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Nicotine's Potential to Protect Brain Cells: The Influence of Nicotine on Alzheimer's Disease Risk in the United States: A Scoping Review

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Abstract

Nicotine consumption increases brain excitability in a dispersed system of brain areas, such as the frontal cortex, amygdala, cingulate, and frontal lobes, in a dose-dependent manner. Stimulation in these areas is compatible with nicotine's ability to arouse and reinforce behaviour in humans. However, the effects of nicotine consumption on brain cells and the way it modifies them to either inhibit AD or facilitate AD is still unknown, therefore, the current scientific article aimed to address this research gap through analysing prior but latest research studies in this domain. Since there was a need to establish and explore more research regarding the positive impacts of Nicotine on patients with AD, a qualitative research design using secondary data was used to conduct the present scientific evidence. Four published papers within the year range 2017 to 2023 were acquired and thematically evaluated. Mixed findings regarding the impact of nicotine on brain cells and probability of getting AD were found however, there has been no clinical trials or enough empirical studies to support this assumption. Therefore, more research will be needed in the prospective to obtain credible and supporting results.

Keywords: *Nicotine, Brain cells, nicotinic receptors, Alzheimer's disease.*

1.0 Introduction

It is an established fact and traditional statement every person may have heard that 'smoking kills.' Besides the presence of published literature and facts regarding the health hazards of tobacco or nicotine intake, there has been an evolution in the findings of recent studies. When a person inhales a nicotine puff from cigarette, nicotine rushes the brain, hooking onto receptors located on the exterior of neurons and causing sensations of happiness and satisfaction. However, nicotine does

not just remain on the cell surface, the substance enters brain cells and changes them from the inside-out (California Institute of Technology, 2019). Nicotine consumption also increases brain excitability in a dispersed system of brain areas, such as the frontal cortex, amygdala, cingulate, and frontal lobes, in a dose-dependent manner. Stimulation in these areas is compatible with nicotine's ability to arouse and reinforce behaviour in humans (Zoli et al., 2015).

As per Texas A&M University study (Winzer-Serhan et al., 2015), nicotine, when administered separately of tobacco, may help preserve the brain as it matures and may even prevent Parkinson's or Alzheimer's disease. Winzer-Serhan and her colleagues (Winzer-Serhan et al., 2015) used mouse models to introduce nicotine to the animals' water supply. There had been three groups that got nicotine at a variety of levels (low, medium, and high), equivalent to infrequent, low, and intermediate smokers, correspondingly, plus a comparison group that administered no nicotine. The two sides who got nicotine at low or moderate dosages had no drug concentrations in their bloodstream and no alterations in food consumption, body mass, or the amount of nicotine receptors located in the brain. The sample that received the greatest dosage of nicotine, on the other hand, ate smaller, acquired less fat, and contained more receptors, showing that at greater doses, the chemical enters the brain and can influence behaviour. Nevertheless, even at large dosages, it did not appear to have any concerning behavioural adverse reactions, such as making the participants more worried, as the researchers had feared.

Nicotine, also known as 3-(1-Methylpyrrolidin-2-yl) pyridine, is a stimulant discovered in the tobacco leaf (Broide et al., 2019). Nicotine usage can result in a variety of health issues, involving heart and lung illness, as well as an increased chance of cancer incidence and vulnerability to a host of diseases, including TB, bronchitis, and sexually transmitted infections like chlamydia (Alhowail, 2021). Nevertheless, growing data shows that nicotine provides health benefits, especially in terms of cognitive performance. Alzheimer's disease (AD) is a neurological illness that typically affects older persons and produces dementia (Neugroschl & Wang, 2011). AD is characterised by harmful amyloid- (A) and tau protein build-up in the hippocampus (Murphy & Levine, 2010). Furthermore, multiple investigations have shown that Amyloid deposition impairs brain biological functions and induces neural malfunction. Regrettably, there is no cure for Alzheimer's disease, and the condition is now controlled by delaying its development using antioxidants and medications like cholinesterase inhibitors (Mendiola-Precoma et al., 2016). However, the effects of nicotine consumption on brain cells and the way it modifies them to either inhibit AD or facilitate AD is still unknown, therefore, the current scientific article aimed to address this research gap through analysing prior but latest research studies in this domain.

