Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/32/20240813

Glucagon-like peptide-1 Analogs for Alzheimer's Disease -- A systematic meta-analysis

Cindy Wang[1, 3, 4, †] and Kailin Ye[2, 5, †]

[1]Basis Independent Silicon Valley, 95126 San Jose, United States
[2]Pierre Elliot Trudeau High School, L6C 2E6 Markham, Canada
[3]Corresponding author

[4]cindywvng@gmail.com
[5]henin0805@gmail.com
[†]These authors contributed equally to this work and should be considered co-first authors.

Abstract. Alzheimer's Disease (AD) poses a serious health concern especially for the aging population above the years of 65. An estimated 6 million Americans are diagnosed with Alzheimer's Disease, and there are at least 50 million Alzheimer's patients in the world. AD affects the daily life of these patients, yet there is no permanent cure. Current treatments involve cholinesterase inhibitors and NMDA-receptor agonists to help alleviate the symptoms. GLP-1 is a peptide often used in the treatment of diabetes. Since there are shared pathological features between diabetes and AD, such as insulin dysfunction and glucose metabolism dysregulation, GLP-1 may be a viable study for AD treatment. To perform a meta-analysis to investigate whether GLP-1 has a beneficiary effect on biological markers and cognitive outcome in AD patients. We searched the following electronic databases: EMBASE, MEDLINE, phycINFO, CINAHL, PubMed, Cochrane CENTRAL, and ClinicalTrials.gov. We only utilized Randomized Control Trials (RCTs) and clinical trials. We also searched with the following Medical Search Headings: Alzheimer's Disease, Alzheimer, Alzheimer's, and GLP-1. We included 2 randomized, double-blind, and placebo controlled clinical trials into our meta-analysis. We extracted the baseline and outcomes from the clinical trials and evaluated its risks of bias. Biological markers were measured by amyloid beta (Aß) accumulation, and cognitive outcomes were measured by the Wechsler Memory Scale - Fourth Edition (WMS-IV) and Mini Mental State Exam (MMSE). For one study, the WMS-IV was used to measure cognitive outcome. The other study measured cognitive outcome with the MMSE. Biological markers were measured by Aß accumulation in one study and with [11C]PIB tracer in another. There was no significant difference between the placebo and experimental group after the treatment period.

Keywords: GLP-1, Alzheimer's Disease, Meta-analysis, Systematic evaluation

1. Introduction

Alzheimer's Disease is a serious neurodegenerative disease that is characterized by the chronic, irreversible loss of nerve cells and tissues in the brain. It is a brain disorder that causes intellectual impairment, which destroys the ability to reason, learn, and memorize [1]. The two most important

DOI: 10.54254/2753-8818/32/20240813

biological hallmarks of AD are the accumulation of extracellular senile plaques and the buildup of intracellular neurofibrillary tangles. These problems are caused by the prevalence of Amyloid beta (Aß) 42 protein and hyperphosphorylated tau protein. As a result of these accumulations, neurons and synapses in the hippocampus and entorhinal cortex of the brain begin to degrade [2,3,4]. AD is extremely widespread with more than 5 million cases in the United States and more than 50 million cases worldwide. Primarily, symptoms of AD begin at the age of 65; however, there are patients who begin experiencing symptoms at around their 40s and 50s. This is known as early onset AD, and it is strongly linked to genetics [1]. Currently, there is no definite cure for AD. The difficulty of finding working treatments for AD lies in the fact that there is not a single underlying cause of AD, it is hard to penetrate the blood brain barrier, and it is hard to diagnose AD patients before they have already suffered irreversible damage [5]. AD is caused by a plethora of factors, environmental, genetic, and neurochemical. So far, no single treatment has been able to target all of the causes of AD nor all of the hallmarks of AD. Some target the acetylcholinesterase while others target the NMDA-receptor [6,7]. While few of these treatments are approved by the FDA, none of them provide a foul-proof cure. This makes treatment for AD extremely difficult because there are so many underlying factors.

