio: 2.58, 95% CI: 1.93–3.43) indicating significant success in patients without any disorders or taking medications for these disorders. $I^2$ value was 0% in this analysis, and Chi-square value was less than degree of freedom showing low heterogeneity in this study (Figure 2). Subgroup analysis was done to check the implant survival rate in patients taking SSRIs compared with SSRI nonusers. Subgroup analysis (Figure 3) showed that SSRI nonusers had a higher implant survival rate than patients taking SSRI (odds ratio: 2.45, 95% CI: 1.82–3.31). Tests for
funnel plot asymmetry [Figure 4] showing both positive and negative studies were included in this study as studies are present on both sides of the vertical line.

**DISCUSSION**

Removable prosthesis manipulation demands a well neuromuscular coordination from the edentulous patients. There is an important role of neuromuscular coordination in functioning of dental prosthesis. It is therefore obvious that neuropsychiatric/NDs can create severe obstacles to the serviceability of the removable dentures. The tremulous muscle motion and lessened muscular power characterizing Parkinson’s disease or other movement disorders render 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 and 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 case of fixed prosthesis.\(^{[34]}\) There is little scientific evidence till now for the use of implants in neurological conditions. Previously, one report based on three cases of edentulous people with Parkinson’s disease rehabilitated with implant-supported dentures showed a positive impact on general health of patients.\(^{[35]}\) Another study used magnets as an attachment system for an implant-supported overdenture.\(^{[36]}\) Implant-retained complete dentures have also been used in patients with cerebral palsy.\(^{[37]}\) Implant survival rate or postoperative complications in patients with these disorders cannot be predicted depending on these case reports. There are a very few number of prospective and retrospective studies available which evaluated implant survival rate in patients with neuropsychiatric/NDs. SSRIs are one of the commonly used groups of drugs in these neurological disorders in recent times. Nam et al.\(^{[38]}\) 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 β-tricalcium phosphate-induced bone regeneration.\(^{[39]}\) Receptor activator of nuclear factor-kappa B ligand-induced osteoclast-like cells generally shows increased expression of serotonin receptor (5-HTT). Fluoxetine, an inhibitor of 5-HTT, showed reduced osteoclast differentiation in the result of the study. Results from the study showed that there may be a role for 5-HTT in osteoclast function and antidepressive agents may affect bone metabolism.\(^{[39]}\) Another study demonstrated that the SSRI group of drugs has a detrimental effect on
Bone mineral density and trabecular microarchitecture.\textsuperscript{[40]} Endocrine, autocrine/paracrine, and neuronal pathways are responsible for the effect of SSRIs on bone metabolism. Previous data from \textit{in vitro}, \textit{in vivo} studies indicate that SSRIs have a negative effect on the bone at the therapeutic dose levels used for the treatment of neurological disorders.\textsuperscript{[41]}

Wu \textit{et al.}\textsuperscript{[29]} conducted a retrospective cohort study on patients rehabilitated with dental implants, in which there were two groups. One group of patients was SSRI users, and the other group consisted of SSRI nonusers. After 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 antianabolic effect of SSRI on bone metabolism. Deepa \textit{et al.}\textsuperscript{[32]} 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 on SSRI usage. SSRI user group showed a greater number of implant failures than the other group. Chrcanovic \textit{et al.}\textsuperscript{[30]} also showed that implant failure rate was 12.5\% for SSRI users compared to 3.3\% for nonusers ($P = 0.007$). Implant failure criteria were the same as in previous studies. In another study by Altay \textit{et al.}\textsuperscript{[31]} 2 out of 36 SSRI users had one failed implant each, and the failure rate was 5.6\%. Eleven nonusers 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 nonusers. Overall, the patients using SSRI s 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 \textit{et al.}\textsuperscript{[33]} evaluated all patients who received at least 1 dental implant placed in their mouth. 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, and 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 long-term use of medications may lead to a sufficient blood
concentration of SSRI that may interfere with bone healing dynamics. All the studies included support the fact.

Packer et al.\textsuperscript{[25]} rehabilitated nine patients with Parkinson’s disease (with an age range of 54–77 years) with either implant-supported fixed/prosthesis. The implant success 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 postinsertion problems aroused in this study during follow-up period such as fracture of overdentures, difficulty in removing appliances due to dexterity problem, and gingival hyperplasia under the attachment systems. Efkeldt et al.\textsuperscript{[28]} used patients suffering from various neurological disorders such as down syndrome, Asperger syndrome, mental retardation, and cerebral palsy as a test group. These patients also showed complications such as fracture of porcelain (due to extreme parafunctional movements), fracture of 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 loosed).

Limitations
The limitations of this study were as follows: nonavailability of randomized controlled clinical trials and a smaller number of prospective and retrospective studies on influence of neuropsychiatric/NDs.

Generalizability
Overall 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
Patients with neuropsychiatric, neurocognitive and neurodegenerative disorders are at an increased risk for implant failures.

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Conflicts of interest
There are no conflicts of interest.

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