Journal of Alzheimers Disease & Parkinsonism

Kamoga, et al., J Alzheimers Dis Parkinsonism 2023, 13:3

Research Article Open Access

Effects of Vagus Nerve Stimulation in Alzheimer's Disease: A Systematic Review and Meta-Analysis of Clinical Studies

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Received: 29-Apr-2023, Manuscript No. JADP-23-98777; **Editor assigned:** 01-May-2023, PreQC No. JADP-23-98777 (PQ); **Reviewed:** 15-May-2023, QC No. JADP-23-98777; **Revised:** 22-May-2023, Manuscript No. JADP-23-98777 (R); **Published:** 29-May-2023, DOI: 10.4172/2161-0460.1000571

Citation: Kamoga R, Rukundo GZ, Nakidde G, Adriko W, Obongoloch J, et al. (2023) Effects of Vagus Nerve Stimulation in Alzheimer's Disease: A Systematic Review and Meta-Analysis of Clinical Studies. J Alzheimers Dis Parkinsonism 13: 571.

Abstract

Background: The most prevalent cause of dementia, which is a significant cause of disability in the elderly, is Alzheimer's disease (AD). A large number of novel treatments have been approved to treat AD, but to date none have been able to stop the progression of the disease, and sadly they are all linked to side effects, necessitating the investigation of brain stimulation techniques in the search for an alternative potential therapy. Numerous Vagus Nerve Stimulation (VNS) investigations in Alzheimer's disease have shown variable findings, including worsening cognitive symptoms in some patients and memory improvements in others. As a result, this study will carefully analyze clinical data on VNS in AD in order to offer a summary of the overall impact of VNS on AD using the Preferred Reporting Items for Systematic analyze (PRISMA).

Methods: The study will be conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) statement. We will include clinical studies that have documented VNS in people living with AD published by April 30th 2023. We will also include accessible grey literature about the topic. We will search different electronic data bases and search engines including PubMed, HINARI, CINAHL, EMBASE, Google Scholar, Scopus, Cochrane, ISI, mRCT, Popline, Sigle, VHL, GHAll , Psych-INFO, Africa wide-information and global health using AD ; VNS, brain stimulation, and dementia as the keywords. We will use a meta-analysis, should we find that there is no heterogeneity between included studies.

Discussion: This protocol describes a systematic review of clinical studies of VNS in people living with AD conducted world-wide. Following the completion and publication of this study, we believe that the findings will provide further details about VNS as a potential therapy for Alzheimer's disease and will have an impact on practice, research, and policy in the field of dementia care.

Systematic review registration: Name of registry-PROSPERO; and Registration number- CRD42023417736

Keywords: Alzheimer's disease; Vagus nerve stimulation; Brain stimulation; Dementia

Introduction

Alzheimer's disease, a progressive, incurable brain illness defined clinically by cognitive impairment and pathologically by the accumulation of aberrant proteins in particular brain regions, is the primary cause of dementia and dependency among the elderly [1,2]. Numerous medications have been approved to treat Alzheimer's disease over the years, but none have been able to reverse its course, and they are all associated with side effects, necessitating the need to find alternative treatments for Alzheimer's disease [1,3]. As a result, research into brain stimulation methods as potential AD therapy alternatives has been explored with vigor, and a sizable number of pilot trials utilizing VNS in AD have produced encouraging results [4]. In addition to its prospective application as an Alzheimer's therapy, VNS is now approved for the treatment of depression, inflammatory bowel disease, cluster headaches, and intractable (treatment-resistant) epilepsy [5-13]. In response to electrical stimulation of the VNS, neuromodulators such as acetylcholine and norepinephrine are produced, which presumably modify disease processes largely by boosting neuroplasticity (nerve regeneration) and decreasing inflammation [14-17]. Previous clinical and preclinical studies on vagus nerve stimulation in AD and following a learning event have shown mixed outcomes, including memory improvements, no effect, or cognitive ability decline. [1,18-24]. The variable outcomes could be a consequence of the differences in the methods of investigation. Vagus Nerve Stimulation (VNS) is becoming more

popular in the treatment of a variety of illnesses, including Alzheimer's [17]; however, the overall effect of VNS on the progression and manifestation of the disease has not been well studied and documented, making it critical to summarize the available literature on VNS in AD. Consequently, this study will carefully review the clinical data on VNS in AD in order to present an overview of the overall effect of VNS on AD using the Preferred Reporting Items for Systematic Review (PRISMA) [25]. Findings from this synthesis will be very valuable to dementia care clinicians, researchers and policy makers in making decisions pertaining to use of VNS in Alzheimer's disease and related dementias [26].

