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EXPANDING THERAPEUTIC HORIZONS OF GLP-1 RECEPTOR AGONISTS: FROM METABOLIC REGULATION TO NEUROPROTECTION IN ALZHEIMER'S DISEASE AND ADDICTION DISORDERS – A COMPREHENSIVE REVIEW

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed and approved for the treatment of type 2 diabetes and obesity, are now demonstrating unprecedented therapeutic potential that extends beyond metabolic regulation alone. This review article aims to provide a comprehensive summary and analysis of the current state of knowledge regarding the expanding clinical horizons of GLP-1RAs, with a particular focus on their neuroprotective properties in Alzheimer's disease (AD) and their use in the treatment of substance use disorders (SUDs), including alcohol dependence. Based on a systematic review of selected literature, including the latest preclinical studies and clinical trials, the multifaceted mechanisms of GLP-1 action in the central nervous system were analyzed. The accumulated evidence indicates that GLP-1 receptor agonists (GLP-1RAs) effectively cross the blood-brain barrier, alleviate systemic and local neuroinflammation, reduce oxidative stress, and improve synaptic plasticity. These effects translate into a halt in neuronal degeneration and beneficial cognitive outcomes in patients with early symptoms of AD. Furthermore, these drugs have been shown to innovatively modulate reward pathways in the brain (including the dopaminergic system), effectively reducing drug cravings, compulsive behaviors, and the consumption of alcohol and other addictive substances. In summary, the repurposing of GLP-1 receptor agonists represents an extremely promising strategy for treating complex neurological and psychiatric disorders. However, further large-scale clinical trials are necessary to optimize dosing protocols and confirm the long-term safety profile.

KEYWORDS

GLP-1 Receptor Agonists, Alzheimer's Disease, Substance Use Disorder, Alcohol Use Disorder, Drug Repurposing

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1. Introduction

Neurodegenerative disorders and substance use disorders (SUD) currently represent some of the greatest, most complex, and most costly challenges facing modern public health, social welfare, and the global economy. With the unprecedented aging of the global population, the incidence of dementia—of which Alzheimer's disease (AD) accounts for as much as 60–70% of all cases—is reaching pandemic proportions. From a socioeconomic perspective, progressive cognitive decline, leading to patients' complete dependence on others, generates enormous direct costs for healthcare systems as well as astronomical indirect costs. The latter result primarily from the loss of productivity among the patients themselves, as well as from the enormous physical, psychological, and financial burden on informal caregivers, who are most often family members. The devastating impact of dementia on the social fabric is undeniable and calls for urgent therapeutic innovations. [10, 11, 28, 29]

In parallel with the crisis associated with age-related diseases, societies around the world are grappling with the destructive effects of substance use disorders. Substance use disorders, including in particular alcohol use disorder (AUD), addiction to opioids, stimulants (such as cocaine), and tobacco, have a devastating impact on individuals' physical and mental health. However, this impact extends far beyond the individual, deeply affecting the social fabric. Addiction contributes to the breakdown of family ties, increased rates of domestic violence, crime, and unemployment, as well as a drastic rise in premature mortality. The development, course, and treatment options for these disorders are greatly influenced by broad sociocultural contexts, substance availability, minority stress, economic conditions, and pervasive marketing—especially in the case of alcohol. This results in a situation where psychosocial interventions alone are often insufficient, and patients require effective pharmacological support. [1, 3, 23, 25]

Despite decades of intensive, multi-billion-dollar investment in scientific research, treatment options for both of these groups of disorders remain highly disappointing and fail to meet basic clinical needs. In the case of Alzheimer's disease, conventional medications (such as acetylcholinesterase inhibitors or NMDA receptor antagonists) offer only temporary and relatively modest symptom relief, without modifying the underlying process of neuronal death or halting disease progression. Although the latest therapies based on monoclonal antibodies targeting amyloid show some potential for clearing senile plaques from the brain, their clinical efficacy remains a subject of debate, and high costs and the risk of serious side effects (including cerebral edema) limit their widespread use. Similarly, in the field of addiction medicine, approved pharmacotherapies (e.g., naltrexone, acamprosate, or disulfiram for the treatment of alcoholism) are characterized by moderate efficacy, poor patient adherence to medical recommendations, and very high relapse rates, often reaching 70% in the first year after treatment begins. [2, 11, 17, 23, 29]

In light of these drastic unmet medical needs, the concept of innovative “drug repurposing” has gained immense significance in global pharmacology and biotechnology. This strategy involves searching for entirely new, non-obvious therapeutic indications for molecules that have already been rigorously tested and approved for the treatment of other diseases. Repurposing allows for a significant shortening of the research process, a reduction in costs, and a minimization of risks related to a drug's safety profile, making it a highly effective technology for bringing medical innovations into clinical practice. In this context, glucagon-like peptide-1 receptor agonists (GLP-1RAs)—a class of drugs that originally revolutionized diabetes care and obesity treatment—are emerging as some of the most fascinating and promising candidates for breaking the impasse in neurology and psychiatry. [8, 14, 16, 19]

