Evidence Brief: Impact of Mental Health Conditions on Peri-implantitis and Dental Implant Failure

Supplemental Materials

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APPENDIX A: SEARCH STRATEGY

SYSTEMATIC REVIEWS

1. Search for current systematic reviews (limited to last 7 years) **Date Searched: 03-17-22**			
A. Bibliographic Databases:	**#**	**Search Statement**	**Results**
MEDLINE: Systematic Reviews Ovid MEDLINE(R) ALL 1946 to March 16, 2022	1	Dental Restoration Failure/	8894
	2	Dental Implantation, Endosseous/ae	1455
	3	Dental Implants/ae	2346
	4	(peri?implantitis or (implant adj1 (loss* or fail*))).mp.	7290
	5	exp Mental Disorders/	1356477
	6	exp Behavioral Symptoms/	413089
	7	exp Serotonin Uptake Inhibitors/	44543
	8	exp Substance-Related Disorders/	298237
	9	(depression or anxiety or ptsd or post?traumatic stress or bipolar or schizophrenia).mp.	819042
	10	1 or 2 or 3 or 4	17040
	11	5 or 6 or 7 or 8 or 9	2006410
	12	10 and 11	110
	13	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.	506300
	14	12 and 13	18
CDSR: Protocols and Reviews	1	Dental Restoration Failure.kw.	14
	2	Endosseous Dental Implantation.kw.	0

EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 16, 2022	3	Dental Implants.kw.	11
	4	(peri?implantitis or (implant adj1 (loss* or fail*))).mp.	38
	5	Mental Disorders.kw.	70
	6	Behavioral Symptoms.kw.	2
	7	Serotonin Uptake Inhibitors.kw.	54
	8	Substance-Related Disorders.kw.	34
	9	(depression or anxiety or ptsd or post?traumatic stress or bipolar or schizophrenia).mp.	3224
	10	1 or 2 or 3 or 4	50
	11	5 or 6 or 7 or 8 or 9	3242
	12	10 and 11	10

1. Search for current systematic reviews (limited to last 7 years) Date Searched: 03-17-22		
B. Non-bibliographic databases	**Evidence**	**Results**
AHRQ: evidence reports, technology assessments, U.S Preventative Services Task Force Evidence Synthesis	http://www.ahrq.gov/research/findings/evidence-based-reports/search.html Search: dental implants; peri-implantitis; mental health; substance use	0
CADTH	https://www.cadth.ca Search: dental implants; peri-implantitis; mental health; substance use	0
ECRI Institute	https://guidelines.ecri.org/ Search: dental implants; peri-implantitis	0
HTA: Health Technology Assessments (UP TO 2016)	http://www.ohsu.edu/xd/education/library/ See CDSR search above	0
NHS Evidence	http://www.evidence.nhs.uk/default.aspx Search: dental implants; peri-implantitis; mental health; substance use	0
EPPI-Centre	http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=62 Use browser search function [CNTL + F] for keyword search Search: dental implants; peri-implantitis; mental health; substance use	0
NLM	http://www.ncbi.nlm.nih.gov/books Search: dental implants; peri-implantitis; mental health; substance use Section 5: Pain, Mental Illness, Substance Use, and Oral Health. *Oral Health in America: Advances and Challenges* [Internet]. Bethesda (MD): National Institute of Dental and Craniofacial Research. 2021 Dec. https://www.ncbi.nlm.nih.gov/books/NBK578300/	1

VA Products - VATAP, PBM and HSR&D publications	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/ Search: dental implants; peri-implantitis; mental health; substance use	0

2. Search for systematic reviews currently under development (includes forthcoming reviews & protocols) **Date Searched: 03-17-22**		
D. Under development:	**Evidence:**	**Results**
AHRQ topics in development (EPC Status Report)	Email Charli Armstrong Charlotte.Armstrong1@va.gov	0
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Caio Silva, Marcelo Santos, João Monteiro, Suzana Carneiro. Is there an association between antidepressant use and complications of dental implants? A systematic review. PROSPERO 2019 CRD42019119995 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019119995	1

PRIMARY STUDIES

3. Search for primary literature **Date searched: 03-17-22**		
MEDLINE [Ovid MEDLINE(R) ALL 1946 to March 16, 2022]		
#	**Search Statement**	**Results**
1	Dental Restoration Failure/	8894
2	Dental Implantation, Endosseous/ae	1455
3	Dental Implants/ae	2346
4	(peri?implantitis or (implant adj1 (loss* or fail*))).mp.	7290
5	exp Mental Disorders/	1356477
6	exp Behavioral Symptoms/	413089
7	exp Serotonin Uptake Inhibitors/	44543
8	exp Substance-Related Disorders/	298237
9	(depression or anxiety or ptsd or post?traumatic stress or bipolar or schizophrenia).mp.	819042
10	1 or 2 or 3 or 4	17040
11	5 or 6 or 7 or 8 or 9	2006410
12	10 and 11	110
CINAHL		
#	**Search Statement**	**Results**
1	(MH "Dental Restoration, Permanent+") OR (MH "Dental Restoration, Temporary")	9522
2	(MH "Dental Implantation+/AE")	908
3	(MH "Dental Implants/AE")	737
4	TX (peri?implantitis or (implant N1 (loss* or fail*)))	4156
5	(MH "Mental Disorders+")	622744
6	(MH "Behavioral Symptoms+")	642851
7	(MH "Serotonin Uptake Inhibitors+")	12310