In systematic review , the key findings of clinical studies on vagus nerve stimulation in Alzheimer's disease will be determined, the scope of clinical research on vagus nerve stimulation in Alzheimer's disease that has been conducted globally will be documented, and the VNS parameters used in clinical research in AD will be noted, along with any agreement.

Materials and Methods

Methods and analysis

The systematic review will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [25].

Study design

We will carry out a systematic review of all clinical experimental studies (randomized, non-randomized, quasi studies regardless blindness type i.e. single blind, double blind, or non-blind) and observational studies (cross sectional, cohort, case control, case studies) that described the effects of vagus nerve stimulation in patients with Alzheimer's disease. Therefore we shall include all studies and then conduct a sensitivity analysis to explore the impact of quality.

Eligibility criteria

All clinical studies research articles on VNS in AD that are published by December 30th April, 2023, will be included. Case reports, conference proceedings, review articles, and all published articles on VNS in diseases other than AD will be eliminated. We will only use studies with readily available full articles. Abstract-only articles that are not accompanied by complete articles will not be included because it may be challenging to compare them to full papers. To account for the differences in the study designs, sub-group analysis will be done on the included studies. There will be no double reporting of the same outcome in the review, and the criteria for selecting articles for inclusion will be rigorously followed.

Study setting

The systematic review will include studies conducted in any part of the world.

Participants

The systematic review will consider clinical brain stimulation studies done in people living with diagnosed AD.

Interventions

The systematic review will consider both invasive and non-invasive vagus nerve stimulation in clinical studies in AD.

Comparisons/comparators

Different control/sham groups used in brain stimulation studies included in the review.

Outcomes

Primary outcomes: The major outcomes of interest in this systematic review will be the main findings of clinical studies on VNS in Alzheimer's disease that is all documented effects of Vagus Nerve Stimulation on cognition (thinking, attention, language, learning, memory and perception) in patients with AD will be included.

Secondary outcomes: It includes

- To ascertain the scope of clinical research on vagus nerve stimulation for Alzheimer's disease conducted globally from the beginning to April 30th 2023.
- To find out which VNS methods/interventions (invasive or non-invasive), have been employed and whether there is agreement.
- To evaluate the most frequently used stimulation parameters and see if they affect the results of VNS in clinical research. Examples of these factors are current magnitude, and duration of stimulation

Search methods

We will do a strategy-based search of the following electronic databases and search engines: PubMed, HINARI, CINHAL, EMBASE, Google Scholar, Scopus, Cochrane, ISI, mRCT, Popline, Sigle, VHL, GHL, Africa Wide-Information, and Global Health. We will manually look over the included studies' references. To find as many studies as feasible, we will create a Medline search method that combines mesh terms, text words, and relevant Boolean operators. Grey literature will also be included. Web searches, web-based catalogs, and bibliographic databases will be used to find pertinent grey literature.

Search string

We will search using various terms as indicated below: Vagus nerve stimulation or brain stimulation or vagal stimulation or cranial nerve stimulation and Alzheimer's disease or dementia or memory loss or cognition or impaired cognitive function or AD or Neurostimulation or Deme* or cognit*.