1.1 Research Objectives

The aim of this scientific article was to explore the mechanism behind impact of nicotine on brain cells and how nicotine impacts the probability of getting Alzheimer’s disease (AD).

2.1 Literature Review

The review of literature serves as an insight into the research topic and provides credibility to the current research issue by backing it with prior research findings. Literature review helps to identify, gather, evaluate, and synthesise prior literature pertinent to current research topic so that an evidence-based scientific paper is formed (Snyder, 2019). The following review of literature is based on the mechanism behind how nicotine saves brain cells and how it impacts the probability of getting Alzheimer’s disease (AD). It discussed the variables and identified research gaps.

The endoplasmic reticulum is a cell's manufacturing place and storage facility, where peptides are synthesised and packaged before being transported to various places within and beyond the cell. Nicotinic receptors (nAChRs) are one of these proteins, which are produced in the ER and subsequently transported to the exterior of the cell. When nicotine atoms arrive in the body, they proceed through the circulation to central nervous system, where they interact with the nAChRs on their surfaces. This causes the cells' incentive and pleasure hormones to be released (See Fig 1). Shivange and colleagues (2019) discovered that certain nAChRs linger in the storehouse (ER), where they may also attach to nicotine. They created a biosensor to visualise where nicotine accumulates within the cells to acquire understanding into nicotine's impact on brain cells. The scientists' revealed nicotine penetrates the ER after a while of arriving beyond a cell by filming cells with biosensors in a contained environment.

Moreover, nicotine concentrations are high enough to influence nAChR formation and escort more nAChRs on their way to the extracellular environment. Consequently, the neurons become more susceptible to nicotine, which increases the pleasurable experiences after smoking a cigarette (Shivange et al., 2019). Precisely, the longer a person consumes nicotine, the quicker and easier it is to achieve a nicotine high. This is a side effect of nicotine dependence. However, this study was based on the authors' own discretion and an outcome of different quantitative results with no unified outcome. Moreover, research regarding the effects of nicotine on brain cells have produced contradicting findings. Prolonged nicotine treatment has been shown to diminish amyloid formation in one mouse model of amyloidosis (Durairajan et al., 2012), yet not in a highly aggressive response (Sabbagh et al., 2008), and to exacerbate tau accumulation in a triple transgenic animal that produces plaques and lesions (Oddo et al., 2005). Similarly, Cotinine, nicotine's major constituent, decreased A-beta accumulation and improved cognitive impairments in AD mouse models (Echeverria et al., 2011) (See fig 3).

Nicotine may also help with Parkinson's disease, possibly through an inside-out process in the ER (Srinivasan et al., 2014). Consequently, research indicate that varenicline has been demonstrated to have preventive advantages in animal trials of Parkinson's disease in addition to other neurodegenerative illnesses such as Alzheimer's disease (McGregor et al., 2017). However, these studies were not backed by studies based on human samples hence making the findings limited. A significant future challenge will be to explore pharmacological observation or direct instruction in practice (Sharma et al., 2018). This is a crucial step toward understanding the biological significance of chaperoning in the setting of nicotine dependence and neuroprotective properties against AD. At the same time, previous studies on the effects of nicotine on attention (Kadir et al., 2006), reasoning, and memory have shown contradictory results (Smith et al., 2006). Grundey et al. (2012) present additional facts that nicotine mist has a detrimental effect on stimulatory plasticity and a reduced decrease in responsiveness following transcranial direct current activation. These findings contrast with the effects found following chronic nicotine treatment.