Glucagon-like peptide-1 (GLP-1) is an endogenous hormone belonging to the incretin family, consisting of 30 amino acids. Under physiological conditions, it is produced and secreted primarily in the peripheral gastrointestinal tract by L cells located in the distal small intestine (ileum and colon), and its secretion is triggered in direct response to food intake and gastric emptying. The classic, well-established role of this hormone is to optimize energy metabolism: GLP-1 stimulates insulin secretion by pancreatic beta cells in a manner strictly dependent on current blood glucose levels, while simultaneously inhibiting the secretion of glucagon (a hormone that raises blood sugar levels), delaying gastric motility and emptying, and stimulating brain centers to generate a strong signal of satiety. These actions occur through interaction with the specific GLP-1 receptor (GLP-1R), which belongs to the extensive family of G protein-coupled receptors (GPCRs). [4, 9, 10, 20]

Understanding the natural role of this peptide served as a catalyst for the development of synthetic GLP-1 analogs (such as exenatide, liraglutide, dulaglutide, and the latest-generation semaglutide). Natural human GLP-1 is extremely short-lived—it is broken down in the blood within just 1–2 minutes by the enzyme dipeptidyl peptidase-4 (DPP-4). Pharmaceutical engineering has produced analogs that are resistant to this

enzyme, extending their half-life to several hours and, in the case of newer generations, even up to a full week. These drugs have achieved spectacular commercial and clinical success, becoming the cornerstone of modern treatment for type 2 diabetes (T2DM) and the obesity epidemic by sustainably lowering blood glucose levels, promoting significant weight loss, and providing unprecedented cardiovascular and renal protection for patients. [4, 19, 20, 27]

However, recent breakthroughs in neurobiology clearly demonstrate that the biological activity of the GLP-1 axis is not limited solely to peripheral organs and metabolic regulation. These mechanisms exert a profound, multidirectional influence on the central nervous system (CNS). A key discovery was the identification that GLP-1 is synthesized not only in the intestines but also endogenously, directly in the human brain. The main site of its central production is a population of neurons located in the brainstem, specifically in the nucleus tractus solitarius (NTS). From this strategic hub, GLP-1-producing neurons send extensive and dense axonal projections to key subcortical and cortical areas. Furthermore, modern GLP-1RA pharmaceuticals, despite their molecular size, have the ability to cross the blood-brain barrier (BBB) or influence the brain by stimulating ascending vagal pathways and periventricular structures that lack a tight barrier. [6, 7, 26, 30]

Detailed brain mapping has revealed the presence of GLP-1R receptors in structures that are absolutely critical for cognitive processes as well as the regulation of emotions and motivation. High expression of these receptors was found, among other places, in the hippocampus, prefrontal cortex, and amygdala—regions that are the earliest and most severely affected by neurodegenerative processes in Alzheimer’s disease. This discovery has established a strong pathophysiological framework for the use of GLP-1R agonists as neuroprotective agents. Evidence from epidemiological studies demonstrates an undeniable link between peripheral insulin resistance and a dramatic increase in the risk of developing dementia, which has led the scientific community to conceptualize Alzheimer’s disease as a form of “type 3 diabetes.” In a brain affected by AD, insulin signaling pathways are drastically impaired (cerebral insulin resistance), leading to disturbances in neuronal glucose metabolism, the onset of chronic neuroinflammation, oxidative stress, and the accumulation of pathological proteins. The use of GLP-1RAs offers a potential rescue mechanism: restoring cellular insulin sensitivity, inhibiting the toxic activation of microglia and astrocytes, and promoting neurogenesis and synaptic plasticity, which ultimately halts the progression of neurodegeneration. [10, 12, 13, 21, 22, 28]

On the other hand, an extremely high density of GLP-1R receptors has been identified in key nodes of the mesolimbic dopaminergic system, which constitutes the brain’s primary center for reward and motivation. This includes the ventral tegmental area (VTA) and the nucleus accumbens (NAc). It has traditionally been believed that the presence of GLP-1 in these regions serves solely to inhibit pathological overeating and signal satiety. However, preclinical studies have shown that the neural pathways responsible for food addiction evolutionarily overlap with those hijacked and pathologically altered by hard drugs and alcohol. GLP-1RA drugs, by stimulating the relevant inhibitory circuits, are capable of drastically attenuating the dopamine release in the nucleus accumbens triggered by the consumption of alcohol, cocaine, or nicotine. At the behavioral level, these drugs significantly reduce the rewarding properties of substances (by lowering so-called “incentive salience”), which translates into a drastic reduction in substance-seeking behavior, the elimination of drug cravings, and the prevention of relapse. This discovery laid the foundation for the use of these molecules in the treatment of the most severe forms of substance use disorders. [2, 3, 4, 6, 24, 26]

Given this exceptionally broad and innovative potential, the primary objective of this review article is to provide a comprehensive, multi-level synthesis of the current state of knowledge regarding the use of GLP-1 receptor agonists beyond their classical metabolic indications. By integrating perspectives from molecular neurobiology, translational medicine, and public health sciences, this work examines in detail the neuroprotective mechanisms of GLP-1RAs in the context of delaying and treating Alzheimer’s disease, as well as their groundbreaking role in alleviating compulsive and addictive behaviors across a broad spectrum of addictions. A thorough analysis of rigorous preclinical studies, evolving data from Phase II and III clinical trials, and the latest reports from real-world evidence (RWE) will allow for an assessment of the true potential of these therapies. The successful repositioning of GLP-1RA drugs could not only represent the first-ever effective, disease-modifying therapy for millions of desperate patients with dementia and addictions, but also set new standards in shaping innovative social welfare and public health policies fit for the 21st century. [5, 8, 16, 17, 18, 19]

2. Methodology

This review article was designed and conducted based on a structured, systematic approach to the search, selection, and synthesis of scientific literature. The overarching goal of the adopted methodology was to ensure the highest level of rigor, objectivity, and reproducibility of the analytical process, which is crucial for minimizing the risk of systematic error (bias) when evaluating such an innovative and multidimensional issue as the repositioning of GLP-1 receptor agonists. Although this study is a comprehensive narrative review, the data collection process employed a conceptual framework typical of systematic reviews to precisely identify those publications that make the most significant contribution to understanding the neuroprotective and behavioral properties of GLP-1RAs.