Data collection

The summary of the variables from which data will be extracted from reviewed articles will include a) Primary (main) outcomes namely, all documented effects of Vagus Nerve Stimulation on cognition (thinking, attention, language, learning, memory and perception) in patients with AD will be included. b) Secondary (additional) outcomes namely, effects of vagus nerve stimulation on quality of life (motor control, postural control, concentration/ attention, sleep, appetite, dementia, anxiety, apathy); Ascertaining the scope of clinical research on vagus nerve stimulation in Alzheimer's disease conducted globally from the beginning to April 2023, documenting the VNS methods/interventions (Invasive or non-Invasive) commonly employed and whether there is agreement, and

see if they affect the results of VNS in clinical research; vagus nerve stimulation parameters (such as frequency (Hz) (continous), current intensity or magnitude (Am) (continous), site of stimulation (dichotomous) and type of stimulation (dichotomous), Control/sham groups used (Dichotomous), and others like sample sizes, year when data was collected collected, geographic location/region/country where the study was done, authors' names, and year of publication

Data extraction

All identified studies' titles and abstracts will be reviewed by Kamango, Wilson Adriko (member of the study team/librarian), Nakidde, and Obongoloch. The EndNote reference manager will then download the full text of the articles for further review. An endnote library will be created specifically for this review. Kamango and Nakidde will independently screen all literature using the Rayyan software program, excluding non-relevant articles based on full-text review. Disagreements will be settled in dialogue with the third author (Rukundo or Ihunwo). The following data will be extracted using standardized electronic data extraction forms: author, year of publication, article country, methodology/study design, sample size, population, and demographic data (age, gender/sex, and education), intervention (kind, duration), parameters (current, frequency, pulse width, on/off time, site of stimulation, instruments used), results, and confounding factors (Figure 1).

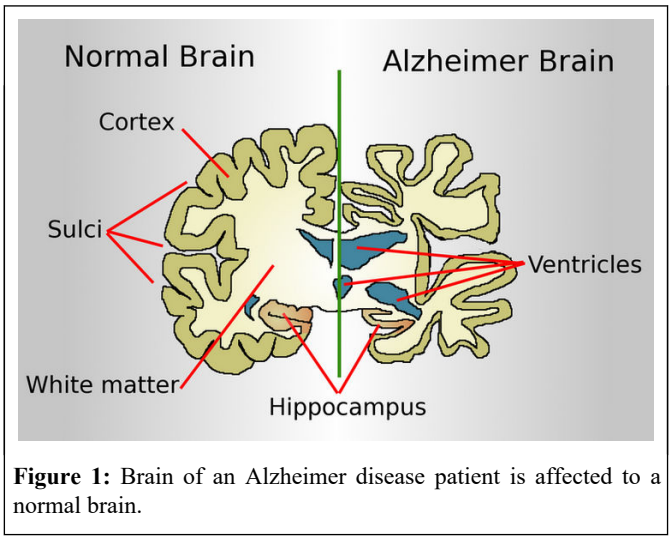

Figure 1: Brain of an Alzheimer disease patient is affected to a normal brain.

Results and Discussion

Quality assessment

The risk of bias (publication bias, methodological bias) in the included articles will be assessed using a risk of bias assessment checklist developed from the Cochrane Risk of Bias (RoB) assessment tool as well as the Quality in Prognostic Studies (QUIPS) tool to assess study participation, confounding measurement and handling, outcome measurement and statistical analysis and presentation. Furthermore, the GRADE will be used to determine the strength of recommendations and the level of confidence in the results of meta-analyses given in the various researches. Kamoga and Nakidde will conduct the quality assessment tests. In the event of any disagreements, those articles will be given to GR or AH, who will also render a decision because they have a solid reputation in the research community and will be able to determine whether bias is a possibility. The quality assessment tests will be executed by Kamoga and Nakidde. If there is a dispute, the papers will be forwarded to GR or AH, who will also make a judgment since they have a good reputation in the scientific community and can assess the probability of bias. Based on the decision of all the reviewers, a paper will be deemed eligible or ineligible for inclusion.

Data synthesis

Qualitative synthesis: We will record essential features of each study using a data extraction form that includes all the items proposed in the extraction such as date, geographical location, study setting (urban/rural), number of participants, age, socio-demographics, sample size, response rate, study design and stimulation parameters. We will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content. We will export the data to STATA V.13.1 for analysis and provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardized mean differences (for continuous outcomes).