However, despite the difficulty surrounding the development of a cure for AD, there are numerous approaches to this vast problem. One of the approaches is utilizing glucagon-like peptide-1 (GLP-1), a gastrointestinal peptide from enteroendocrine L-cells. This peptide is released in response to food intake in order to decrease blood sugar levels [8]. Additionally, GLP-1 is present in certain neurons in the nucleus of the solitary tract. It serves neurogenesis and neuroprotective effects, which protects neurons and promotes growth [9]. This feature makes GLP-1 a viable treatment for AD. Despite this, GLP-1 is more commonly used as a treatment for type-2 diabetes because it enhances the secretion of insulin. However, it is important to note that there are a few shared pathological features between diabetes and AD. One of which is insulin dysfunction and the other is glucose metabolism dysregulation [10]. As a result, the drug for the treatment of diabetes may be a possible treatment for AD as well due to the shared pathological features. Throughout several preclinical trials, the effect of GLP on AD patients have revealed positive results, including the benefits of improved glucose transporters and blood flow. For example, in Chang et al., 2020, researchers treated cells with Aß protein with semaglutide, a GLP-1 analogue [11]. The results showed enhanced autophagy and a decline in apoptosis. Although these results do not show how GLP-1 works in AD patients, they give a clue about how GLP-1 may defend against AD. As a result, more research is needed in order to conclude the effects. Other preclinical trials conducted on mice have also shown positive results. When Liraglutide was administered to mice, the results showed protection against memory impairment and for insulin receptors and synapses [12].

This meta-analysis serves to evaluate the effects of GLP-1 on AD patients. Although there is no certain cure for AD, treatments may improve AD patients' lifestyle and even prolong their life. It is uncertain whether GLP-1 is a viable treatment for AD; thus, it is necessary to use a meta-analysis in order to conclude the experimental results of several clinical and preclinical trials as well as the efficacy of GLP-1 as a treatment for AD. This meta-analysis serves as a useful tool for scientists and researchers who are racing to find better treatments for AD. As a disease that affects millions of people worldwide, AD needs to be addressed properly, and all treatment methods must be thoroughly investigated. This meta-analysis on the effect of GLP-1 on AD patients will thoroughly investigate one of many treatment methods.

2. Methods

2.1. Search Strategy

The following electronic databases will be searched from their inception until February 2021: EMBASE, MEDLINE, phycINFO, CINAHL, PubMed, Cochrane CENTRAL, and ClinicalTrials.gov. Only Randomized Control Trials (RCTs) and clinical trials will be included. The following Medical Search Heading (MeSH) will be used: Alzheimer's Disease, Alzheimer, Alzheimer's, and GLP-1.

DOI: 10.54254/2753-8818/32/20240813

2.2. Including Criteria

The review will include all relevant Clinical Trials and Randomized Controlled Trials (RCTs) studying the effectiveness and safety of GLP-1 for Alzheimer's Disease. Following PRISMA guidelines, studies that are: duplicates, ongoing trials, case reports, chart reviews, non-AD patients, conference abstracts, and or have no full-text available, will be excluded. There is no criteria and limitation on the types of participants. The type of intervention selected is GLP-1 receptor agonists, however, because we have not defined which specific agonists to include, all GLP-1 receptor agonists can be the intervention.

2.3. Data Extraction

The two primary outcomes include biomarker measurements, in particular the measurement of Amyloid beta (Aß) and cognitive measurements of the Wechsler Memory Scale - Fourth Edition (WMS-IV) system. The reasoning of choosing the two measurements is because the two included studies vary in their measurement choice and Aß measurement and cognitive measurement are their common reporting reporting measurement. Furthermore, Aß is also known to be an important contributor towards the development of Alzhimer's disease, as it is commonly known that Aß is the main component of the amyloid plaques found in the brains of people with Alzheimer's disease. However, due to the studies not having a shared cognitive measurement system, the decision of choosing two similar cognitive measurement systems of the extracted outcomes had to be made.

2.4. Bias assessment

Review Manager (RevMan) V5.4 software will be used to perform bias assessments on the included studies. This evaluation was conducted by creating a risk of bias graph to determine the level of bias risk, and a funnel plot to assess for any publication bias.

