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REVIEW ARTICLE

Disease Modification: Comparing Diverse Approaches to Alpha-Synuclein Targeting Therapies in Parkinson's Disease

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ABSTRACT: Parkinson's disease (PD) is a prevalent neurodegenerative disorder that mainly affects people over the age of 60. The characteristic movement-related complications, including tremors, akinesia, as well as nonmotor symptoms such as mood disorders, arise when neurodegeneration within the substantia nigra causes a lack of dopamine, creating dysfunction in many systems. A key pathological hallmark of PD is the accumulation of misfolded α-synuclein (ASYN), forming toxic aggregates responsible for disease progression. Even with billions spent on healthcare, millions of lives affected, and multiple symptomatic treatments available, there are currently no disease-modifying therapies to slow PD progression. This review compares ten current alpha-synuclein-targeting disease-modifying therapies in clinical trials explored in the Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update. Because each clinical trial used different biomarkers to prove the slowing neurodegeneration, the drugs were compared on whether they showed a decrease in ASYN aggregates and viability on a cellular level. These therapeutic approaches aimed to reduce pathologic ASYN levels through various mechanisms ranging from antibodies, neurotransmitter regulators, and small molecule therapies. Among them, the small molecule therapies, specifically UCB0599 and Anle-138b, seemed to be the most promising given the greatest blood-brain barrier penetration and decreased pathological alpha-synuclein levels.

KEYWORDS: Biomedical and Health Sciences, Genetics and Molecular Biology of Disease, Parkinson's Disease, Disease Modification, Alpha-Synuclein.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder globally, after Alzheimer's disease.[1] In the United States alone, 500,000 - 1 million people are afflicted,[2] increasing by 90,000 annually.[3] The many determinants for PD are not yet fully explored or understood. Risk factors for PD include head injury, pathologic genetic variants, and pesticide exposure. The most significant risk factor for Parkinson's disease is age, with the average onset of the disease at 60 years.4 As advancements in healthcare lead to longer life expectancies, PD is becoming an increasingly urgent focus for researchers, as more individuals are at risk for this condition.

Individuals with PD experience a variety of motor and non-motor symptoms, including rigidity, postural instability, autonomic dysfunction, and mood disorders.[4,5] These symptoms are caused primarily by neurodegeneration of the dopaminergic neurons in the substantia nigra but also in other regions of the brain and the peripheral nervous system.[4] Although many factors contribute to neuronal loss, such as neuroinflammation, oxidative stress, and lysosomal dysfunction,[6-8] there is a consensus that the misfolding of a protein, alpha-synuclein (ASYN), is associated with cell death.[9,10] Under disease conditions, ASYN misfolds from soluble, nontoxic monomers that help control neurotransmitter release to insoluble, toxic oligomers that aggregate to form Lewy Bodies, which are large, spherical clumps of protein mainly composed of ASYN.[4,10] ASYN aggregation has been associated with oxidative stress, lysosomal dysfunction, and apoptosis.[4,6,7] However, recent studies suggest that in addition to aggregation, ASYN may interact aberrantly with cellular membranes, especially lipid membranes, early in the disease process. Membrane binding can influence the membrane's curvature and stability, disrupting many critical cellular functions such as synaptic vesicle trafficking, neurotransmitter release, and more. This newer model proposes that membrane-bound ASYN could be part of an early stage of neurodegeneration.[11] Aberrant membrane binding may be concurrent with the aggregation of ASYN, a dual mechanism that reveals the multifactorial nature of PD pathology. With advancing neurodegeneration, PD progresses, leading to more severe symptoms.[11]

A treatment that stops or delays cell death and preserves function would be considered disease-modifying, meaning that it would delay the clinical progression of PD. Nevertheless, no disease-modifying treatments for PD, except for physical activities and exercise, exist to date.[4,13-15] However, many symptomatic therapies are available to alleviate symptoms.[13]