The literature search was conducted exhaustively, using major international medical and interdisciplinary databases, including PubMed and Google Scholar. The search strategy covered literature published in English, with particular emphasis on the most recent reports from 2015 to 2026. To optimize the search, advanced combinations of keywords and MeSH (Medical Subject Headings) terms were used, linked by logical operators (Boolean search operators: AND, OR, NOT). The main search strings were based on three thematic pillars. The first pillar concerned pharmacological interventions (“glucagon-like peptide-1 receptor agonist,” “GLP-1RA,” “liraglutide,” “semaglutide,” “exenatide,” “dulaglutide”). The second pillar defined the field of neurodegeneration (“Alzheimer’s disease,” “dementia,” “mild cognitive impairment,” “neuroprotection,” “neuroinflammation”). The third pillar covered the field of addiction studies (“substance use disorder,” “alcohol use disorder,” “addiction,” “craving,” “reward system,” “alcohol consumption”). Searches were conducted both for each of these areas separately and in cross-combinations to identify literature linking metabolic pathways to central nervous system pathologies.

Independent researchers undertook a multi-stage selection process. In the first stage, titles and abstracts were reviewed to exclude articles that clearly did not meet the inclusion criteria. In the second stage, the full texts of the selected articles were obtained and then subjected to an in-depth evaluation in terms of their substantive relevance and methodological quality. A corpus of 30 fully validated scientific publications was selected for the final data extraction.

Particular attention was paid in the methodological process to an interdisciplinary approach, which is a key requirement from the perspective of innovative social technologies and public health. This means that during the analysis of the selected texts, emphasis was placed not only on specific intracellular pathways (e.g., PI3K/Akt signaling or the reduction of oxidative stress), but equally on how these biochemical changes manifest in individual behavior and what long-term social implications they may have.

3. Results

As a result of a systematic literature search and rigorous selection process, 30 key, validated scientific publications were identified that provide consistent and highly compelling evidence that GLP-1 receptor agonists (GLP-1RAs) exhibit potent pleiotropic effects in the central nervous system (CNS). The collected data, encompassing a broad spectrum of studies—ranging from in vitro molecular-level analyses, through in vivo animal models, to advanced Phase II and III clinical trials and retrospective studies of large patient cohorts (Real-World Data)—unequivocally demonstrate the efficacy of this class of drugs in modulating neurodegenerative pathologies and reward circuits. The following subsections provide a detailed synthesis of the extracted results, organized by cellular mechanisms, effects in Alzheimer’s disease (AD), and outcomes in the treatment of substance use disorders (SUD), including primarily alcohol use disorder (AUD). [5, 11, 14, 19, 24]

3.1. Central Mechanisms of Action and Intracellular Signaling of GLP-1 Receptor Agonists (GLP-1RAs)

A fundamental prerequisite for the neuroprotective and neuromodulatory effects of any systemic drug is its ability to cross the blood-brain barrier (BBB). The results of the analyzed pharmacokinetic studies demonstrate that the natural human GLP-1 peptide and its engineered analogs (such as liraglutide, exenatide, and semaglutide) possess this ability, although the degree of their penetration varies depending on the molecule’s lipophilicity and size. It has been demonstrated that liraglutide and semaglutide, despite their strong binding to plasma albumin, successfully reach the brain parenchyma via transmembrane transport as well as through diffusion in the circumventricular organs, where the BBB is inherently permeable (e.g., in the subventricular zone or the area postrema). In addition to direct penetration, GLP-1RAs activate receptors

located on the afferent terminals of the vagus nerve within the abdominal cavity, generating a strong ascending signal that ultimately reaches the nucleus of the solitary tract (NTS) in the brainstem, from where it spreads in a cascade to higher levels of the CNS. An alternative, highly innovative route of administration being investigated in the latest experimental models is intranasal delivery of GLP-1RAs, which allows for direct transport of the drug to the brain via the olfactory and trigeminal pathways, completely bypassing systemic metabolism and minimizing peripheral side effects (e.g., nausea) . [4, 6, 8, 10, 18, 20]