2.5. Statical Analysis

Stata software will be used for statistical analysis for the purpose of meta-analysis using a fixed-effect model. Effect size will be calculated using the data collected from the two studies. A forest plot will be generated from synthesised data for two separate outcomes of biomarker measurement and cognitive measurement. The heterogeneity level will be determined using heterogeneity determination tools. Whereas sensitivity analysis will not be able to be conducted due to an insufficiency of the number of included studies.

3. Results

3.1. Literature Search Result

We examined studies reporting the effects of GLP-1 on Alzheimer's disease. Using advanced search, we determined the amount of abstracts and titles regarding this topic. We searched the key words of Alzheimer's disease, Alzheimer, Alzheimer's, and GLP-1 from 6 database (EMBASE, phycINFO, CINAHL, PubMed, Cochrane CENTRAL, and ClinicalTrials.gov.) and identified 500 relevant studies. After removing 34 duplicates, there were 466 studies left. For further screening, we excluded the review papers, studies with the wrong intervention and outcome, case series, ongoing trials, and secondary analyses. Lastly, we included 2 full-text papers into our analysis. The selection process flow diagram is shown in Figure 1.

DOI: 10.54254/2753-8818/32/20240813

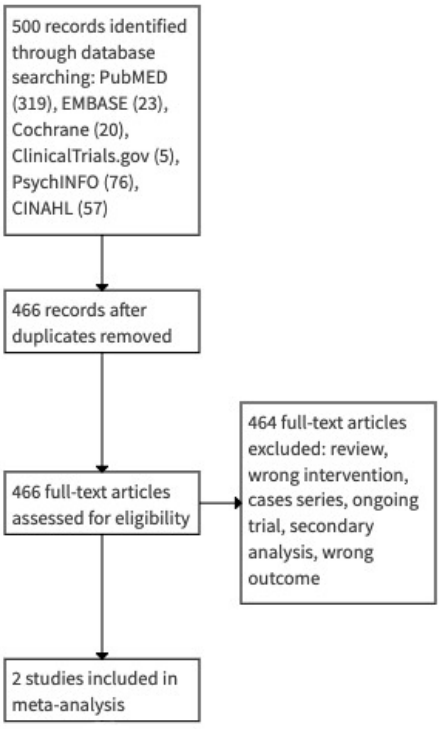


Figure 1. PRISMA flow chart

3.2. Study Quality Evaluation

We reviewed the risk of bias for the 2 clinical trials included in the meta-analysis. The assessment of risk of bias results are illustrated in Figure 2. In Geji 2016, there is a low risk of bias in all the categories other than attrition biases and other biases, in which there is an unclear risk of bias. In Mullins 2019, other than having an unclear risk of bias in other biases, there is a low risk of bias in all the categories. Overall, as can be seen in Figure 2, there is no major risk of bias for our included studies.

