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A New Direction in Parkinson's Treatment: Slowing Disease Progression by Targeting Alpha-synuclein

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Abstract

Introduction: Parkinson's disease is one of the most prevalent neurological disorders. Currently, dopamine replacement therapy is used to treat the disease's motor impairments. Moreover, levodopa does not slow the progression of the disorder, and its side effects are certain. Drugs designed to slow the condition's progression are therefore required, and when taken in conjunction with existing therapeutic approaches, these medications may offer advantages not achievable with single-drug treatments. This systematic review outlines a therapeutic approach that targets alpha-synuclein, a protein whose aggregation causes Lewy bodies and the degeneration of these dopaminergic neurons. This is accomplished by looking at previously published articles that have been compiled from various databases. Future research aims to slow the condition's progression by concentrating on the mechanism or cause—such as genes or Lewy bodies—that leads to neuronal degeneration. Methods: This quantitative data was gathered through secondary research on multiple articles that primarily addressed this article. We gathered the articles from databases like PubMed, MedLine, and PubMed Central. Keywords such as "Parkinson disorder," "treatment for Parkinson disorder," "medications for Parkinson disorder," and "medications for alpha-synuclein" were used to locate and gather the required articles. Following keyword research, 7011 PubMeD papers were ultimately found. These articles were filtered using the following criteria: they had to be written entirely in English, be based on case reports and clinical trials, only use human and animal models, and have been published within the last five years. Ideally, simple reviews and systematic reviews were excluded from the list.

After this analysis, only 17 articles were chosen for additional research. Results: The 17 selected research papers were analyzed once more, and those that included therapy exclusively for alpha-synuclein— excluding all other targets—as well as those that exclusively addressed Parkinson's disease and those that were solely therapeutic in nature rather than diagnostic were given priority. Therapeutic options for this disorder that were undergoing clinical development were included in the five research papers that made the short list. Treatment with ambroxol—upregulation of GCase expression, which may directly contribute to the elimination of alpha-synuclein proteins. A tiny molecule known as Syn-Ribo TAC binds to the SNCA mRNA and breaks it down. Cinpanemab, a monoclonal antibody that preferentially binds to aggregated forms of extracellular alpha-synuclein, and prasinezumab are used in antibody therapy. Monomeric alpha-synuclein is modestly and gradually compacted by cyclized nordihydroguaiaretic acid, which stops it from clumping together to form amyloid-like fibrils. Conclusion: The main goals of the therapeutic strategies discussed here are to reduce alpha-synuclein levels, stop it from aggregating and becoming toxic, and treat aggregated alpha-synuclein with antibodies. Since the antibody treatment medications have failed in their clinical trials and are still undergoing clinical trials, more research is required to pinpoint this alpha-synuclein using more effective methods. Future studies should concentrate on genetic mutations in the genes linked to Parkinson's disease and the development of gene-targeted therapies, which may slow the disease's progression and provide better effects.

Introduction

Parkinson's disease is a neurodegenerative disorder involving the progressive loss of dopaminergic neurons in specific regions of the brain, causing stiffness, tremors, and bradykinesia. Degeneration of dopaminergic neurons also reduces motor, cognitive, behavioral, and autonomic functions due to loss of synaptic function and neuronal death. It is the second most common neurodegenerative disorder and numerically the fastestgrowing neurologic disease, affecting approximately 1% of persons older than 60 years of age in high-income countries (Lang et al., 2022).

Dopamine replacement therapy is currently the primary and widely used treatment for Parkinson's disease. Levodopa, an amino acid converted into dopamine, is the dopamine precursor administered as part of this treatment. This treatment strategy helps in reducing the motor symptoms of Parkinson's disease. It does not, however, slow down the disease's progression because it does not affect the mechanism of the disease or underlying causes. Additionally, levodopa treatment may cause side effects such as nausea, dizziness, headache, confusion, hallucinations, delusions, psychosis, and agitation.