The key cellular mechanism responsible for the neuroprotective effects of GLP-1RAs is the reversal of so-called cerebral insulin resistance, an early and destructive stage in the pathogenesis of Alzheimer's disease, often referred to in the literature as "type 3 diabetes". Postmortem pathological studies of the brains of patients with AD have demonstrated a drastic reduction in sensitivity to endogenous insulin, manifested by abnormal, excessive serine phosphorylation of the insulin receptor substrate-1 (IRS-1). This process completely blocks the intracellular 3-phosphatidylinositol kinase (PI3K) and protein kinase B (Akt) pathways, leading to a catastrophic energy deficit in neurons. Administration of GLP-1 agonists effectively reactivates this pathway. Activation of the GLP-1R, a classic G-protein-coupled receptor, leads to an increase in intracellular cAMP levels and the activation of protein kinase A (PKA). This cascade cross-stimulates the PI3K/Akt/mTOR pathway, which restores metabolic homeostasis in neurons, facilitates glucose transport into cells, and promotes the transcription of genes responsible for cell survival, synaptogenesis, and normal axonal growth. [9, 10, 12, 13, 22, 28]

Furthermore, an analysis of available sources highlights the extremely potent anti-inflammatory effects of this class of drugs. Chronic neuroinflammation, driven by hyperactivated microglia and reactive astrocytes, is a major driver of neuronal death in both Alzheimer's disease and Parkinson's disease. In vitro and in vivo studies have shown that stimulation of the GLP-1R directly inhibits the pro-inflammatory phenotype of microglia (by inhibiting the NF- κ B pathway), drastically reducing the secretion of neurotoxic cytokines such as tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6). These drugs simultaneously promote the conversion of microglia to the M2 phenotype, which is responsible for reparative processes, phagocytosis of damaged proteins, and the release of neurotrophins (e.g., BDNF). In the context of glial cells, it has been observed that GLP-1RAs protect the blood-brain barrier by increasing the integrity of tight junctions in endothelial cells and preventing pathological activation of astrocytes, which collectively stabilizes the CNS microenvironment and reduces oxidative stress. [8, 12, 14, 21, 27, 29]

3.2. Research Findings on Alzheimer's Disease (AD) and Cognitive Disorders

By translating the signaling pathways described above into specific pathologies characteristic of Alzheimer's disease, preclinical studies using advanced genetic models (e.g., double- and triple-transgenic APP/PS1 and 3xTg mice) provide excellent evidence of the efficacy of GLP-1R agonists. It has been found that exenatide, liraglutide, and the newest agent, semaglutide, all demonstrate the ability to significantly reduce amyloid-beta plaque burden in the hippocampus and cerebral cortex of experimental animals. This efficacy results from the stimulation of A β peptide clearance, as well as the inhibition of tau protein hyperphosphorylation—the two main biomarkers of neurodegeneration in AD. This occurs via an Akt-dependent pathway that leads to the phosphorylation, and thus inactivation, of glycogen synthase kinase 3 beta (GSK-3 β). Inhibition of GSK-3 β directly prevents the formation of pathological tau neurofibrillary tangles. At the behavioral level, treatment of animals with GLP-1RAs consistently prevented cognitive decline, significantly improving performance on spatial memory tests (e.g., the Morris water maze) and the ability to recognize novel objects. [8, 10, 11, 14, 22, 28, 29]

The optimism emerging from the laboratories is increasingly reflected in the results of human studies, although these remain in the early stages of implementation. Direct clinical evidence comes from carefully selected placebo-controlled trials. A key milestone was the British Phase 2b trial known as ELAD (Evaluating Liraglutide in Alzheimer's Disease), in which patients with mild to moderate early-stage AD were administered 1.8 mg of liraglutide for 52 weeks. Although this study did not show a statistically significant difference in the primary endpoint regarding total cerebral glucose metabolism assessed by PET (FDG-PET), significant secondary benefits were identified. Liraglutide drastically slowed the rate of brain volume loss—as measured by structural magnetic resonance imaging (MRI)—compared to the placebo group. Furthermore, a highly significant improvement was observed in composite cognitive tests (particularly in the domains of executive function on the ADAS-Exec scale). The success of these early clinical trials, combined with remarkable results for the related Parkinson's disease (Phase II trials with exenatide), served as a catalyst for large-scale, ongoing multicenter Phase III trials with oral semaglutide (the EVOKE and EVOKE+ programs), which have the potential to ultimately demonstrate these drugs' ability to structurally modify the progression of AD. [8, 11, 17, 27, 29]

Equally fascinating results were yielded by a meta-analysis of real-world evidence (RWE) from healthcare systems involving patients with type 2 diabetes. Retrospective analyses of massive national patient registries from Scandinavia and large insurance databases in the United States and the United Kingdom allowed for a comparison of dementia incidence rates in patients treated with GLP-1RA with those receiving older classes of antidiabetic drugs (e.g., sulfonylureas, DPP-4 inhibitors, insulin). The cumulative results of these large-scale epidemiological analyses demonstrate with striking consistency that exposure to GLP-1RA drugs is associated with a statistically highly significant reduction in the risk of developing Alzheimer's disease and other forms of dementia, often by more than 40–50% compared to the control group. Even given the fact that the diabetic population is inherently at a much higher risk of neurodegeneration due to coexisting microvascular and macrovascular pathologies, the protective effect of GLP-1 appears to be entirely indisputable and independent of glycemic control (blood sugar levels) alone, suggesting a unique neuroprotective mechanism specific to this receptor axis. [9, 11, 15, 16, 22]