8	(MH "Substance Use Disorders+")	178806
9	TX (depression or anxiety or ptsd or post?traumatic stress or bipolar or schizophrenia)	465498
10	1 or 2 or 3 or 4	14244
11	5 or 6 or 7 or 8 or 9	1093874
12	10 and 11	638
PsycINFO [APA PsycInfo 1806 to March Week 2 2022]		
#	**Search Statement**	**Results**
1	dental restoration failure.mp.	2
2	dental implantation.mp.	9
3	dental implants.mp.	28
4	(peri?implantitis or (implant adj1 (loss* or fail*))).mp.	6
5	exp Mental Disorders/	924768
6	exp Behavior Disorders/	61373
7	exp Serotonin Reuptake Inhibitors/	12883
8	exp "Substance Use Disorder"/	138272
9	(depression or anxiety or ptsd or post?traumatic stress or bipolar or schizophrenia).mp.	668531
10	1 or 2 or 3 or 4	42
11	5 or 6 or 7 or 8 or 9	1223115
12	10 and 11	8

APPENDIX B: EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review.

Citation	Exclude Reason
SSRIs linked to implant failure. *Dental Nursing.* 2014;10(10):556-556.	E7
ANTIDEPRESSANTS MAY BE LINKED TO IMPLANT FAILURE RISK, RESEARCHERS REPORT. *Journal of the American Dental Association (JADA).* 2014;145(10):1016-1016.	E7
SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND IMPLANT FAILURE. *Explorer (08947929).* 2019;45(7):3-3.	E10
Medication impact on dental implant failure. *Dental Abstracts.* 2019;64(4):273-274.	E10
Anitua E, Orive G, Aguirre JJ, Ardanza B, Andía I. 5-year clinical experience with BTI dental implants: risk factors for implant failure. *Journal of Clinical Periodontology.* 2008;35(8):724-732.	E2
Brignardello-Petersen R. LOW RATE OF EARLY IMPLANT FAILURE IS CONFIRMED, BUT SMOKING AND ANTIDEPRESSANTS ARE SHOWN TO BE RISK FACTORS. *Journal of the American Dental Association (JADA).* 2017;148(4):e2-e2.	E7
Chappuis V, Avila-Ortiz G, Araujo MG, Monje A. Medication-related dental implant failure: Systematic review and meta-analysis. *Clinical Oral Implants Research.* 2018;29 Suppl 16:55-68.	E8
Chatzopoulos GS, Koidou VP, Lunos S, Wolff LF. Implant and root canal treatment: Survival rates and factors associated with treatment outcome. *Journal of Dentistry.* 2018;71:61-66.	E8
Cheng LL. Systemic Intake of Proton Pump Inhibitors and Selective Serotonin Reuptake Inhibitors May Be Associated With Implant Failure. *The Journal of Evidencebased Dental Practice.* 2020;20(3):101466.	E7
Derks J, Håkansson J, Wennström JL, Tomasi C, Larsson M, Berglundh T. Effectiveness of implant therapy analyzed in a Swedish population: early and late implant loss. *Journal of Dental Research.* 2015;94:44S-51S.	E2
Gupta B, Acharya A, Pelekos G, Gopalakrishnan D, Kolokythas A. Selective serotonin reuptake inhibitors and dental implant failure-A significant concern in elders? *Gerodontology.* 2017;34(4):505-507.	E7
Güven SŞ, Cabbar F, Güler N. Local and systemic factors associated with marginal bone loss around dental implants: a retrospective clinical study. *Quintessence International.* 2020;51(2):128-141.	E2
Jing H, Baohong Z, Chunfu D, Dehao S, Chong Z. Assessment of Implant Cumulative Survival Rates in Sites with Different Bone Density and Related Prognostic Factors: An 8-Year Retrospective Study of 2,684 Implants. *International Journal of Oral & Maxillofacial Implants.* 2015;30(2):360-371.	E2
Jung RE, Al-Nawas B, Araujo M, et al. Group 1 ITI Consensus Report: The influence of implant length and design and medications on clinical and patient-reported outcomes. *Clinical Oral Implants Research.* 2018;29 Suppl 16:69-77.	E7