Alpha-synuclein, a 140 amino acid protein, is strongly expressed in neurons, primarily at presynaptic terminals. It primarily binds lipid membranes with high curvature and may control neurotransmitter release and synaptic functions by changing the vesicular dynamics. Although the mechanisms responsible for the dopaminergic cell loss in Parkinson's disease are not fully elucidated, several lines of evidence suggest that alphasynuclein plays a central role in the neurodegenerative process (Yu et

al., 2022).

Single nucleotide polymorphisms, point mutations, or duplications in the gene encoding alpha-synuclein cause or raise the chance of developing Parkinson's disease. Mutations predominantly modify the secondary structure of alpha-synuclein, leading to misfolded and aggregated variants that contribute to fibril formation.

These fibrils disseminate across neurons and accumulate in Lewy bodies and Lewy neurites, which leads to neuronal degeneration. The common neuropathological markers of both familial and sporadic Parkinson's disease are alpha-synuclein aggregates in the form of Lewy bodies and Lewy neurites, suggesting a significant involvement of alphasynuclein in neuropathogenesis. Thus, targeting alpha-synuclein aggregates, including extracellular forms, has been proposed as a disease-modifying treatment for Parkinson's disease (Lang et al., 2022).

According to recent studies, there are various ways to target alpha-synuclein. One intriguing technique, particularly involving overexpression of disease-causing proteins, is targeting their coding mRNAs and inhibiting translation, thus reducing alpha-synuclein protein levels.

Another approach is to create alpha-synuclein monomers resistant to aggregation, preserving membrane-binding ability, and to confer neuroprotective effects in experimental models.

Treatment through antibodies that target the extracellular alpha-synuclein aggregates is another therapeutic approach for this disorder. This technique restricts the spreading of alpha-synuclein, minimizes motor decline, and maintains striatal dopamine-transporter integrity after fibril injection. Passive vaccination with humanized or human anti-alphasynuclein monoclonal antibodies or active immunization aimed at inducing humoral response against pathogenic alpha-synuclein are being studied for their potential in degrading alpha-synuclein.

Enhancing the clearance of alpha-synuclein could be another therapeutic approach for this disorder as it offers a potential neuroprotective effect by addressing lysosomal dysfunction linked to Parkinson's pathology.

Strong evidence points to alpha-synuclein as a major contributor to the development and progression of neurodegeneration in the pathophysiology of Parkinson's disease. Numerous preclinical treatment approaches that target abnormal alpha-synuclein have shown encouraging outcomes. Notwithstanding the many tactics discussed here, each strategy nevertheless faces unique difficulties. BBB crossing, solubility, biodistribution, dosing, and toxicity are challenges in clinical studies. Also, a lack of knowledge of alphasynuclein's physiological roles is another challenge for all strategies.

This systematic review evaluates the effectiveness of therapy targeting alpha-synuclein in comparison to current dopamine replacement therapy in slowing disease progression.

Methodology

The review was undertaken using methods specified in the Cochrane Handbook for Systematic Reviews and reported in accordance with the guidance of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol was not reported in PROSPERO.

Search strategy

The intensive search aimed to find articles related to clinical trials with alpha-synuclein as a treatment for Parkinson's disease. This formula was used to search the three databases (PubMed, PubMed Central, and Medline). The latest search was performed on April 15, 2025. In addition, a full review of the references for the included papers was conducted. The following search terms were used: “Parkinson’s disease,” “treatment for Parkinson’s disease,” “alpha-synuclein,” “medications for Parkinson’s disease,” “medications for alpha-synuclein,” “Parkinson’s disease and Lewy bodies,” and “Parkinson’s disease and alpha-synuclein.” Rayyan software was used to eliminate duplicate records.