Meta-analysis

Statistical tests for heterogeneity will be used to assess the degree of variability in the prevalence measures between the included studies. Specifically, we will use the I^2 statistic to report the percentage of variation across studies that is due to heterogeneity. In case we find no statistically significant heterogeneity (I^2=zero), we will go ahead and conduct meta-analysis [14]. I^2 statistic is preferable because it is independent of the quantity of studies examined. Otherwise, in circumstances of statistically significant heterogeneity, we will not conduct meta-analysis but we will summarize the studies as a narrative review [26-28]. We will use the Random-effects models employed when researchers think that the effect/main outcome varies widely in the population which is the case for our study. We are not confident that all the variables we will identify will be measured in the same way and with the same values. The prevalence, odds ratios and confidence intervals of individual studies will be presented in forest plots and we will generate a summary prevalence and confidence levels. We will also conduct sensitivity and sub-group analyses to determine the influence of selected independent variables on the effect size (cognition and quality of life). We will use funnel plots to show small-study effects that will help point towards publication bias.

Relevant expertise

Dr. Godfrey Zari Rukundo (GR) is a consultant psychiatrist and mental health researcher; Dr Ronald Kamoga (PI)(RK) is a dementia researcher/scholar; Adriko Wilson(WA) is an information scientist/ librarian; Prof. Amadi .O. Ihunwo (AOI) is a senior neuroscience researcher, Gladys Nakidde is a graduate nurse with experience in data collection.

Conclusion

We anticipate that using several approaches/methodologies and terminology to refer to the same thing may present challenges or limitation. We predict that once this review is finished and published, our findings will be of great interest to the community of clinicians and academics in neuroscience, particularly those engaged in dementia

care practice, research and policy making as a basis for decision making. We purpose to share our findings by presenting them at conferences and publishing them in peer-reviewed journals. When conducting the review, any modifications to this protocol will be noted in PROSPERO and reflected in the final manuscript. In summary, our goal is to conduct a systematic review that will summarize the clinical data on the effects of VNS in people living with Alzheimer's disease.

Declarations

Ethics approval and consent to participate

No ethical approval will be required for the performance of this systematic review. We shall utilize secondary data without necessity to interact with the people diagnosed with AD directly.

Consent for publication

We shall not require consent for publication because we will not use any raw data. We will use already published data.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Ronald Kamoga conceived the study and wrote the first draft with Godfrey Zari Rukundo, Amadi Ogonda Ihunwo and Johnes Obongoloch, and all authors revised the protocol. Ronald Kamoga, Godfrey Zari Rukundo, Johnes Obongoloch and Amadi Ogonda Ihunwo developed the search strategy while the data abstraction form was developed by Ronald Kamoga, with input from Godfrey Zari Rukundo, Gladys Nakidde and Amadi Ogonda Ihunwo. Ronald Kamoga, Gladys Nakidde and Wilson Adriko will do the data extraction. All authors will read and approve the final manuscript. Godfrey Zari Rukundo is the senior researchers on the team providing overall guidance.