Many experimental treatments are under clinical investigation, such as decreasing neuroinflammation, correcting aberrant lipid homeostasis responsible for PD, and stem cell therapy. However, since ASYN misfolding occurs early in pathogenesis and is associated with cell death, targeting misfolded ASYN may represent the most promising approach. Due to the multifaceted nature of ASYN in PD, these drugs aim to reduce ASYN through multiple strategies, such as reducing its overall level, reverting it into a nontoxic form, or training the immune system to attack aggregated forms of ASYN. As of 2023, there were 10 ASYN-targeting disease-modifying treatments in clinical trials,[16] as summarized in Table 1. Therapies in phase 1

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of clinical trials focus on safety and dosage of the drug on humans, as well as preclinical research through animal and other *in vitro* studies. Phase 2 clinical trials largely focus on the effectiveness of the new drug, and phase 3 clinical trials are very large and aim to confirm the continued effectiveness and safety of the drug on large populations. It is also important to note that this list represents efforts in clinical testing as there may be a larger list of preclinical programs in development as well.

Table 1: List of ten investigational[14] ASYN disease-modifying therapies. Drugs were classified by method and each therapeutic's clinical trial phase.

Drug	Method	Phase
Memantine	Neurotransmitter Inhibitor	3
Buntanetap	Small Molecule (RNA Transcription Inhibitor)	3
UCB0599	Small Molecule (ASYN Aggregate Inhibitor)	2
Pasinezumab	Antibody	2
Citalopram	Neurotransmitter Inhibitor	2
KM-819	Small Molecule (Cell Death inhibitor)	2
Hypoestoxide	Inflammation Inhibitor	1
Anle-138b	Small Molecule binding to ASYN Aggregates	1
UB-312	Antibody	1
UCB7852	Antibody	1

The 10 ASYN-targeting drugs fall into three main categories: small molecules that directly target ASYN aggregates, antibodies, or small molecules that indirectly lower ASYN aggregate levels. From the following trials from each drug, the antibody approach has shown difficulty in crossing the blood-brain barrier, resulting in a less effective drug. As a result, small molecule therapies were generally shown to yield better results when it came to reducing the levels of aggregated ASYN.

Discussion

Immune Therapies:

Immune therapies are another form of treatment that has been investigated. Two different forms of vaccines are currently under clinical trials. Active vaccination with UB-312, a synthetic peptide-based vaccine that resembles aggregated ASYN, clears ASYN aggregates by activating phagocytosis. In contrast, passive vaccination with Prasinezumab and UCB7853 is supposed to immobilize misfolded ASYN and mark it for degradation by immune cells.

Prasinezumab: Prasinezumab is a monoclonal antibody that binds to the C-terminal of aggregated ASYN, immobilizing it and signaling to the immune system that the protein aggregates should be destroyed (Figure 1). This differs from the traditional sense of a vaccine, as instead of being an antigen that causes the body to promote natural antibodies, prasinezumab marks aggregated ASYN for the body's immune system to target.

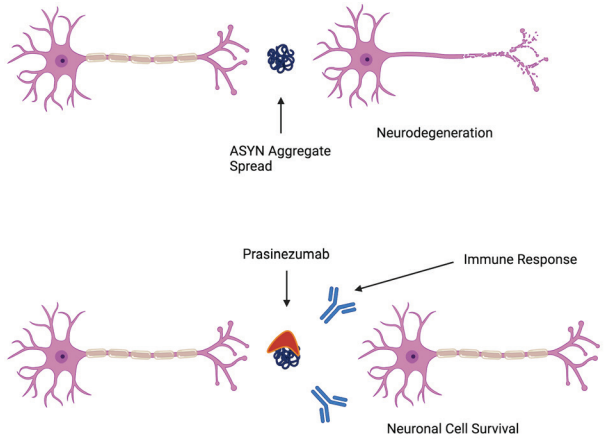

Figure 1: The proposed mechanism of action for prasinezumab and UCB7853: Both antibodies may improve neurodegeneration by binding to aggregated ASYN and alerting the immune system to it.