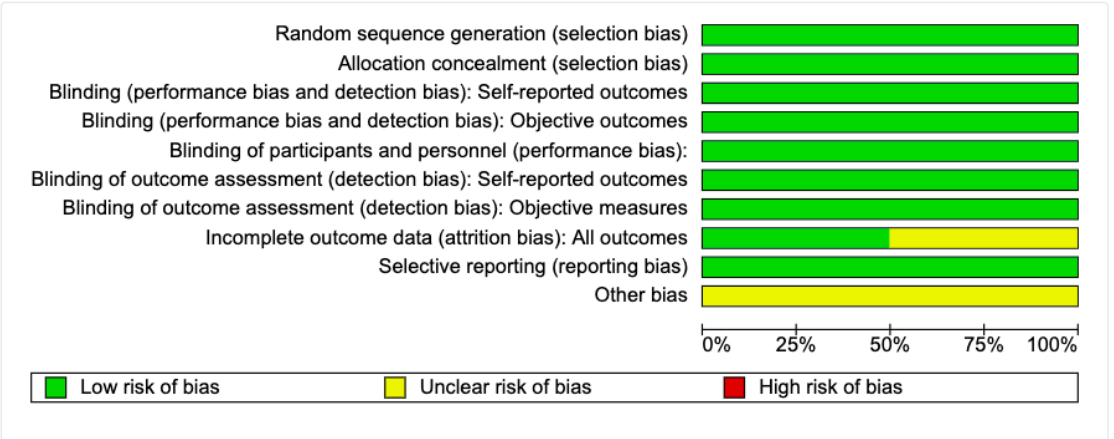


Figure 2. Risk of bias Graph

DOI: 10.54254/2753-8818/32/20240813

3.3. Patients and Study Characteristics

Table 1. Summary of Study Characteristics

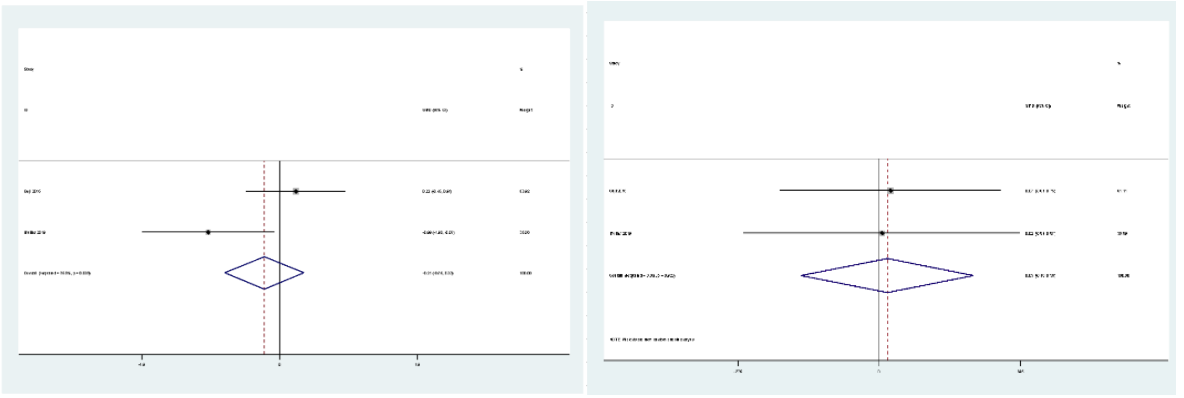
Author Year of Publication	Study Design Randomized? Double-blind or single blind? Placebo-controlled? Cross-over trial or paralle trial?	Study Duration	Drug type/Dose	Sample size Total number (no.of dropouts)	Sex (% Male)	Age,Mean (SD),y	Cognitive /behavioral outcome	A-beta outcome	Tau protein outcome
Gejl,2016	Randomized,double blind, placebo-controlled parallel clinical tria	26 weeks	Liraglutide	34	61.76% 75% (Placebo) 42.86% (Liraglutde)	66.6(Placebo) 63.1 (Liraglutide) SD not available	27.2 (Placebo) 27.1(Liraglutide)	No definitive value (shown in a graph in the study	Not studied.
Mullins, 2019	Randomized,double blind, placebo-controlled parallel phase II clinica trial	18 months	Exenatide	21	52.38% 40% (Placebo) 63.64% (Exenatide)	74.0(Placcbo) 71.7 (Exenatide) SD not available	26.0(Placebo 25.5(Exenatide)	4.997 (Placebo) 4.055(Exenatide)	2017.9 (Placebo) 1841.0 (Exenatide)

We examined studies reporting the effects of GLP-1 on Alzheimer's disease. Using advanced search, we determined the amount of abstracts and titles regarding this topic. We searched the key words of Alzheimer's disease, Alzheimer, Alzheimer's, and GLP-1 from 6 database (EMBASE, phycINFO, CINAHL, PubMed, Cochrane CENTRAL, and ClinicalTrials.gov.) and identified 500 relevant studies. After removing 34 duplicates, there were 466 studies left. For further screening, we excluded the review papers, studies with the wrong intervention and outcome, case series, ongoing trials, and secondary analyses. Lastly, we included 2 full-text papers into our analysis. The selection process flow diagram is shown in Figure 1.