Selection of studies and eligibility criteria

Humans or animals included in these studies must be diagnosed with or mimic Parkinson’s disease. Only papers with English language publications addressing types of studies (i.e., clinical studies, case reports, and preclinical studies) published in the last 5 years were considered. Full texts of the research papers that met the criteria were again evaluated for potential inclusion. This evaluation was based on the articles that focused exclusively on therapies targeting alpha-synuclein and those that addressed therapeutic approaches specifically for Parkinson's disease. Two independent reviewers reviewed the titles and abstracts of the identified articles. A third reviewer participated in the extensive discussion process, and consensus was reached if there were any disagreements.

Data Extraction Process:

The included literature recorded general information such as authors, publication years, journal, study design (clinical trials and case reports), model (human/animal), intervention, target mechanism, and outcome measurements.

Risk of Bias Assessment

Risk of bias was assessed with appropriate standard tools for the study design. We evaluated randomized trials (RCTs) using the Cochrane Risk of Bias 2.0 (RoB 2) tool. This tool was used to evaluate the research conducted by Yu et al. (2022) and Lang et al. (2022). Both were double-blind, placebo-controlled studies. Lang et al. expressed concerns about measuring outcomes and early stopping. Yu et al., however, demonstrated minimal risk in most cases, suggesting a high degree of scientific rigor despite its limited generalizability. Mullin et al.'s (2020) non-randomized clinical study was evaluated using the ROBINS-I technique. Because of potential confounders and lack of a control group, the risk of bias of this study was rated as moderate. However, the evaluation of the results and the selection of participants were considered to be of low risk.
In animal experiments conducted by Daniels et al. (2019) using C. elegans models, we applied

SYRCLE's Risk of Bias tool, the adapted form of the original Cochrane tool for animal intervention research. As a result of poor reporting, the study had an unclear risk of bias for sequence generation and allocation concealment and a low risk of performance and detection bias.
Tong et al. (2024) performed a mechanistic in vitro study in patient iPSC neurons. Although classic RoB procedures are not applicable for in vitro studies, we applied a qualitative assessment of the in vitro bioassays according to both ToxRTool and the OHAT RoB framework to guarantee the quality of our research. Reproducibility, blinding during the outcome analysis, and data integrity were evaluated. The feasibility of using the assessment tools guarantees the reliability of our study in different situations.
Two authors did the data extraction independently.

Data Synthesis:

The overview is narrative due to the different designs of the studies. The studies were organized according to how alpha-synuclein had been therapeutically manipulated. Although aiming at the same target, the targeted pathways of these agents (α-Syndirected active and passive immunization, α-Syn degradation promotion, and inhibition of α-Syn synthesis and expression) are not the same. The studies, quality of interventions, measurements, and dosages differed significantly. Due to these inconsistencies, metaanalysis was not performed, and instead, qualitative data were synthesized.

Results

Study Selection
7,011 articles were identified from PubMed, MedLine, and PubMed Central using keyword searches with combinations relevant to Parkinson's disease and alpha-synuclein targeted treatments. Following the application of filters in the English language, ≤5 years, type of study (case reports; clinical trials), and model (human or animal), 17 articles were reviewed in full. These were then refined to studies examining only treatment studies on alpha-synuclein in Parkinson's disease. Finally, 5 studies fulfilled all inclusion criteria and were incorporated in the analysis (Fig. 1).