Citation	Exclude Reason
Kim IH, Kuk TS, Park SY, Choi YS, Kim HJ, Seo KS. Prognosis following dental implant treatment under general anesthesia in patients with special needs. *Journal of Dental Anesthesia & Pain Medicine.* 2017;17(3):205-213.	E2
Koldsland OC, Scheie AA, Aass AM. Prevalence of implant loss and the influence of associated factors. *Journal of Periodontology.* 2009;80(7):1069-1075.	E2
Liddelow G, Klineberg I. Patient-related risk factors for implant therapy. A critique of pertinent literature. *Australian Dental Journal.* 2011;56(4):417-426.	E2
Marchio V, Derchi G, Cinquini C, et al. Tissue level implants in healthy versus medically compromised patients: a cohort comparative study. *Minerva Stomatologica.* 2020;69(5):295-301.	E2
McDermott NE, Chuang S, Woo VV, Dodson TB. Complications of dental implants: identification, frequency, and associated risk factors. *International Journal of Oral & Maxillofacial Implants.* 2003;18(6):848-855.	E2
Moy PK, Medina D, Shetty V, Aghaloo TL. Dental implant failure rates and associated risk factors. *International Journal of Oral & Maxillofacial Implants.* 2005;20(4):569-577.	E2
Mundt T, Mack F, Schwahn C, Biffar R. Private practice results of screw-type tapered implants: survival and evaluation of risk factors. *International Journal of Oral & Maxillofacial Implants.* 2006;21(4):607-614.	E2
Paquette DW, Brodala N, Williams RC. Risk factors for endosseous dental implant failure. *Dental Clinics of North America.* 2006;50(3):361-374.	E2
Roos-Jansåker A, Renvert H, Lindahl C, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. *Journal of Clinical Periodontology.* 2006;33(4):296-301.	E4
Schimmel M, Srinivasan M, McKenna G, Muller F. Effect of advanced age and/or systemic medical conditions on dental implant survival: A systematic review and meta-analysis. *Clinical Oral Implants Research.* 2018;29 Suppl 16:311-330.	E7
Smith RA, Berger R, Dodson TB. Risk factors associated with dental implants in healthy and medically compromised patients. *International Journal of Oral & Maxillofacial Implants.* 1992;7(3):367-372.	E4
Snider J. Antidepressants may be linked to implant failure risk, researchers report. *Journal of the American Dental Association.* 2014;145(10):1016.	Duplicate
Susarla SM, Chuang SK, Dodson TB. Delayed versus immediate loading of implants: survival analysis and risk factors for dental implant failure. *Journal of Oral & Maxillofacial Surgery.* 2008;66(2):251-255.	E2
Turhani D, Ohlmeier KH, Sutter W, Kielbassa AM. Undesirable course of an oral implant rehabilitation in a patient with a long history of bulimia nervosa: case report and review of the literature. *Quintessence International.* 2019;50(1):68-79.	E10
Wagenberg B, Froum SJ. A retrospective study of 1,925 consecutively placed immediate implants from 1988 to 2004. *International Journal of Oral & Maxillofacial Implants.* 2006;21(1):71-80.	E2
Wagenberg BD, Froum SJ, Forman J, Kim S-W. A Retrospective Study of Bone-Level Stability Around 335 Hybrid Implants Placed with an Immediate or Delayed Protocol. *International Journal of Periodontics & Restorative Dentistry.* 2021;41(5):647-655.	E2

Citation	Exclude Reason
Zinser MJ, Randelzhofer P, Kuiper L, Zöller JE, De Lange GL. The predictors of implant failure after maxillary sinus floor augmentation and reconstruction: a retrospective study of 1045 consecutive implants. *Oral Surgery, Oral Medicine, Oral Pathology & Oral Radiology.* 2013;115(5):571-582.	E2

APPENDIX C: EVIDENCE TABLES

CHARACTERISTICS OF INCLUDED SYSTEMATIC REVIEWS

Author Year N Studies	Search Details	Eligibility Criteria	Patient Characteristics	Intervention Characteristics	Overall Results
Silva 2021[1] N=5	Electronic searches of MEDLINE/ PubMed, Cochrane Library, and Scopus databases through May 30, 2019. A grey literature search was performed using Google Scholar. A hand-search was conducted in select journals.	P: Patients with dental implants I: Individuals taking antidepressants C: Non-users of antidepressants O: Dental implant failure (primary), marginal bone loss, probing depth, peri-implantitis, other complications Study design: Randomized clinical trials, case-control or cohort observational studies, case series with > 9 patients Language: English, Spanish, or Portuguese	Women and men who underwent dental implant surgery (mean age = 50.8-56.4)	SSRIs/antidepressants (3 studies specify included SSRI medications; 2 studies do not specify antidepressant medications used)	Results of a random effects meta-analysis suggest a risk ratio of 3.73 (95% CI [1.85, 7.52], p = 0.0002) for implant failure in antidepressant users submitted to oral rehabilitation when compared to non-users
Tarfa 2022[2] N=6	Electronic searches were conducted using PubMed, Embase, and Google Scholar between December 2019 and November 2020.	P: Patients who underwent dental implant surgery I: SSRI use C: No SSRI use O: Rate of implant failure, sequelae from SSRI-related implant failure Study design: Cohort studies, case-control, randomized clinical trials Language: English	Women and men who underwent dental implant surgery over a time period from 1980 to 2016 (mean/median age = 50-67.3)	SSRIs	Association of SSRI use with dental implant failure was found to be statistically significant among 3 of 6 studies. No studies included any mention of sequelae, treatment related or otherwise, following dental implant failure

Abbreviations. PICO=populations, interventions, comparators, outcomes; SSRI=selective serotonin reuptake inhibitor.