3.3. Treatment Outcomes for Substance Use Disorders (SUD) and Alcohol Use Disorder (AUD)

A second promising area for the innovative use of GLP-1 receptor agonists, as outlined in the reviewed literature, is the treatment of substance use disorders, particularly alcohol use disorder (AUD), which carries a heavy social burden. From an anatomical and functional perspective, the evolutionary pathways regulating food intake—for which GLP-1 is responsible—closely intersect with the pathways of the reward system, which are pathologically altered by addictive substances. A very high density of GLP-1R receptor expression has been observed in key nodes of the mesolimbic dopaminergic system: the ventral tegmental area (VTA) and the nucleus accumbens (NAc), as well as in the bed nucleus of the stria terminalis (BNST). Preclinical studies conducted on carefully selected rodent genetic lines (e.g., rats and mice bred for high alcohol preference) have shown that peripheral administration of GLP-1RA (liraglutide, semaglutide, or exenatide) immediately and in a dose-dependent manner reduces total alcohol intake, eliminates the preference for ethanol over water, and, most importantly, drastically suppresses compulsive substance-seeking behavior and relapse into drinking following a period of enforced abstinence. Neurochemically, these drugs achieve this by dampening the sharp surges of dopamine in the NAc induced by the administration of alcohol, cocaine, nicotine, or opioids, thereby acting as a sort of buffer for the brain's motivational system, while not inducing anhedonia in animals with respect to natural rewards (e.g., social interaction or ordinary food). [2, 3, 4, 5, 6, 23, 26, 30]

Findings from the preclinical setting have been strongly supported by initial tests in human models, including those using functional magnetic resonance imaging (fMRI). Imaging studies conducted in obese patients undergoing incretin therapy, as well as early studies involving patients with diagnosed alcohol use disorder, have shown that drugs such as exenatide significantly reduce the activation of the prefrontal cortex and subcortical circuits in response to exposure to alcohol-related cues (so-called cue-reactivity, e.g., images of alcoholic beverages). In randomized, controlled trials of patients with AUD receiving liraglutide (as well as in tobacco-smoking patients receiving oral therapies), an absolute efficacy rate comparable to that observed in animal studies in terms of total abstinence has not yet been observed; this is due to the significantly greater complexity of the human psyche and the social determinants of addiction. Nevertheless, it has been demonstrated that GLP-1RA interventions significantly reduce the number of days of heavy drinking among the most severely affected patients and also greatly facilitate the maintenance of tobacco abstinence among smokers, while preventing the rapid weight gain typical of smoking cessation, which dramatically increases patients' willingness to remain in treatment. [1, 2, 7, 24, 25]

Retrospective analyses of massive datasets of electronic health records (EHRs) represent a major step forward in this regard. Systematic reviews examining the association between GLP-1RA use and the drinking behaviors of patients with metabolic diseases have documented self-reported significant reductions in the desire to consume alcohol among these patients, a reduction in episodes of heavy drinking, and a decrease in the number of medical diagnoses related to alcohol abuse (e.g., alcohol-induced acute pancreatitis or psychiatric interventions) within the first few months of starting treatment with semaglutide or liraglutide, compared to other SGLT-2 inhibitors or metformin. Equally promising observational data pertain to reductions in opioid maintenance therapy doses among patients undergoing treatment for addiction to hard drugs. The convergence of so many lines of evidence—ranging from the inhibition of mesolimbic pathways in vivo to population-level declines in alcohol and tobacco consumption during the pandemic—regarding the treatment of obesity with these agents—reinforces the hypothesis that in the coming decade, GLP-1RAs may play an absolutely fundamental role in redefining pharmacological treatment protocols for the most severe forms of chemical and behavioral addictions. [1, 3, 5, 6, 7, 19, 23, 24, 30]

4. Discussion

4.1. A Paradigm Shift in the Pharmacotherapy of Central Nervous System Disorders

The findings compiled and synthesized in this systematic literature review clearly demonstrate the ongoing revolution in the approach to treating neurodegenerative diseases and mental disorders that are resistant to conventional therapies. For decades, the dominant paradigm in psychopharmacology and neurology was based on designing drugs that strictly and selectively targeted individual neurotransmitter systems (e.g., acetylcholinesterase inhibitors for Alzheimer's disease, or modulators of GABAergic and opioid receptors for the treatment of alcoholism). Unfortunately, this highly reductionist strategy has yielded only limited clinical success, failing in the face of the extraordinary complexity, plasticity, and redundancy of the human brain. The discovery and confirmation of the central action of glucagon-like peptide-1 receptor agonists (GLP-1RAs) introduces a completely new dimension: a multisystemic intervention that targets the foundations of cellular pathology, such as bioenergetic disorders, cerebral insulin resistance, chronic oxidative stress, and generalized neuroinflammation. The repositioning of these powerful metabolic molecules—which have been successfully used for years in the treatment of diabetes and obesity—currently represents one of the most promising and innovative directions in translational medicine. The analyses conducted unequivocally indicate that restoring metabolic balance at the level of individual neurons and glial cells can exert a cascading, protective effect on entire neural networks, shielding them from the toxic effects of pathological proteins (amyloid-beta, hyperphosphorylated tau) and pathological remodeling caused by chronic exposure to addictive substances. [8, 10, 14, 19, 28, 29]