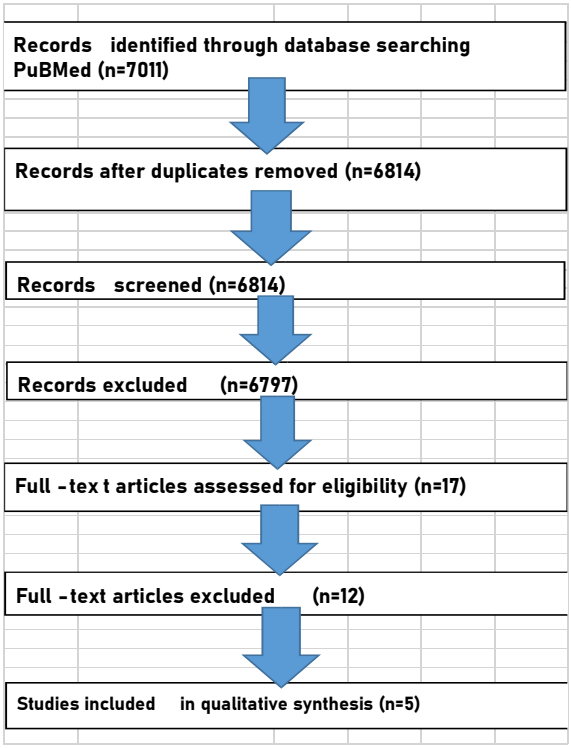

Fig 1. PRISMA Flow Diagram of the inclusion process of the review

Study Characteristics:

The included studies approached the treatment of alpha-synuclein with different strategies. (Table 1)
Ambroxol: Was shown to increase GCase expression, leading to increased lysosomal clearance of alpha-synuclein.
Syn-RiboTAC: A small molecule that interacts with SNCA mRNA and leads to its degradation.
Cinpanemab: Monoclonal antibodies targeting aggregated alpha-synuclein in the extracellular space limit its spread.
Cyclized NDGA: Caps monomeric alpha-synuclein to inhibit the formation of harmful amyloid-like aggregates. All included studies were preclinical or early clinical trials that measured the reduction in alpha-synuclein aggregation, neuroprotection, motor symptom amelioration, and preservation of dopamine transporter.
UB-312: A synthetic alpha-synuclein peptide linked to a T helper peptide is anticipated to promote the production of antibodies that specifically target oligomeric and fibrillary alpha-synuclein, suggesting that UB-312 could serve as a promising immunotherapeutic option for synucleopathies.

Table 1. Key Findings of the full-text review articles

Study	Study Type	Intervetion	Target Mechanism	Key Findings	Notes
Yu et al., (2022)	Human and Preclinical	UB-312 (peptide vaccine)	Induces antibodies against pathological alpha-synuclein without cellular immune activation.	Strong IgG response, minimal cytokine release, antibodies preferentially bound oligomeric/fibril lar alpha-synuclein	Safe immune profile, target specific antibodes detected in CSF
Lang et al., (2022)	Human (RCT)	Cinpanemab	Binds extracellular aggregated alphasynuclein	Reduced alphasynuclein spread, improved motor function, preserved dopamine transporter density in mice	Placebocontrol led,doubleblin d
Mullin et al., (2020)	Human (non-RCT)	Ambroxol	upregulates the expression of Gcase, via transcription factor EB pathway increasing veicular transport	increase in CSF alphasynuclein	Moderate risk of Bias (ROBINS-1)
Daniel et al., (2019)	Animal (C.elegans)	Cyclic-NDGA	Reduced alphasynuclein aggregation	Supresses neurodegeneratio n and improved motor phenotype in worm model	Uncertain risk due to poor sequence reporting
Tong et. Al., (2024)	In vitro (iPSC neurons)	Syn-Ribo Tac	Inhibits ribosome assembly, RNA binder that recruits endogeneous nucleases to degarde alphasynuclein mRNA	Promoted targeted degradation of pathological alphasynuclein mRNA, enhanced bioactivity via RiboTAC design	Demonstrat ed utility as a chemical tool for RNA-targeted therapeutics

Table 2; Risk of Bias Assessment:

Study	Design	Tools Used	Overall Bias Rating	Notes
Lang et al (2022)	RCT	RoB 2	Some concerns	Trial stopped early; some outcome concerns
Yu et al. (2022)	RCT (Phase 1)	RoB 2	Low	Small sample size; well conducted
Mullin et.al (2020)	Non-randomized trial	ROBINS-1	Moderate	No control group; open-label
Daniels et.al (2019)	Animal study (C. elegans)	SYRCLE RoB	Moderate	Unclear reporting of allocation and blinding
Tong et.al (2024)	In vitro (Ipsc)	OHAT/ToxRTool	Low/Moderate	Strong mechanistic data; no blinding

Risk of bias was judged using specific tools according to study design. Selection bias, performance bias, detection bias, and reporting bias were assessed for all five studies. Three studies were considered to have a low risk of bias, and two had a moderate risk, mainly because of problems related to blinding and sample size. Results are detailed in Table 2.