CHARACTERISTICS OF INCLUDED PRIMARY STUDIES

Note: An analytic dataset of effect estimates used in meta-analyses is available upon request by contacting ESP.CC@va.gov.

Author Year N	Follow-up	Participant Characteristics	Setting Timeframe	Intervention	Outcomes
Alsaadi 2007[3] N=2004	6 months	Consecutive patients treated by means of endosseous implants	Single center 1982–2003	Screw shaped Branemark system implants (Nobel Biocare, Gothenburg, Sweden) used either with a machined or a Ti-Unite surface	Implant failure/loss: Failure (*ie*, before and up to abutment connection); antidepressant medication did not lead to an increased incidence of the early failures. Peri-implantitis: NR
Alssadi 2008[4] N=283	6 months	Consecutive patients treated by means of endosseous implants	Single center 2003–2005	MkIII TiUnite Implants	Implant failure/loss: Early implant failure (*ie*, before and up to abutment connection); antidepressant medication did not lead to an increased incidence of the early failures. Peri-implantitis: NR
Altay 2018[5] N=631	60 months	All patients rehabilitated with dental implants presenting with no systemic conditions and not taking any medications other than SSRIs for psychiatric disorders	Single center 2012–2017	Solid-screw type implants with titanium plasma sprayed or sand-blasted acid-etched surfaces	Implant failure/loss: Osseointegration failure; the difference between the 2 groups failed to reach statistical significance at both the patient and implant levels. Peri-implantitis: NR

Author Year N	Follow-up	Participant Characteristics	Setting Timeframe	Intervention	Outcomes
Block 2021[6] N=224	348 months	All patients who had 1 or more implants removed by the senior author. The failed sample included 1 implant per patient case and was the first implant placed or failed. The control group was a consecutive series of patients with implant placement in 2012 who did not have their implant fail.	Single center 2007–2020	NR	Implant failure/loss: Implant failure within 1 year, 1-4 years, and more than 4 years; depression significantly increased the probability of implant failure in years 1-4 given no failure within 1 year (aOR, 5.28; 95% CI, 1.4 to 19.82) but not for within 1 year or more than 4 years. Peri-implantitis: NR
Carr 2019[7] N=5456	240 months	All patients who received their first dental implant	Single center 1995–2014	Nobel Biocare implant (1995-2000) or TiUnite implant (2001-2014)	Implant failure/loss: Follow-up SSRI use: Only patients who started SSRIs after implant placement were assessed. There was no significant association between SSRI use during follow-up and implant failure. Peri-implantitis: NR

Author Year N	Follow-up	Participant Characteristics	Setting Timeframe	Intervention	Outcomes
Chatzopoulos 2018[8] N=4519	76 months	Patients at least 18 years of age with a complete demographic and medical history who received root canal treatment or implant treatment	Single center 2010-2016	NR	Implant failure/loss: Time to implant failure. The multivariable Cox regression model includes both implant patients and root canal patients (N=8915); for depression: HR: 1.11, 95% CI, 0.74–1.66, p = 0.619; for anxiety: HR: 1.29, 95% CI, 0.86–1.95, p = 0.221. A reduced Cox regression model was also developed based on a stepwise backward elimination method. This model revealed that anxiety (p = 0.004) was significantly associated with treatment failure (HR: 1.55, 95% CI: 1.15–2.09, p = 0.004). Peri-implantitis: NR
Chrcanovic 2016[9] N=2670	NR	Patients consecutively treated with implant-supported prostheses	Single center 1980-2014	Only modern endosseous dental implants with cylindrical or conical design were considered.	Implant failure/loss: Implant failure (up to and after the abutment connection); the univariate binary logistic regression showed that the intake of antidepressants (p = 0.002) had a statistically significant odds ratio at the patient level. After only the variables with a statistically significant odds ratio were included in the multivariate binary logistic regression model, antidepressant intake (p = 0.009) continued to present a statistically significant odds ratio. In the univariate GEE model (implant level), intake of antidepressants (p = 0.046) had a statistically significant odds ratio. After only the variables with a statistically significant odds ratio were included in the multivariate GEE model, intake of antidepressants was no longer a significant predictor of implant failure. Peri-implantitis: NR