3.4. Effect of GLP-1 on AD

We did a meta-analysis on the effectiveness of GLP-1 on patients with Alzheimer's disease. Our result in Figure 3. illustrated the effect of GLP-1 on Alzheimer's disease of the two types of outcomes of our included studies. One of them looks for the biological markers while the other focuses on the Psychiatric and Cognitive Outcomes. Summary of the meta-analysis indicates that patients who were randomized did not significantly reduce their symptoms compared to those patients with placebo. As written in Figure 3(a) the plot for biological markers has a p-value of 0.446. Because its p-value is higher than 0.05, it indicates that it has no significance. Similarly, the plot for Psychiatric and Cognitive Outcomes shown in Figure 3(b) has a p-value of 0.853, which also suggests that it is statically insignificant. Furthermore, the plots have a z-value of 0.76 and 0.19 respectively, signifying that both of their scores are higher than their mean.

DOI: 10.54254/2753-8818/32/20240813



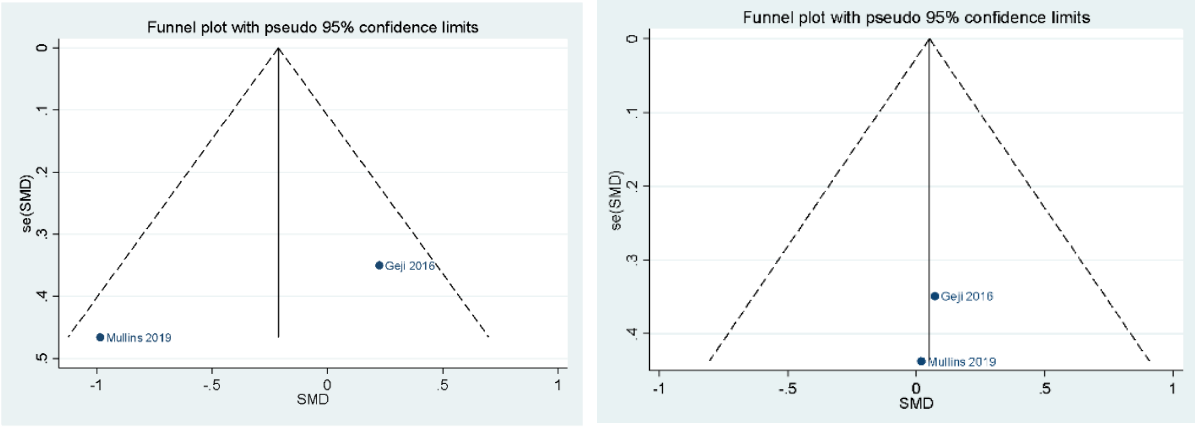
(a) Forest Plot for Biological Markers

(b) Forest Plot for Psychiatric and Cognitive Outcomes

Figure 3. Forest Plots

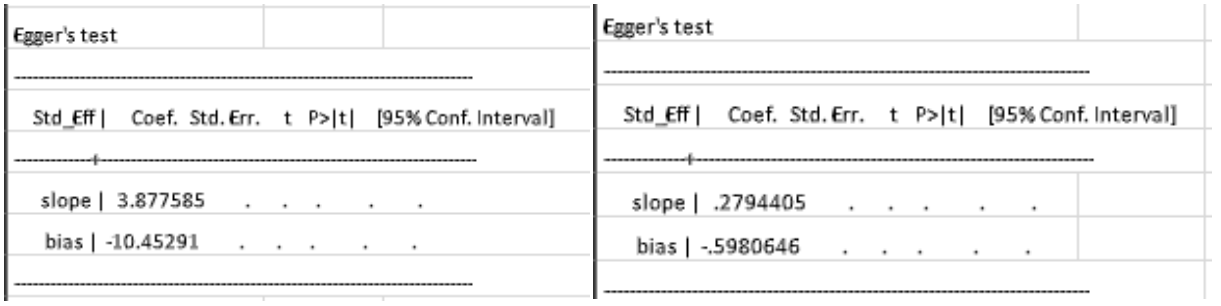
3.5. Publication bias assessment

The funnel plot illustrated in Figure 4 demonstrates that the top of the plot is symmetrical, suggesting that there is unlikely to be any publication biases present in this data set.