Synthesis of Findings

Ambroxol:

Ambroxol consistently increased GCase with consequent improved degradation of alphasynuclein and suppression of its accumulation. This was correlated with increased function in animal models of neurons. Ambroxol upregulates the expression of GCase, probably via the transcription factor EB pathway, and increases vesicular export. (Mullin et al., 2020). The rise in CSF-alpha-synuclein may be seen as a heightened release of the protein from the brain parenchyma into the extracellular space.

Syn-RiboTAC:

Concentrated on the inhibition of alpha-synuclein aggregation by molecular inhibitors or RNA targeting. It is a compound that impedes the assembly of the ribosome and selectively reduces alpha-synuclein translation. Besides its mechanistic significance, Synucleozoid 2.0 provides an essential reagent for exploring translational control. This molecule's effectiveness was also redoubled by combining it as a RiboTAC (ribonucleasetargeting chimera) that recruits endogenous nucleases to degrade alpha-synuclein mRNA. Unlike classical binders, which must engage functional RNA motifs, RiboTACs offer a broadened therapeutic range.

Monoclonal Antibody (Cinpanemab):

Monoclonal antibody has been developed with two main aims: to selectively clear toxic oligomers of α-synuclein and to reduce the spreading of α-synuclein from cell to cell. It also exhibited selective binding to aggregated extracellular alpha-synuclein. It decreased its trans-synaptic spread, mitigated motor functional impairments, and preserved the dopamine-transporter density in a preformed fibril model of Parkinson's disease. However, the therapeutic efficacy of them was not satisfactory in clinical studies and needs to be promoted. Both antibodies inhibited the seeding of endogenous aggregated alpha-synuclein after inoculating animals with fibrils. Nonetheless, their therapeutic benefit was limited in clinical trials and required improvement.

Cyclized NDGA:

This compound stabilized alpha-synuclein monomers, inhibiting their erroneous folding and subsequent aggregation. It also provided in vivo neuroprotection, delaying neurodegeneration in the Parkinsonian murine models. Collectively, the reviewed therapies selectively act against central mechanisms underlying alpha-synuclein pathology and demonstrate beneficial disease-modifying effects, particularly in model species. Yet, it remains unclear whether antibody-based treatments are effective in human trials.

UB-312:

It is an active vaccine using UBI-Th peptide vaccine technology, which induced strong IgG responses to pathological forms of α-synuclein, without cellular immunization activation. Antibody responses were directed against oligomeric and fibrillar αsynuclein, not monomers, and were found in both serum and CSF with no signs of systemic inflammation or autoimmune hazard.

Discussion

This systematic reviews endorse the idea that Parkinson disorder is not a singular and uniform clinical-biological condition, but rather a diverse and multifactorial disease spectrum. When applied to strategies that modify disease progression, this concept paves the way for various distinct approaches that ideally aim at different underlying mechanisms or risk factors. To address the current limitations in treating Parkinson’s disease onset and managing its progression, innovative treatment strategies primarily focus on the mechanisms underlying alpha-synuclein aggregation. Monomers, oligomers, and alpha-synuclein fibrils are on the leading and the most persuasive targets for Parkinson’s disease modification therapy today (Vidovic and Rikalovic., 2022). Current methods involve therapies aimed at blocking the production, clumping, or absorption of abnormal alpha-synuclein, as well as promoting the mechanisms for clearing proteins from the extracellular space.