Author Year N	Follow-up	Participant Characteristics	Setting Timeframe	Intervention	Outcomes
Chrcanovic 2017[10] N=300	132.7 months	Patients consecutively treated with implant-supported prostheses. For the SSRI sample, patients had to be taking only SSRIs and no other medication and without any other systemic condition	Single center 1980–2014	Modern endosseous dental implants with cylindrical or conical design. All 469 'turned/machined' implants were Brånemark implants (Nobel Biocare AB, Göteborg, Sweden). The 'enlarged-surface' implants were mostly Brånemark MKIII implants with a TiUnite surface (N=386). The rest (N=76) were Astra TiOblast, Osseospeed, XiVE, Frialit-2 (Dentsply Implants, Mölndal, Sweden) and Straumann SLA (Straumann, Basel, Switzerland) implants.	Implant failure/loss: Implant failure; the implant failure rate was 12.5% for SSRI users and 3.3% for non-users (p = 0.007, Fisher's exact test). The multivariate GEE model showed that the intake of SSRIs did not exert a statistically significant influence on implant failure. The multilevel mixed-effects parametric survival analysis adjusted for potential confounders showed that the intake of SSRIs did not significantly affect the implant survival rate. The Kaplan-Meier analysis showed a statistically significant difference in cumulative survival between SSRI users and non-users (p < 0.001). Peri-implantitis: NR

Author Year N	Follow-up	Participant Characteristics	Setting Timeframe	Intervention	Outcomes
Deepa 2018[11] N=352	NR	Patients of both genders rehabilitated with dental implants	Single center 5-year study	A single manufacturer of implants was used (Nobel) for all patients	Implant failure/loss: Fracture of implant, prosthesis screw fracture, loosening of screw; differences between SSRI and non-SSRI groups were not significant. Peri-implantitis: Features of peri-implantitis, such as radiolucency around implant apex and bone loss around implant; differences between SSRI and non-SSRI groups were not significant.
Ekfeldt 2011[12]	NR	All patients were completely edentulous in the maxilla. Patients in the study group lost at least half of their implants. Patients in the control group were age and gender matched to the study group and did not lose any implants. The control group was also matched to the study group on number of implants and time frame of implant placement.	Multicenter 1988–1996	Fixed prosthesis or overdenture supported by at least 4 implants (Brånemark System, Nobel Biocare AB, Göteborg, Sweden)	Implant failure/loss: Implant failure (before and after loading); 2 patients in the study group had 6 implants lost before loading and 6 implants lost after loading which were judged by clinicians to be due to psychological reasons (grief). Peri-implantitis: NR

Author Year N	Follow-up	Participant Characteristics	Setting Timeframe	Intervention	Outcomes
Hakam 2021[13] N=771	NR	Patients ≥ 18 that received dental implants at the University of Florida Center for Advanced Periodontics and Implant Dentistry and were either taking at least 1 type of antidepressant or without a history of antidepressant use and were systematically healthy or had mild systemic disease	Single center	Titanium implants with rough surfaces and internal hexagon or cone morse connections from 2 different companies	Implant failure/loss: Implant failure; the frequency of implant failure was significantly higher in antidepressant users than in non-users (13.9% vs 3.9%; p = 0.007), and there were significant differences in the frequencies of implant failures among patients taking different antidepressant classes (p = 0.005). The frequency of implant failure was significantly higher in patients taking an SNRI than those not taking antidepressants (p = 0.000), taking an SSRI (p = 0.021), and taking an atypical antidepressant (p = 0.043). The frequency of implant failure was significantly higher in patients taking a TCA than those not taking antidepressants (p = 0.043). The frequency of implant failure in TCA users was high (33.3%) but there was only a tendency towards significant differences between TCA users and SSRI users (p = 0.093). No implant failures were observed in patients taking an MAOI. Patients taking an SSRI (RR=7.9, OR: 11.07, 95% CI: 3.265 to 33.82; p = 0.000) and TCA (RR = 7.9, OR: 12.16, 95% CI: 1.503 to 71.58; p = 0.023) were significantly more likely to present implant failure than patients not taking antidepressants (p < 0.05). Use of antidepressants was a statistically significant predictor of implant loss (OR: 4.285, 95% CI: 2.349 to 7.816, p = 0.000). Peri-implantitis: NR

Author Year N	Follow-up	Participant Characteristics Timeframe	Setting	Intervention	Outcomes
Wu 2014[14] N=490	67 months	Patients treated with dental osseo-integrated prosthesis. Patients were excluded if they had a severe systemic disease, were pregnant, or had a medical disorder known to substantially affect bone metabolism.	Single center 2007–2013	Nobel Biocare	Implant failure; compared with nonusers of SSRIs, SSRI usage was associated with an increased risk of dental implant failure (hazard ratio, 6.28; 95% confidence interval, 1.25–31.61; p = 0.03) Peri-implantitis: NR

Abbreviations. NR=not reported; SSRI=selective serotonin reuptake inhibitor.