(a) Funnel Plot for Biological Markers

(b) Funnel Plot for Psychiatric and Cognitive Outcomes



(c) Egger's Test for Biological Markers

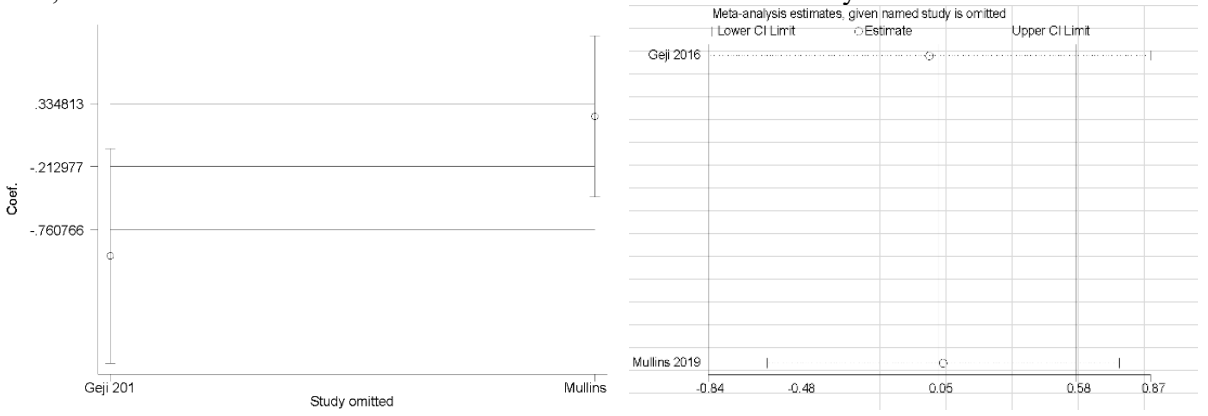
(d) Egger's Test for Psychiatric and Cognitive Outcomes

Figure 4. Funnel Plot and Egger's Test

DOI: 10.54254/2753-8818/32/20240813

3.6. Sensitivity analysis

Sensitivity analysis is conducted by excluding studies to examine the robustness of the pooled effects. By using STATA software, we conducted a sensitivity analysis on 2 of the included studies. As shown in Figure 5, the effect sizes are all still lower than 0. This suggests that there is a limited practical significance between the studies. We can also see from the sensitivity analysis, each effect size has overlap between CI. This suggests that each study does not have a significant effect on our meta-analysis. Thus, we could conclude that all the included studies have low sensitivity.



(a) Sensitivity Analysis for Biological Markers

(b) Sensitivity Analysis for Psychiatric and Cognitive Outcomes

Figure 5. Sensitivity Analysis

4. Discussion

Based on meta-analysis of two clinical trials with Aß and cognitive measurements, our result shows that GLP-1 does not have a statistically significant beneficial effect in treating the symptoms of AD. AD patients who received a GLP-1 agonist treatment did not show a statistically significant improvement in Aß and cognitive measurement throughout the study period compared to AD patients who received a placebo. Cognitive level was measured with the Wechsler Memory Scale, a commonly covered scale by included studies for our analysis. As a result, it is unclear whether GLP-1 analogs have the potential to be involved in future treatments of AD.

We included Aß and cognitive measurement as primary outcomes in this meta-analysis because they are indicators of worsening AD symptoms. The increased concentration of Aß in the brain is a hallmark of AD, and declining cognitive measurement signals to cognitive impairment, which is a symptom in AD. We also investigated agitation in our meta-analysis because agitation is an indicator of AD and may have drastic effects on the quality of life for AD patients.