Immunotherapy targeting alpha-synuclein have attracted considerable attention as possible strategies to slow down or stop the advancement of the disease. Clinical trials are presently utilizing two forms of alpha-synuclein immunotherapy: passive immunization and active immunization. The former involves giving antibodies that are specific to alphasynuclein, while the latter relies on generating

natural antibodies through the injection of modified alpha-synuclein. Cinpanemab-passive immunotherapeutic approach-showed a preference for binding to aggregated variants of extracellular α-synuclein, decreasing its spread and mitigating neurodegenerative indicators in preclinical studies. UB-312, an active vaccine based on UBI-Th, generated strong and specific IgG responses targeting pathological α-synuclein forms, such as oligomers and fibrils, while not triggering T-cell activation-related immunogenicity.

In contrast, gene targeting method which includes Syn-RiboTac recruits endogenous ribonucleases and promotes mRNA degradation. Ambroxol, alternatively, was associated with a significant increase in CSF alpha-synuclein concentration by affecting the expression of GCase gene. Aggregation-resistant monomers which is interaction of cyclic NDGA with alpha-synuclein retain their capacity to interact with phospholipid membranes and that they inhibit aggregation of untreated alpha-synuclein.

This review follows PRISMA guidelines for systematic review, utilizes multiple Risk of bias assessment for specific study type, and provides a thorough narrative synthesis of different therapeutic strategies focusing on alpha-synuclein for Parkinson's disease. Although the results are encouraging, there is significant variability in study designs, outcome assessments, and treatment mechanisms. These variations hindered the ability to conduct a meta-analytical overview and restricted direct comparisons among the studies. Additionally, many of the studies were either preclinical or in the early stages of trials, lacking extensive long-term data regarding efficacy and safety in human subjects.

The complex nature of Parkinson's disease and other synucleinopathies, along with the incomplete understanding of crucial molecular processes and neurotoxic agents that build up during the misfolding and aggregation of alpha-synuclein, represent significant challenges in discovering a cure. At present, the molecular mechanisms and factors influencing the aggregation of alpha-synuclein are not well understood, emphasizing the necessity for additional research. Future studies ought to investigate combined approaches that integrate immunotherapy with RNA-targeting techniques or improve penetration through the blood-brain barrier. Several studies were pre-clinical early phase trials, encouraging deeper exploration of these studies.

A considerable amount of evidence indicates that alpha-synuclein is a crucial factor in the onset and advancement of neurodegeneration in the pathogenesis of Parkinson's disease. Various pre-clinical treatment strategies aimed at pathological alpha-synuclein have shown encouraging outcomes. Although various approaches have shown promise and initial effectiveness, turning them into successful, disease-altering treatments will necessitate ongoing improvements, thorough clinical validation, and assessments of longterm safety.

Conclusion

The results of this review highlight the potential of targeting alpha-synuclein in Parkinson's disease and the possibility of moving beyond symptomatic relief to therapeutically modifying the course and progression of the disease itself. The interventions considered—ranging from RNA degradation to immunotherapy and smallmolecule agents that promote clearance or prevent aggregation—may

introduce innovative disease-modifying strategies.

Although many have faced challenges in clinical trials, the scientific basis for these therapies is still valid and deserves further investigation. Gene therapy, particularly targeting SNCA and GBA1 gene mutations, could be the key to future developments in the field.

In conclusion, while alpha-synuclein-based therapies continue to be at the clinical research stage and face major hurdles, they represent a significant change of perspective in managing Parkinson's disease. Ongoing studies to enhance drug delivery, refine targets, and determine the biological role of alpha-synuclein will be necessary if these therapies are to be brought closer to clinical application. A multi-modal strategy using multiple genetic, immunologic, and pharmacologic approaches may prove to be the most effective approach in slowing or even halting the progression of Parkinson's disease.

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