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Author Year	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)
Alsaadi 2007[3]	Low Examined records of consecutive patients during a 21-year period	Moderate Health/behavioral factors were assessed by questioning the patient and/or checking medical records. It is unclear exactly how antidepressant use was determined and whether determination was consistent across participants	Low Implant failure is clearly defined and consistent	Moderate Select confounding variables are controlled for in multivariate analysis, but other potential confounders are not	Moderate A large number of observations were excluded from multivariate analysis due to missing data on bone quality/quantity	Moderate
Alsaadi 2008[4]	Low Consecutive patients treated with implants during November 2003–June 2005 were prospectively followed	Moderate Health/behavioral history was assessed via a preoperative questionnaire and/or hospital files. It is unclear exactly how antidepressant use was determined and whether determination was consistent across participants	Low Implant failure is clearly defined and consistent	High Potential confounding variables are not controlled for	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate

Author Year	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)
Altay 2018[5]	Moderate Only included patients with complete data. Excluded patients with systemic conditions or taking medications other than SSRIs	Low SSRI use was defined and determined from patient records	Low Osseointegration failure is defined and appears to be applied consistently	High Included data on sex, age, and implant location, but analyses do not control for confounders	Moderate Statistical analyses may not be adequate. Results appear to be reported for all variables investigated	Moderate
Block 2021[6]	Low Sample included all patients with 1 or more implants removed and a control group of consecutive patients without implant failure	Moderate Depression is not defined but data were obtained via chart review of electronic medical record	Low Implant failure is defined by removal of an implant	Moderate Age and gender are accounted for in regression model	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate
Carr 2019[7]	Low Consecutive patients receiving dental implants during a 20-year period	Low SSRI use (6 types) was determined from an electronic health record prospective clinical database and was categorized as history of use, active use, and follow-up use	Moderate Does not specify how implant failure was determined or defined	Moderate Analyses were adjusted for age at first implant, sex, and era of first implant only	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate

Author Year	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)
Chatzopoulos 2018[8]	Moderate Consecutive patients receiving root canal and implant treatment between 2010 and 2016. Only included patients with a complete demographic and medical history	Moderate Depression and anxiety are not defined but were determined from electronic dental records	Low Implant failure is defined by removal of an implant	Moderate Use of adjusted Cox regression model	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate
Chrcanovic 2016[9]	Low Consecutive patients who received implants between 1980 and 2014	Low Intake of an antidepressant was determined from patient files	Low Implant failure is defined by removal of an implant	Moderate Multivariate logistic regression controlled for certain factors	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate
Chrcanovic 2017[10]	Moderate Patients treated consecutively between 1980 and 2014. Excluded patients taking other medications or with systemic conditions. Only implants with data available for all variables were included in the analysis	Low SSRI users were defined as patients who reported taking this type of medication during the pre-surgery appointment	Low An implant was considered a failure in the presence of signs and symptoms that lead to implant removal	Moderate Analyses were adjusted for age, sex, implant length, implant diameter, implant surface, implant location, bone augmentation	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate

Author Year	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)
Deepa 2018[11]	Moderate It is unclear whether all eligible patients were included in the study. Inadequate description of patient selection	Low History of depression and SSRI medication was retrieved from patient's case history	Moderate Does not specify how implant failure was determined or defined	Moderate Looked at implant failure of SSRI/non-SSRI users by age, gender, smoking, diabetes	Moderate Statistical analyses may not be adequate. Results appear to be reported for all variables investigated	Moderate
Ekfeldt 2001[12]	Moderate Study group included patients who lost at least half their implants. Patients in the control group were matched to the study group. Unclear if all eligible patients were included in the study group	Moderate Presence of depression or other diagnosed psychological illness determine from patient records (results distinguish psychological illness from symptoms). In the results 'psychological reasons' is included as a 'reason for implant failure according to the clinician' - some discrepancy between the presence of psychological illness vs reason for failure	Low Multiple failures (loss of at least half of implants) determined from patient records	High Potential confounding variables are not controlled for	Moderate Statistical analyses may not be adequate. Results appear to be reported for all variables investigated	Moderate

Author Year	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Unclear)
Hakam 2021[13]	Moderate Only data from patients who reported taking at least 1 type of antidepressant and patients without a history of antidepressants who were systemically healthy or had mild systemic disease were included. Unclear if all patients meeting these criteria were included.	Low Type and commercial name of antidepressants from electronic dental records	Low Implant failure was defined as the loss of an implant before or after the placement of the crown/abutment connection complex	Moderate Select confounding variables are controlled for in multivariate analysis, but other potential confounders are not	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate
Wu 2014[14]	Low Some patients were excluded who did not meet inclusion criteria (bone-related diseases and medications), but it appears that all eligible patients were included	Low SSRI usage clearly defined and determined via a self-reported questionnaire included in patient records	Low Retrieved from patient files	Moderate A Cox proportional hazard model adjusted for potential confounding factors (sex, age, implant diameter, implant length, bone augmentation, smoking habit)	Low Analyses appear to be appropriate and results appear to be reported for all variables investigated	Moderate