These discrepancies were attributable to the adaptable nicotinic receptor alterations caused by continued nicotine administration. These disparate effects might be the consequence of NADs acting differently depending on cognitive process. Counotte et al. (2012) clarify how nicotine impacts attention diversely depending on a variety of factors such as the level of exposure, smoking behaviour, the phase of progression at which the brain is exposed to nicotine, and the presence of mental health diseases such as schizophrenia and Alzheimer's disease (AD). The role of nicotine function in Alzheimer's disease is a tough study topic, and it is uncertain if neurological dysfunction in Alzheimer's disease is predominantly induced by a reduction in the amount of

nAChRs and their function induced by Amyloid-beta neurotoxicity. Zappettini et al. (2012) offer evidence that A1-40 inhibits glycine synthesis in the hippocampus area of the brain via a nAChR-mediated route but not muscarinic circuits (Zappettini et al., 2012).

A growing number of studies are concentrating on identifying "changeable" potential risks for AD, such that, circumstances that may be treated successfully to lower their frequency during the undiagnosed early stage (Jagust, 2013), resulting in a considerable drop in the occurrence of AD (Barnes & yaffe, 2011). In the cholinergic theory, cognitive impairment in Alzheimer's disease is caused by defects in underlying neural synaptic transmission caused by acetylcholine deficiency (Grossberg, 2003). Therefore, cholinesterase inhibitors, which impede acetylcholine hydrolysis, are the first-line treatment for recovering underlying neuronal performance in Alzheimer's disease. Nevertheless, there is much disagreement over the severity of the link between Alzheimer's disease and possibly modifiable risk factors.

Cataldo and colleagues (2010) conducted a convincing and conclusive meta-analysis on 43 worldwide case-controlled and cohort scientific studies from 1984 to 2009, and discovered that tobacco company links (like research funding provided by the cigarette industry, investigations currently funded by the cigarette manufacturers) were inherently connected to the extent and direction of smoking as a possible cause of AD. In case-controlled research with a tobacco company relationship, smoking was associated with a significantly decreased risk of Alzheimer's disease, while no link was found in trials with no tobacco industry linkage. However, the number of participants, period that subjects were observed (for prospective studies), and variables varied significantly across the above case-controlled and cohort research.

Nicotine use may prevent against Alzheimer's disease neurotoxicity by activating nicotinic acetylcholine receptors (nAChR) (Helstrom-Lindahl et al., 2004). In preclinical Alzheimer's disease, there is a dramatic decrease of neurons and/or synapses encoding nAChRs, and A-beta aggregation is commonly seen at nAChRs (Buckingham et al., 2009). The cells in the brain link to create circuits that are arranged by activity (Pulvermuller et al., 2014). Establishing these linkages enables specific sections of the cortex to be activated and documented to track neurotransmission and receptor activation in particular parts of the brain. Long-term potentiation (LTP) is a biological model for learning and memory encoding that is used to quantify neuronal plasticity. Prior research has found that transient nicotine administration improves LTP in people who are sleep deprived (Aleisa et al., 2011). Furthermore, persistent nicotine treatment has been shown to enhance LTP in AD, psychological stress, and hypothyroidism paradigms (Alkadhi, 2011). As a result, nicotine treatment may enhance connections between two neurons, resulting in better cognition in both healthy persons and those suffering from disorders, such as Alzheimer's or hypothyroidism.

Similarly, nicotine treatment, both acute and chronic, has been demonstrated to improve cognitive impairments in Alzheimer's disease patients (Newhouse et al., 2012). (See fig 3). Moreover, rapid nicotine administration while electroencephalography (EEG) was discovered to bring EEG needed to convey baseline limits in Alzheimer's disease (AD) patients using cholinesterase inhibitors (Srivareerat et al., 2011). As a result, nicotine treatment may have a beneficial impact on the cognitive impairment seen in Alzheimer's disease. Smoking cigarettes has been shown to regulate chromatin control in the respiratory system by changing the functioning of HDACs (Histone deacetylase), such as HDAC6 (See fig.2), and it may have a massive effect on the brain. Likewise, nicotine has been shown to suppress HDACs in the cortex, hence improving memory performance

(Volkow, 2011). Nevertheless, further research is needed to evaluate nicotine's influence on cognitive performance via chromatin modification.