References

1. Metin B, Krebs RM, Wiersema JR, Verguts T, Gasthuys R, et al. (2015). Dysfunctional modulation of default mode network activity in attention-deficit/hyperactivity disorder . J Abnorm Psychol 124(1):208-214.
2. Wolf A, Bauer B, Abner EL, Ashkenazy-Frolinger T, Hartz AM (2016). A comprehensive behavioral test battery to assess learning and memory in 129S6/Tg2576 mice. PloS one 11(1):e0147733-e0147733.
3. Shafqat S (2008). Alzheimer disease therapeutics: perspectives from the developing world. J Alzheimers Dis 15(2):285-287.
4. Chang CH, Lane HY, Lin CH (2018). Brain stimulation in Alzheimer's disease. Front Psychiatry. 9:201-201.
5. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, et al. (2015). Clearance systems in the brain-implications for Alzheimer disease. Nat Rev Neurol 11(8):457-470.
6. Heck A, Fastenrath M, Coynel D, Auschra B, Bickel H, et al. (2015). Genetic analysis of association between calcium signaling and hippocampal activation, memory performance in the young and old, and risk for sporadic Alzheimer disease. JAMA psychiatry 72(10): 1029-1036.
7. Kumar S, Reddy AP, Yin X, Reddy PH (2019). Novel MicroRNA-455-3p and its protective effects against abnormal APP processing and amyloid beta toxicity in Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis 1865(9):2428-2440.
8. Ponce FA, Asaad WF, Foote KD, Anderson WS, Cosgrove GR, et al. (2016). Bilateral deep brain stimulation of the fornix for Alzheimer's disease: surgical safety in the ADvance trial. J Neurosurg 125(1):75-84.
9. Ruffoli R, Giorgi FS, Pizzanelli C, Murri L, Paparelli A, et al. (2011). The chemical neuroanatomy of vagus nerve stimulation. J Chem Neuroanat 42(4):288-296.
10. Conway CR, Gott BM, Azhar NH (2015). Vagus nerve stimulation for treatment-refractory depression. Neuromodulation Psychiatry 30:335-52.
11. Heck C, Helmers SL, DeGiorgio CM (2002). Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. Neurology 59(6 suppl 4):S31-s37.
12. Láinez MJ, Guillamón E (2017). Cluster headache and other TACs: Pathophysiology and neurostimulation options. Headache 57(2):327-235.
13. Pisapia J, Baltuch G (2015). Vagus nerve stimulation: Introduction and technical aspects. Neuromodulation in Psychiatry 30:325-34.
14. Ma X, Wang Q, Ong JJ, Fairley CK, Su S, et al. (2018). Prevalence of human papillomavirus by geographical regions, sexual orientation and HIV status in China: a systematic review and meta-analysis. Sex Transm Infect 94(6):434-442.
15. Pesavento E, Capsoni S, Domenici L, Cattaneo A (2002). Acute cholinergic rescue of synaptic plasticity in the neurodegenerating cortex of anti-nerve-growth-factor mice. Eur J Neurosci 15(6):1030-1036.
16. Engineer ND, Kimberley TJ, Prudente CN, Dawson J, Tarver WB, et al . (2019). Targeted vagus nerve stimulation for rehabilitation after stroke. Front Neurosci 13:280-280.
17. Fried I (2016). Brain Stimulation in Alzheimer's disease. J Alzheimers Dis 54 789–791.
18. Roy DS, Arons A, Mitchell TI, Pignatelli M, Ryan TJ, et al. (2016). Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. Nature 531(7595):508-512.
19. Kosel M, Schlaepfer TE (2003). Beyond the treatment of epilepsy: new applications of vagus nerve stimulation in psychiatry. CNS spectr 8(7): 515-521.
20. Ansari S, Moutaery KCKAAI (2007). Vagus nerve stimulation: indications and limitations. Operative Neuromodulation 297(2):281-286.
21. Ghacibeh GA, Shenker JI, Shenal B, Uthman BM, Heilman KM (2006). The influence of vagus nerve stimulation on memory. Cogn Behav Neurol 19(3):119-122.
22. Sun Q, Xie N, Tang B, Li R, Shen Y (2017). Alzheimer's disease: from genetic variants to the distinct pathological mechanisms. Front Mol Neurosci 10:319-319.
23. Merrill CA, Jonsson MA, Minthon L, Ejnell H, Silander HC, et al. (2006). Vagus nerve stimulation in patients with Alzheimer's disease: additional follow-up results of a pilot study through 1 year. J Clin Psychiatry 67(8):1171-1178.
24. Sjogren MJ, Hellstrom PT, Jonsson MA, Runnerstam M, Silander HC, et al. (2002). Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: a pilot study. J Clin Psychiatry 63(11): 972-980.
25. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst rev 4(1):1-9.
26. Drummond E, Wisniewski T (2017). Alzheimer's disease: experimental models and reality. Acta neuropathologica 133:155-1575.
27. Kwan H, Garzoni L, Liu HL, Cao M, Desrochers A, et al. (2016). Vagus nerve stimulation for treatment of inflammation: systematic review of animal models and clinical studies. Bioelectron Med 3:1-6.
28. Kontopantelis E, Springate DA, Reeves D (2013). A re-analysis of the Cochrane Library data: the dangers of unobserved heterogeneity in meta-analyses. PloS one 8(7):e69930-e69930.