4.2. Implications from Alzheimer's Disease Research: Advantages Over Current Therapies

In the context of Alzheimer's disease (AD), the potential of GLP-1RA drugs must be considered against the backdrop of recent, highly controversial developments in the field of neuropharmacology. The recent approval by regulatory agencies of monoclonal antibodies targeting amyloid (such as aducanumab and lecanemab) has caused enormous divisions within the scientific and medical communities. These drugs, although capable of removing senile plaques from brain tissue, offer relatively modest cognitive benefits (often bordering on clinical insignificance), while simultaneously carrying a dramatic risk of adverse events associated with amyloid-related imaging abnormalities (ARIA), including, among others, dangerous brain edema and microbleeds. Against this backdrop, the mechanism of action of GLP-1 agonists appears to be incomparably safer and more biologically nuanced. Liraglutide and semaglutide do not directly “attack” accumulated amyloid in a mechanical manner that induces vasculitis, but rather alter the brain's microenvironment, making it more resistant to the toxicity of these deposits while simultaneously suppressing the destructive activity of microglia. The ELAD (Evaluating Liraglutide in Alzheimer's Disease) study clearly demonstrated that patients treated with GLP-1RAs exhibit a significantly slower rate of brain atrophy on MRI scans, which constitutes hard, objective evidence of structural neuroprotection. If the large Phase III clinical trials currently underway (the EVOKE program) with oral semaglutide confirm these observations in a broad population, we will be dealing with the first therapy in the history of medicine that safely, comprehensively, and systemically halts the progression of neurodegeneration. Furthermore, many years of experience with GLP-1RAs in diabetic patients provide us with a unique level of confidence regarding their long-term systemic safety profile. [11, 15, 16, 17, 27, 29]

4.3. A Revolution in Addiction Studies: The Biopsychosocial Dimension of Addiction

The shift in focus from research on metabolic and dementia-related diseases to the field of addiction studies fully reveals the phenomenal adaptive potential of the incretin axis. Substance use disorders, particularly alcohol use disorder (AUD), are characterized by a profound disruption of the patient's hierarchy of values and goals, where the pursuit of the substance becomes a biological imperative that destroys all of the individual's social, professional, and family structures. Traditional pharmacotherapy (naltrexone, acamprosate) faces the problem of low efficacy and dramatically low compliance. Meanwhile, GLP-1 agonists demonstrate the ability to suppress the most fundamental symptom of addiction: the irresistible craving for the substance. From a clinical and psychological perspective, this phenomenon is absolutely groundbreaking. By reducing the excitability of the mesolimbic reward system and dampening the sharp spikes in dopamine release following alcohol consumption or cocaine use, these medications effectively “unlearn” the brain's pathological

habit. As analyses indicate, dampening this biological compulsion provides the patient with a crucial “therapeutic window”—a mental space in which the patient can consciously engage in cognitive-behavioral therapy, group therapy, and the process of rebuilding social bonds. We cannot ignore the fact that the environment, psychological stress, trauma, and socioeconomic factors play a fundamental role in the development and maintenance of addiction. GLP-1RA medications alone do not heal these psychosocial wounds, but they act as a chemical stabilizer—a buffer that protects the patient from physiological relapse while they work through their difficulties in therapy. Such a synergistic approach, integrating advanced pharmacotherapy targeting subcortical circuits with holistic psychotherapeutic and social care, represents the future of modern addiction medicine. [1, 2, 3, 5, 23, 25, 26, 30]

4.4. Implications for Public Health and Social Welfare Policy

The implications of the repositioning of GLP-1R agonists are absolutely enormous and multifaceted. Alzheimer’s disease and other forms of dementia pose one of the greatest threats to the stability of pension and long-term care systems in the aging populations of developed countries (the so-called “silver tsunami”). Currently, in the absence of effective causal treatment, the bulk of the care burden falls on informal caregivers—most often middle-aged and older women (daughters and spouses of patients)—leading to their mass withdrawal from the labor market, drastic impoverishment, and a surge in mental health issues. Reducing the number of new cases of dementia or significantly delaying a patient’s progression from mild cognitive impairment (MCI) to full-blown dementia by just 5 years would reduce total healthcare and social care costs by hundreds of billions of dollars globally, freeing up vast human resources to return to the labor market. Similarly, the economic costs associated with alcohol use disorder (AUD)—resulting from sick leave, crime, property damage, alcohol-related traffic accidents, premature mortality, and domestic violence—range from a fraction of a percent to as much as several percent of GDP in many European countries and the United States. An effective, long-term pharmacological intervention that reduces relapse rates among the addicted population could generate unprecedented savings for national budgets, correctional systems, and social welfare programs, becoming an investment with a massive return on investment in the realm of public health policy. The repositioning of these drugs thus demonstrates how a biological breakthrough directly shapes and resolves crises at the macrosocial level. [11, 15, 22, 25, 29]

4.5. Pharmacoeconomic Challenges, Systemic Barriers, and Inequalities in Access

Despite their phenomenal therapeutic potential, the widespread use of GLP-1 agonists in the prevention of neurodegenerative diseases and the treatment of addiction faces significant barriers within healthcare systems, the most serious of which are financial and access-related barriers. These drugs (especially long-acting formulations, such as semaglutide administered once a week) remain very expensive. Due to the rapid rise in the popularity of these molecules for the treatment of commercial obesity (often outside strict medical indications, so-called off-label use), the global supply chains of pharmaceutical companies have collapsed, leading to unprecedented international drug shortages. In the context of health economics, this raises serious ethical dilemmas and threatens to drastically exacerbate social inequalities in health. In private and mixed healthcare systems, there is a huge risk that innovative neuroprotective and anti-addiction therapies will become “medicine for the rich,” completely inaccessible to the lowest-income groups, ethnic minorities, and marginalized populations, who are statistically at the highest risk for diabetes, dementia, and environmentally-induced substance use disorders. The integration of GLP-1RA therapies into standard psychiatric and neurological treatment guidelines will require radical changes in the architecture of health insurance systems, bold government interventions in price negotiations with pharmaceutical companies, and strong support for generic drug programs once patent protection for these drugs expires. Only then will these technologies become a viable and equitable tool of social policy. [1, 5, 16, 19, 24]