3.0 Material and Methods

The methodology section of a scientific article serves as a roadmap for readers since it helps them know the research procedure and design used to conduct the research and how credible was the research approach to reach the study outcomes. Therefore, research methodology is a critical component of a scientific article which allows future researchers to replicate or reproduce the study (Patten, 2017). The following methodology comprised the research design, data collection methods, sample and the data analysis used to reach the study findings along with the ethical considerations used while conducting the research.

Research design is a methodical strategy to conduct research and involves either quantitative (empirical) research design or Qualitative (interpretive) research design and often both (mixed method design). A qualitative study helps to gain a more thorough understanding, and it is a type of research technique that concentrates on how individuals view their surroundings and society at large (Patten, 2017). It is beneficial for doing in-depth investigation on the topic of interest and studying people's ideas and opinions in a natural context. The investigator and responder have a special connection due to their common concern for the subject and their equity as individuals. While quantitative research techniques place a focus on numbers and contain quantifiable assessment tools such as surveys or observable data collecting procedures like charts and statistical evidence, qualitative research approaches do not (Punch & Oancea, 2014). However, because of its vast generalizability, quantitative data is totally dependent on objective judgments, and it may also be prone to certain errors like response bias and social desirability bias (Fellows & Liu, 2021). Likewise, while qualitative research style allows for greater insights and in-depth exploration of the study topic, there is a risk that the results are subjective and difficult to analyse owing to a loss of impartiality.

Wilson and Fox (2013) distinguish between primary and secondary data gathering approaches. Primary data is first-hand data that the researcher collects then and there and is recent evidence for the investigation, whereas secondary data is material that is currently existent in the shape of journal articles, government websites, and textbooks discovered on databases and collected previously by the researcher. For the current research topic, secondary data in the form of recent published articles between the year ranges of 2015 and 2022 were acquired. Because the author sought to investigate recent and up-to-date information on impact of nicotine on brain cells and its significance in AD patients, a literature search was undertaken between the years 2015 and 2022 using databases like Google Scholar and PubMed. Because these databases produce a wealth of peer-reviewed journal papers, they were utilised to extract relevant information on nicotine and its impact on AD. Specific keywords such as “Nicotine AND Brain cells, “Nicotine AND AD,” were used to retrieve relevant papers using Boolean operators to narrow down search results.

The data analysis techniques represent the method used to evaluate and interpret data collected during the research. There are different analytical techniques used for secondary qualitative research such as Systematic Literature Review, Critical Literature Review, or thematic literature review. However, for the current research, thematic review of literature was deemed appropriate because of the number of sample studies which were few and since the author organises and analyses existing material based on themes or theoretical notions that he or she believes are vital to comprehending the subject, it is a credible method of analysis. Thematically categorizing the

material can help establish and determine which regions may have a major scarcity of current literature/studies. It emphasises any inadequacies in the present corpus of work and show the necessity for or prospects for expanding earlier studies. However, while thematic analysis is adaptable, this adaptability might result in inconsistencies and a lack of coordination when constructing themes based on research findings. Nevertheless, in the current research, the four studies were critically evaluated based on the themes emerging from their findings.

4.0 Findings and Discussion

The current scientific article was based on the topic of impact of nicotine on brain cells and how it affects Alzheimer's disease. Four studies were found to be appropriate for the thematic literature review as discussed below.

The research papers found between the years 2015 and 2022 were found to have researched on the positive effects of nicotine on the brain in terms of cognitions, learning and memory. Therefore, these studies can serve as a basis for future research studies and acquisition of primary data.

Alhowail's review (2021) focused on the purported advantages of nicotine in the hippocampus and outlines the underlying principles. Nicotine treatment has been shown to enhance cognitive deficits in Alzheimer's disease (AD) as well as hypotonia and cognitive problems in Parkinson's disease (PD). Nicotine reduces cognitive decline in Alzheimer's disease by increasing protein kinase B (commonly known as Akt) activation and boosting phosphoinositide 3-kinase/Akt signalling, which modulates cognition and memory functions. Nicotine's influence on chromatin remodelling via suppression of histone deacetylases, which induces regulatory alterations in memory-related pathways, may enhance memory performance. Nicotine provides multiple cognitive advantages in both healthy people and those with cognitive impairment caused by different disorders. More study is needed, nevertheless, to offer information on the impact of both acute and long-term nicotine administration on memory performance. Nevertheless, this was a review based on published data which is rare and therefore the findings cannot be generalised.