In a phase II trial, prasinezumab's efficacy was tested at two different dosages: 1500 mg and 4500 mg. Antibodies are typically inefficient at crossing the blood-brain barrier, explaining why such a high treatment dosage was used. However, no significant differences in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores were reported between the placebo and treatment groups. Additionally, the administration of prasinezumab also caused frequent adverse events, in 91.5% for the 1500mg and 93.3% for the 4500mg prasinezumab patient groups, due to infusion reactions. The study also sought to determine the neuroprotective properties of prasinezumab through 123I-ioflupane Single Photon Emission Computed Tomography (SPECT) imaging, or radionuclide imaging that evaluates the integrity of nigrostriatal dopaminergic synapses, which reports on the levels of dopaminergic neurons by detecting dopamine transporters. No differences between the neuroimaging dopamine transporter levels were observed, suggesting that prasinezumab may have no or weak neuroprotective benefits.[17] However, subsequent studies have suggested some potential signals of benefits, indicating that prasinezumab may slow motor decline in certain subpopulations, particularly in patients with rapidly progressing early-stage Parkinson's disease. These findings justify continuing the development of prasinezumab, as they point to the possibility that it may be effective in specific patient groups, even though the broader trial results were inconclusive.[18]

This initial trial tested for the short-term benefits of prasinezumab, such as the immediate increase in dopamine transporter levels. Despite the negative results, a second phase II clinical trial is currently underway to study prasinezumab's long-term benefits. Set to be completed in 2026, the study will explore how the drug may influence ASYN levels over an extended period of time, potentially offering insights into its therapeutic potential despite the challenges that antibody drugs face, such as poor blood-brain penetration.

UCB7853: UCB7853 is another passive immunization vaccine drug similar to prasinezumab. It likely faces similar challenges to prasinezumab as antibodies have difficulty crossing the blood-brain barrier and cannot enter cells.

A phase I study testing for its safety and pharmacokinetics started on 12/14/20 and ended on 7/20/23. However, results have yet to be posted.[19]

UB-312: In contrast, UB-312 is an active ASYN vaccination that intends to train the immune system to target and phagocytose misfolded ASYN. The antibodies cannot bind to soluble monomers, increasing specificity and ensuring autoimmune effects (Figure 2).

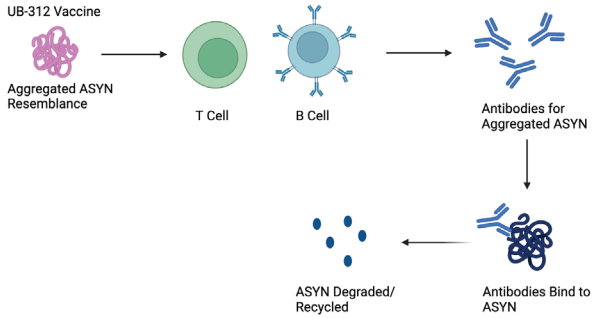

Figure 2: The mechanism of action for UB-312: UB-312 is a synthetic peptide-based vaccine that resembles aggregated ASYN to train the immune system to attack aggregated ASYN.

A phase I clinical trial tested the safety, tolerability, and immunogenicity of UB-312. Fifty healthy participants received three vaccine treatments over 44 weeks. No serious adverse events were recorded, but each patient had at least one treatment-emergent adverse event, with the most common symptoms being headaches and pain at the vaccination site. Two patients experienced flu-like symptoms after the second vaccination. As the symptoms were mild, UB-312 was considered safe and tolerable for PD patients. As for immunogenicity, the vaccine proved to be dose-dependent as anti-ASYN antibody levels increased with increasing doses. Interestingly, the anti-ASYN antibody levels present in the CSF were almost 1000 times less than the antibodies found in the serum. This again indicates the antibody's poor ability to penetrate the blood-brain barrier. Further studies will need to be conducted to determine if these trim levels of antibodies can still be adequate to remove ASYN aggregates in meaningful amounts.[20]