However, there were limitations to our meta-analysis that restricted our interpretation of the results. Firstly, not all of included studies were involved into the analysis of the Baseline for Agitation. This may lead to insufficiencies in our data and an incomplete conclusion. Furthemore, there is heterogeneity in our study because the first trial is a randomized, double blind, crossover trial, but the second trial is a systematic intervention trial. Because we do not have a third trial to investigate heterogeneity across subgroups, there is inefficient data to conclude whether the trial type has an effect on the study. Additionally, the trials used different drugs and doses for a GLP-1 analog, contributing to another source of heterogeneity. The first trial utilized Liraglutide for 26 weeks while the second trial utilized Exenatide for 18 weeks. Second, the sample size of our meta-analysis is small since we only included 2 clinical trials. There are a few ongoing clinical trials investigating the effect of a GLP-1 analog on AD patients; however, those were not included because there were no published results. The inclusion of these studies would make our meta-analysis more conclusive and reliable. Finally, on another note, we excluded one study from the analysis because the study mix used two kinds of drugs. The above limitations led to us not being able to conclude a significant beneficial effect of GLP-1 on AD patients.

DOI: 10.54254/2753-8818/32/20240813

Our analysis poses a significance in AD research as this is the first meta-analysis concluding the effects of GLP-1 on AD patients and symptoms. Because GLP-1 drugs have been approved by the FDA for the treatment of diabetes and obesity, it has a guaranteed safety profile and effect on patients. Furthermore, GLP-1 has shown many beneficial effects in multiple preclinical trials, which suggests the promising potential of GLP-1 in AD patients. Although there are only a small number of clinical trials conducted so far, there is still a possibility for GLP-1 to become a treatment in future studies.

5. Conclusion

In conclusion, while the meta-analysis of the two clinical trials did not reveal a statistically significant beneficial effect of GLP-1 agonist treatment on Alzheimer's Disease (AD) symptoms, it is essential to acknowledge the complexities of AD and the multifaceted nature of its progression. The study's findings emphasize the need for continued exploration and research in the field of AD treatment, considering the intricate interplay of various factors influencing cognitive decline. Future investigations may benefit from refining study designs, expanding sample sizes, and exploring potential synergies with other therapeutic approaches. Despite the current uncertainty, the pursuit of innovative treatments remains crucial in the ongoing mission to alleviate the burdens of AD on individuals, families, and society as a whole.

References

[1] Alzheimer's A. 2014 Alzheimer's disease facts and figures.
[2] Tolnay M, Probst A. 1999. REVIEW: tau protein pathology in Alzheimer's disease and related disorders. Europathol Appl Eurobiol.
[3] Gandy S. 2005. The role of cerebral amyloid beta accumulation in common forms of Alzheimer disease. J Clin Invest.
[4] Walsh DM, Klyubin I, Fadeeva JV, Rowan MJ, Selkoe DJ. 2002. Amyloid beta oligomers: their production, toxicity and therapeutic inhibition. Biochem. Soc. Trans.
[5] Alavijeh MS, Chishty M, Qaiser MZ, Palmer MA, 2005. Drug metabolism and pharmacokinetics, the blood–brain barrier, and central nervous system drug discovery. NeuroRx.
[6] McGleenon B, Dynan K, Passmore A. 1999. Acetylcholinesterase inhibitors in Alzheimer's disease. Br J Clin Pharmacol.
[7] Lipton S, Chen HS. 2004. Paradigm shift in neuroprotective drug development: clinically tolerated NMDA receptor inhibition by memantine. Cell Death Differ.
[8] Kim W, Egan JM. 2008. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev.
[9] Nauck MA. 2004. Glucagon-like peptide 1 (GLP-1) in the treatment of diabetes. Horm Metab Res.
[10] Femminella GD, Edison P. 2014. Evaluation of neuroprotective effect of glucagon-like peptide 1 analogs using neuroimaging. Alzheimers Dement.
[11] Chang YF, Zhang D, Hu WM, Liu DX, Li L. 2020. Semaglutide-mediated protection against Aβ correlated with enhancement of autophagy and inhibition of apoptosis. J Clin Neurosci.
[12] Batista AF, Forny-Germano L, Clarke JR, Silva NM, Brito-Moreira J, Boehnke SE, Winterborn A, Coe BC, Lablans A, Vital JF, et al. 2018. The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease. J Pathol.