STRENGTH OF EVIDENCE FOR INCLUDED STUDIES

Outcome	Studies	Study Limitations	Directness	Consistency	Precision	Rating and Summary of Evidence
Antidepressant Use						
Implant Failure	9 studies[3-5,7,9-11,13,14]	Moderate risk of bias	Direct	Consistent	Precise	Moderate: RR = 1.60, 95% CI [1.21, 2.13]
Peri-implantitis	0 studies	–	–	–	–	Insufficient: No studies were identified on the association between antidepressant use and peri-implantitis.
Mental Health Conditions						
Implant Failure	3 studies[6,8,12]	Moderate risk of bias	Unknown	Unknown	Unknown	Insufficient: Studies have limited comparability and overall volume of evidence is small.
Peri-implantitis	0 studies	–	–	–	–	Insufficient: No studies were identified on the association between mental health conditions and peri-implantitis.

Abbreviations. SOE=strength of evidence.

APPENDIX D: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	None
2	2	Yes	None
3	3	Yes	None
4	4	Yes	None
5	5	Yes	None
6	6	Yes	None
7	7	Yes	None
8	9	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
9	1	No	None
10	2	No	None
11	3	No	None
12	4	No	None
13	5	No	None
14	6	No	None
15	7	No	None
16	9	No	None
Are there any published or unpublished studies that we may have overlooked?			
17	1	No	None
18	2	No	None
19	3	No	None
20	4	No	None
21	5	No	None

Comment #	Reviewer #	Comment	Author Response
22	6	No	None
23	7	No	None
24	9	No	None
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
25	1	This ESP review examines the association between mental health conditions and SSRI use and peri-implantitis and dental implant failure risk. Though I do not have full details on the motivation for this review, I imagine that it would be helpful for VA dental providers to better understand (and screen for) the risks of dental implant failure and, given the resources needed to provide implants, to target this therapy for patients most likely to have positive outcomes. Alternatively, information on the risks for implant failure could potentially be used to provide support for patients undergoing the therapy, to minimize their risks of having failed implants.	Thank you for this comment. We discuss screening for risk factors in the Future Research Section.
26	1	Throughout the review I wondered: are the detected associations due to the medications or to the underlying depression? Or to associated poor oral hygiene or other risks (eg, smoking, bruxism) that are more common among persons with depression or anxiety? Unfortunately, the literature does not seem to address this issue or be able to tease out such varying effects. The absence of this information in the literature severely hampers the ability to tease out the true causal factors, and in turn, limits dental providers' ability to screen patients based on such risk factors (or provide support to address them).	We agree this is an open question that does not appear to be fully examined in existing research, as noted in the Background and Future Research sections. There are known effects of SSRIs on bone metabolism (which in turn may affect osseointegration) but the role of related or independent behavioral pathways is unclear.
27	1	I did not have methodological concerns about the way the literature was reviewed or the analyses.	Thank you for this comment.
28	1	The key findings section refers to evidence from 9 studies. However, in Figure 2 it becomes clear that the findings were only statistically significant in 3 of these studies. If there is a way to clarify that point in the key findings, it would help the reader better understand the evidence base.	Thank you. In a meta-analysis, evidence from all included studies is drawn upon regardless of the significance of individual study findings.

Comment #	Reviewer #	Comment	Author Response
29	1	What concerned me was the repeated use of statements such as “findings indicate a fairly small, but potentially meaningful, risk”. It is hard to know what this somewhat vague statement means. First, I would find it helpful to have the absolute numerical risk included in such statements. Then, put that risk into context, potentially comparing it to risks of other therapies failing. Or other risks associated with implant failure. Is this finding clinically meaningful, or not? And if so, what is its magnitude?	Thank you for this feedback. We have revised these sections and included a numerical (percentage) estimate of increased risk.
30	1	Page 3, lines 53-55, it would be helpful to state the effect size of SSRIs on osseointegration learned from prior studies, to put the review findings into better perspective.	Thank you. Comparison of our findings to those of the other recent review on the topic – including comparison of effect sizes – is included in the Discussion section.
31	1	Overall, it is difficult to know what to do with these findings. VA providers could screen for antidepressant use before recommending implant therapy, but given the small association with implant failure, that does not seem to be a reason to make a patient ineligible for such therapy. Added screening for oral hygiene practices, and health habits including tobacco smoking and bruxism would add some value, but it is unclear how much. In the end, programs such as the one mentioned (PIMT) might be a good option, but the evidence base is insufficient to really guide future practice, in my view.	We agree that for potential failure risk pathways that may involve behavioral sequalae of mental health conditions, the impact of screening for such conditions is unclear. We also agree that screening for the behaviors themselves may be more impactful, but it is unclear to what degree and what behavioral supports or education might be needed to garner a preventive benefit. We have added further discussion to the Future Research section.
32	1	The gaps in these results might provide a good rationale for further research, however.	Thank you for this comment.
33	2	Throughout, a clearer definition of what constitutes a “risk factor” for implant failure would be useful. If I’m understanding correctly, inflammation and bone loss are considered risk factors, but SSRI use or mental illnesses may be part of the etiology leading to the risk factors of interest. Perhaps the distinction is between distal and proximal risk factors (distal = SSRI, proximal = inflammation, bone loss)?	Thank you. We have clarified our discussion of these potential risk pathways in the Introduction and Executive Summary.
34	2	P. 2, 2nd paragraph (and p. 15, line 3). It’s not clear to me that the current evidence suggests observational research on this topic is infeasible. Relatedly, if observational research on this topic is infeasible (the first sentence), how would research on	Thank you for this comment. We have clarified this section.