4.6. Limitations of the Current State of Research (Translational Gaps)

Despite immense enthusiasm, the current research landscape surrounding GLP-1R agonists is not free from significant methodological limitations. In the field of substance use disorders, the vast majority of hard evidence comes from preclinical studies in rodents. Animal models (such as the two-bottle test, lever-press self-administration, and conditioned place aversion) are excellent tools for mapping neurochemical circuits; however, they are unable to fully simulate the human phenotype of addiction, which is deeply entangled with language, culture, social status, intergenerational trauma, and environmental triggers (so-called “social cues”). The transfer of findings from the sterile laboratory cage to the complex reality of a patient with AUD has

repeatedly ended in failure throughout the history of science; therefore, caution is warranted. Furthermore, early clinical trials on addiction treatment in humans often suffer from small sample sizes and short follow-up periods (typically less than 12 weeks), which prevents a reliable assessment of the impact of medications on long-term relapse prevention. In the field of neurodegenerative diseases, although meta-analyses of patients with diabetes show a reduced risk of dementia, we must remember that this evidence is associative and observational, not causal. Individuals without diabetes or obesity who develop Alzheimer's disease exhibit a slightly different pathophysiological trajectory of the vascular system; therefore, real-world evidence (RWE) findings may not be 100% applicable to the normoglycemic population, a point that continues to be rigorously tested in Phase III trials. [4, 6, 7, 11, 25, 26, 30]

4.7. Side Effects and Long-Term Safety of the Intervention

Another key aspect of the discussion is the tolerability of the therapy and the patients' safety profile, which determine the likelihood that a patient will remain in the treatment process (the so-called retention rate). GLP-1RA medications are associated with severe gastrointestinal side effects, such as nausea, vomiting, diarrhea, and delayed gastric emptying, which are most pronounced during the initial dose-escalation phase. In the population of psychiatric patients and those struggling with addiction—where the ability to take unpleasant medications regularly and conscientiously is often severely limited—these side effects can lead to premature discontinuation of treatment and a rapid relapse into compulsive behaviors. Furthermore, recent medical reports highlight the phenomenon of significant loss of lean body mass (sarcopenia), including muscle mass, in individuals on long-term treatment with, for example, semaglutide. In elderly patients with early-stage Alzheimer's disease (which in itself often leads to physical wasting—dementia-related cachexia), excessive loss of muscle tissue caused by incretin-based medications can lead to the development of frailty syndrome, an increase in falls, and a rapid deterioration in prognosis, which requires precisely defined strategies for nutritional support and strength training as part of an integrated therapy. Continuous population-based monitoring is also necessary, although concerns regarding an increased risk of pancreatitis, medullary thyroid cancer, or sudden exacerbations of suicidal ideation in adults have largely been allayed by major regulatory agencies (FDA, EMA) thanks to the latest epidemiological data. [9, 17, 19, 20, 24]

4.8. Future Prospects: Polypharmacy and Targeted Routes of Administration

The development of biotechnology is not limited to unidirectional intervention in the GLP-1 system. Recent preclinical studies suggest that the future of incretin neuropharmacology may lie in a new generation of drugs, namely dual and triple agonists known in scientific jargon as “twincretins.” These combine, within a single molecule, stimulation of the GLP-1 receptor, the glucose-dependent insulinotropic polypeptide (GIP) receptor, and the glucagon (Gcg) receptor (e.g., molecules such as tirzepatide or retatrutide). It is believed that the synergistic stimulation of several peptide receptors in the central nervous system may exert an even stronger neuroprotective and anti-inflammatory effect while allowing for the use of lower total doses, which will significantly reduce the patient's gastrointestinal burden. Another highly innovative area of research, of crucial importance to neurology, is the attempt to bypass the blood-brain barrier (BBB) and hepatic metabolism through the use of intranasal administration. Aerosol medications, deposited in the upper nasal cavity, can diffuse directly along the olfactory bulb and the trigeminal nerve straight into the cerebrospinal fluid and brain parenchyma. This would maximize the therapeutic dose reaching key areas for memory (the hippocampus) and motivation (the nucleus accumbens), while minimizing systemic circulation of the drug—a true breakthrough in the tolerability and efficacy of pharmacotherapy for degenerative nervous system disorders. Although these studies are still in the early stages of in vivo experimentation, they point to a horizon of innovations that could transform the face of translational medicine for decades to come. [7, 8, 10, 18, 28, 29]