While nicotine has been shown to have neuroprotective properties, the chemical mechanism(s) through which this happens is unknown. Some scholars suggest an "outside-in" neuroprotection process in which nicotine stimulates membrane nAChRs, causing Ca2+ inflow and transcriptional alterations (Toulorge et al., 2011). However, due to lack of data to support such claims, little has been established regarding the action of nAChRs (nicotine receptors) in memory and cognition. The alpha-7 nAChR is a ligand-gated ion circuit that is found in key brain areas important for intellectual performance (like the brain cortex and hippocampal region). The 7 nAChR is found pre- and postsynaptically, in which it initiates intracellular signalling pathways. Its activator has been studied in clinical trials to enhance cognitive functioning in Alzheimer's disease. A review (Ma & Qian, 2019) detailed the essential facts on the structures and roles of the 7 nAChR, the localization and activity of the 7 nAChR, and the involvement of the 7 nAChR in regulating A-beta internalisation in their review. Therefore, the review suggested AD therapy that facilitates the alpha 7nChR. However, the findings are conflicting and thus the review is limited because of a lack of clinical trials and empirically backed studies.

Brooks and Henderson (2021) finding of an inverse association between smoking and Parkinson's disease, and subsequently Alzheimer's disease, prompted researchers to investigate nicotine as a restorative drug. Some researchers have found that nicotine improves cognitive performance. The hippocampal region of brain, along with the subventricular zone (SVZ), is a unique brain area that allows for continuing embryonic regeneration into adulthood and plays a critical role in cognitive

activities such as memory and cognition. As a result, putative effects on progenitor cells and brain precursor cells are one theory behind nicotine-induced neuroprotective properties. Contrary to this, nicotine withdrawal typically causes cognitive deficits, particularly in hippocampus-dependent activities, indicating that nicotine consumption may impede brain neurogenesis (Waisman Campos et al., 2016). The existing body of research on nicotine's impact on brain cells and brain precursors was examined in this review. The effects of acute and chronic nicotine on neural stem cells growth, survivability, molecular activity, and maturation were studied. Nevertheless, research on nicotine's impacts on the brain cells is still in its inception, and much remains to be found. However, this research study was based on a systematic review there may be a chance of bias and expression of strong opinions through stealth.

Deutsch et al. (2016) examined how A-beta peptide interaction to the 7nAChR (alpha 7 Nicotinic Acetylcholine Receptor) may impact the structure of lipoproteins on the cell surface. This interaction can be harmful to cells that contain the 7nAChR on their membrane. Furthermore, internalisation of the 7nAChR-A combination may result in cell disruption and external amyloid plaque formation. As a result, it has been proposed that activating the 7 nAChR shields brain cells from A-beta induced apoptosis. This may improve cognitive function as well as provide further therapeutic efficacy by decreasing the course of AD. Similarly, Barbier et al. (2015) performed two single-dose investigations in healthy participants to evaluate the comparative absorption, pharmacokinetic properties, acceptability, and neuroprotective properties of encenicline (a 7nAChR agonist). The results showed that encenicline was effectively absorbed at single doses up to 180 mg. With doses as low as 1 mg, potential therapeutic effects on the nervous system were dose- and time-dependent. The oral dose form and the solution were determined to be bioequivalent. Food has no effect on encenicline's pharmacokinetic characteristics (Barbier et al., 2015). More clinical trials, however, are needed to assess the projected procognitive advantages of encenicline, as well as its tolerance and efficacy after numerous dosages.