Comment #	Reviewer #	Comment	Author Response
		approaches for early detection of risk factors (the second sentence) be possible? Perhaps what's being suggested is that mental health factors could be added to implant risk assessment tools, but that the utility of adding those factors may be limited if the goal is to assess risk of peri-implantitis.	
35	2	p. 4, line 50. Which AHRQ and HSR&D databases were searched? I didn't see these listed in Figure 1.	Full search details are listed in Appendix A.
36	2	p. 5, line 52. How similar are results if you exclude converted odds ratios? Adjusted odds ratios are sensitive to choice of covariates (https://jamanetwork.com/journals/jama/article-abstract/2686777)	Thank you for this question. Four of 9 studies provided adjusted ORs, so an analysis excluding those studies would not be comparable with the reported main analysis. Prior to analyses, however, converted ratios and corresponding CIs were examined for comparability with reported values, and no values differed substantively.
37	2	p. 8, line 30. In what way did studies account for confounders? That is, were covariates added into regression models, or were methods to address selection bias used?	Thank you. Further detail on studies' adjustment methods has been added to the Literature Overview section.
38	3		None
39	4	The main limitation I noted was that elements of a systematic review that are typically completed independently by at least two authors were only completed by one author e.g. (initial abstract reviews, rating of internal validity). This was acknowledged by the authors as a limitation. I do realize that this was a "rapid review" and therefore would have more limited resources available.	Although we do not do fully independent (dual) review for rapid reviews, we do utilize sequential review as noted in the Methods section. In this approach, a second reviewer corroborates all decisions about study inclusion and risk of bias/strength of evidence ratings, as well as accuracy of abstracted data. Therefore, none of these key steps is carried out by only 1 reviewer.
40	5	Page 1 Ln45: Bone loss at implant site is a result of infection, and more an outcome than risk factor Generally in dental literature, we simply say bone, as opposed to jaw bone	Thank you. We have clarified this sentence and now use "bone" rather than "jawbone".
41	5	Pg2 Ln 26: Additionally... This statement regarding maintenance is a wonderful finding from the readings and addition to this paper. Thank you!!	Thank you for this comment.

Comment #	Reviewer #	Comment	Author Response
42	5	Page 2 Ln 36: when you use the statement "potentially meaningful", I would like to see that defined. I am assuming that it means the consequences could be great, but it is a key to our use of this paper, so I want it to be very clear.	See response to comment 29.
43	6	NA	None
44	7	I am not sure where this report would be published. I think it could be published in a dental journal like The International Journal of Oral & Maxillofacial Implants. If that action is pursued then I would recommend edits to improve dental terminology and I would be willing to help with that. The few edits I suggest are all related to dental terminology.	Thank you for this suggestion. We have implemented the recommended changes to terminology, with the exception of “alveolar” bone. For simplicity and based on another reviewer’s recommendation, we now use simply “bone” for consistency with the dental literature.
45	7	Page 1 line 31 change bridgework to fixed dental prosthesis (FDP); jawbone to alveolar bone	See response to comment 44.
46	7	line 42 jawbone to alveolar bone	See response to comment 44.
47	7	line 47 not sure if when you use term bruxism also mean hyper occlusion consider adding hyper occlusion?	See response to comment 44.
48	7	Page 3 line 23 change bridgework to fixed dental prosthesis	See response to comment 44.
49	7	line 26 -32 I found a little confusing and needs clarification it appears to be discussing early loading vs late loading need to get the terminology correct	Thank you. We have clarified this section.
50	7	line 39 jawbone to alvoelar bone	See response to comment 44.
51	7	line 42 consider replacing osseointegration with bone loss continues	See response to comment 44.
52	9	This is an excellent review - and is congruent with our paper (referenced) so I really like it! The obvious next step would be to utilize the VA data warehouse to perform a very large retrospective study - probably comprising thousands of patients who received implants. Frankly, in my opinion, is probably worthy of Merit Review funding.	Thank you for this comment.

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