5. Conclusions

5.1. A Paradigm Shift and Confirmation of the Repositioning Hypothesis

This comprehensive review article provides exceptionally strong, multifaceted evidence that glucagon-like peptide-1 receptor agonists (GLP-1RAs) currently represent one of the most groundbreaking and promising therapeutic classes in all of modern translational medicine and neuropharmacology. The compiled and rigorously analyzed literature—comprising 30 key publications spanning basic science, clinical research, and public health analyses—allows for the definitive rejection of the outdated dogma that the role of incretins is limited solely to the peripheral regulation of glycemia and gastrointestinal motility. The discovery of endogenous GLP-1 synthesis in the nucleus of the solitary tract (NTS) and the mapping of an extensive network of GLP-1R receptors in the central nervous system (CNS) have permanently blurred the artificial boundaries between endocrinology, neurology, and psychiatry. The successful repositioning of these drugs demonstrates that conditions as seemingly disparate as type 2 diabetes, Alzheimer's disease, and alcohol dependence share fundamental, intersecting pathophysiological pathways: disturbances in energy homeostasis, chronic inflammation, and dysregulation of intracellular signaling. The use of molecules with proven cardiometabolic safety to protect and remodel brain architecture is an innovation that has the potential to completely redefine standards of patient care in the coming decade. [8, 14, 19, 20, 27]

5.2. Summary of Neuroprotective Potential in Alzheimer's Disease

Given that Alzheimer's disease (AD) remains one of the most devastating challenges facing aging societies, and that classic symptomatic treatments as well as the latest therapies based on monoclonal antibodies face significant limitations in terms of efficacy and safety, GLP-1R emerge as a safe alternative capable of modifying the course of the disease. As demonstrated in this review, these drugs effectively cross the blood-brain barrier and target the very core of the pathological process—cerebral insulin resistance. By reactivating the PI3K/Akt/mTOR pathways, GLP-1R agonists restore neurons' ability to metabolize glucose, protect against amyloid plaque toxicity, and inhibit tau protein hyperphosphorylation. Equally important, the potent anti-inflammatory effects of these drugs suppress the destructive activity of microglia and astrocytes, stabilizing the neural microenvironment. Evidence from the landmark Phase IIb clinical trial (ELAD) with liraglutide, demonstrating objective inhibition of cerebral cortical atrophy and improvement in cognitive function, combined with extensive retrospective (Real-World Evidence) demonstrating a reduced risk of dementia incidents in patients treated with GLP-1RAs, provides a solid foundation for the definitive confirmation of this hypothesis in ongoing Phase III trials (EVOKE/EVOKE+). The convergence of these data suggests that we are one step away from implementing the first systemic neuroprotective therapy for AD. [10, 11, 13, 17, 22, 28, 29]

5.3. A Revolution in Addiction Science and the Treatment of Substance Use Disorders (SUD) and Alcohol Use Disorders (AUD)

At the same time, the field of addiction and substance use disorders (SUD)—including, above all, alcohol use disorders (AUD)—is gaining a powerful biological intervention tool thanks to GLP-1R agonists. An analysis of preclinical literature and early clinical trials unequivocally confirms that stimulation of GLP-1R receptors located in the mesolimbic system (VTA, NAc) radically suppresses the dopaminergic hyperactivity induced by psychoactive substances. This translates into a spectacular reduction in the motivation to seek alcohol, cocaine, or nicotine, a significant attenuation of craving, and a dramatic decrease in relapse rates following a period of abstinence. This discovery is absolutely crucial for addiction medicine, as pharmacotherapy with GLP-1 analogs directly targets the biological component of loss of control, creating a safe therapeutic window for the patient—one that is essential for undertaking effective psychotherapy and social rehabilitation. Thus, these medications promote a holistic, biopsychosocial model of recovery from addiction, avoiding the pitfalls of anhedonia characteristic of older reward system blockers. [2, 3, 4, 6, 23, 26, 30]

5.4. Implications for Innovative Social Technologies and Public Health

From the perspective of innovative social technologies and health economics, the integration of GLP-1-based therapies into global healthcare systems could yield unprecedented macroeconomic benefits. Effectively delaying the progression of dementia and reducing the burden of care for patients with AD offers an opportunity to save millions of informal caregivers from exclusion from the labor market and mental health crises. Similarly, reducing population-level alcohol and tobacco consumption through the widespread use of incretins would strike at the very root of costs generated by employee absenteeism, crime, and the treatment of chronic complications (e.g., liver cirrhosis or heart disease). However, barriers such as high treatment costs, inequalities in access to innovative therapies, and problems with global supply chains remain highly concerning, the potential return on investment (ROI) for national health systems justifies the immediate implementation of reimbursement programs and targeted health policies that facilitate access to these medications for the most vulnerable social groups. [1, 5, 15, 24, 25]

5.5. A Vision for the Future

In summary, the expanding therapeutic horizons of GLP-1 receptor agonists represent one of the most significant biomedical breakthroughs of the 21st century. Future research should focus on bridging translational gaps by designing large-scale, long-term randomized controlled trials (RCTs) in non-diabetic populations and investigating the efficacy of novel dual and triple agonists (GIP/GLP-1/glucagon). It is also essential to develop innovative drug delivery technologies, such as intranasal delivery, which will optimize drug penetration into the brain while minimizing adverse gastrointestinal symptoms. Success in these areas will ultimately cement the position of GLP-1R agonists not only as a cornerstone in the fight against the global obesity and diabetes epidemic, but also as a universal therapeutic platform that protects the architecture of the human brain from degradation and addiction. [7, 9, 12, 16, 18, 21]

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