Discussion

Alhowail (2021) review found that nicotine provides multiple cognitive advantages in both healthy people and those with cognitive impairment caused by different disorders. This could be justified through the fact that long-term potentiation (LTP) is a biological model for learning and discernment that is used to quantify neuroplasticity. Increased glutamate discharge from presynaptic to postsynaptic membrane, for instance, was observed to boost excitatory postsynaptic current in the hippocampal region during spatial learning tasks (Aleisa et al., 2006). Previous research has found that acute tobacco administration improves LTP in people who are sleep deprived. Furthermore, persistent nicotine treatment has been shown to enhance LTP in AD, psychological stress, and thyroid problems (Alkadhi, 2011). While Ma and Qian (2019) detailed the essential facts on the structures and roles of the 7 nAChR, the localization and activity of the 7 nAChR, and the involvement of the 7 nAChR in regulating A-beta internalisation in their review, other studies in the past have not supported the positive functions of Amyloid-beta.

It was thought to be accountable for synapse malfunction, impaired memory, and cerebral structural failure in subsequent stages of Alzheimer's disease. Current findings, though, suggests that Amyloid-beta is more than just a "junk" result of APP degradation that produces cognitive deficiencies at a specific point; it is a peptide that can assist in neurotransmitter and synaptic plasticity in both referencing and situational fear memory (Puzzo & Arancio, 2013). On the contrary, Brooks and Henderson (2021) found an inverse association between smoking and

Parkinson's disease, and subsequently Alzheimer's disease. To contradict these findings, Cohen et al. (2015) found nicotine dependency and depletion raises numbers of juvenile neurons in the SGZ (subgranular zone) of the DG (Dentate Gyrus) in another investigation that showed a nicotine-induced boost in neuronal regeneration. The investigators also discovered that nicotine corresponds with the number of young neurons in the hippocampus after prolonged nicotine exposure in rats.

To facilitate the claim that Nicotine aids in neurogenesis and cognitions in AD, Barbier et al. (2015) performed two single-dose investigations in healthy participants to evaluate the comparative absorption, pharmacokinetic properties, acceptability, and neuroprotective properties of encenicline (a 7nAChR agonist). It was found to improve cognitive function as well as provide further therapeutic efficacy by decreasing the course of AD as time-dependent and dose-dependent. These findings can be justified and backed by another study where in scientific Phase I and Phase II studies with Alzheimer's disease patients, encenicline was evaluated. In Phase I and II studies including individuals with mild-to-moderate Alzheimer's disease, encenicline medication was well accepted and seemed to dramatically improve cognitive and psychological assessments in comparison to the placebo group. Additionally, two Phase III trials called COGNITIV AD assessed the effectiveness and acceptability of encenicline in individuals with mild-to-moderate Alzheimer's disease (Deardorff et al., 2015). Given the results of the clinical studies and the postulated principle of action, encenicline may be a promising option for treatment in conjunction with cholinesterase inhibitors.

5.0 Conclusion

The current scientific article sought to acquire a better understanding of the subject by investigating the effect of nicotine on the chance of developing Alzheimer's disease. Emerging evidence suggests that nicotine has health advantages, particularly in terms of cognitive ability. Moreover, several studies have revealed that Amyloid accumulation inhibits brain biological functioning and causes neurological dysfunction. Because there was a need to establish and explore additional study on the favourable effects of Nicotine on people with Alzheimer's disease, a qualitative research design employing secondary data was chosen a good alternative for conducting the current scientific evidence. Four research were assessed critically based on the themes that emerged from their findings. Between the years 2015 and 2022, study articles were discovered that investigated the good effects of nicotine on the brain in terms of cognitions, learning, and memory. Treatment with nicotine has been proven to improve cognitive deficiencies in Alzheimer's disease (AD), as well as hypotonia and cognitive issues in Parkinson's disease (PD).

It is thought that activating the 7 nAChR protects brain cells against A-beta-induced apoptosis. This may improve cognitive function as well as give additional treatment efficacy by slowing the progression of Alzheimer's disease. However, most of the research papers were reviews and based on author's own discretion thereby limiting the outcomes. Moreover, the reviews did not contain any empirical or clinical studies which may have added credibility to the research issue. Therefore, future research is needed to probe into the issue and determine the efficacy of nicotine on AD and its mechanisms. It is recommended that more primary quantitative research, clinical trials and experiments be conducted to study the impact of nicotine on AD such that knowing the network of signal channels is critical for future AD therapeutic research.

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