Another ongoing phase Ib study is testing the safety, tolerability, and immunogenicity of UB-312, and it is projected to end in April 2025.[21] Overall, antibody drugs have several strengths and weaknesses. Antibodies tend to be highly specific and effective. However, they also tend to have poor blood-brain penetration, making them potentially less effective when treating neurodegenerative brain disorders. Even with heavily optimized antibodies that target ASYN aggregates efficiently, getting them to reach the brain in meaningful amounts seems challenging. Another flaw of this approach is that antibodies cannot enter cells or vesicles. These treatments assumed that aggregating ASYN is primarily located outside the cell or that when ASYN aggregates spread, they travel without vesicles. Thus, antibodies would be inefficient if ASYN aggregates are primarily inside the cell and, if transmitted at all, travel from cell to cell without exposure to extracellular fluid, such as through vesicles. Further studies aiming to improve the blood-brain barrier penetration of antibodies should also be done to confirm whether this vaccination can effectively clear up aggregated ASYN.

Small Molecule ASYN Aggregate Inhibitors:

Small molecule drugs targeting ASYN aggregates have also been investigated as disease-modifying treatments for PD. These drugs are designed to bind toxic ASYN oligomers and revert them into their nontoxic monomeric forms or at least stop them from aggregating further. Small molecules have different binding affinities and tend to bind misfolded ASYN to varying stages with slightly different purposes. Currently, two main drugs under this category are being explored in clinical trials: UCB0599 and Anle138b.

UCB0599: UCB0599 is a molecule identified by screening for compounds that target ASYN aggregates. By binding specifically to ASYN aggregates, UCB0599 prevents the protein from aggregating specifically on vesicle membranes. As ASYN is primarily found outside of a vesicle, stopping aggregation from occurring on membranes is crucial, as these have been suggested to be sites for primary nucleation.[22] UCB0599 aims to bind to aggregating ASYN on membranes and, in doing so, expels the misfolded proteins from the membranes and reverts them from insoluble, toxic proteins to soluble, nontoxic ones. Preventing ASYN aggregation from occurring is a testable and promising idea in inhibiting aggregation on a cellular level (Figure 3).

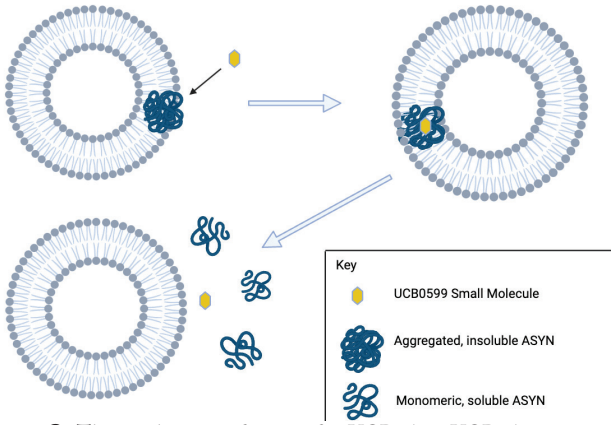

Figure 3: The mechanism of action for UCB0599: UCB0599 is a small molecule that binds to aggregated ASYN on membranes. It then expels the ASYN off the membrane into soluble, nontoxic monomers.

In several previous studies, the effects of this drug were investigated using both *in vitro* and *in vivo* models. The results showed that UCB0599 improved motor symptoms in PD mouse models. Specifically, it reduced the number of slips by nearly 50% on a round beam test. ASYN levels were also reduced, with ASYN immunolabelling showing a statistically significant decrease in corrected optical density from around 300 to 200 in MPTP (Parkinson symptom-induced) mice versus MPTP mice receiving the treatment. A neuroprotective property for the drug was also shown, with neuroinflammatory markers such as GFAP decreasing significantly from 200 corrected optical density levels to 150 in the neocortex of mice.[23]

With these promising results in mice, a clinical trial (phase I/Ib) tested the safety and tolerability of UCB0599 in PD patients. There was no statistical difference between the TEAEs

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of the control group and treatment groups, indicating acceptable safety for the drug. Additionally, the CSF samples showed an increasing concentration of UCB0599 with increasing dosage concentrations, suggesting good blood-brain barrier penetration.[24]

A phase II trial, which started on 12/20/20 and is estimated to be completed on 10/10/24, is underway. The study includes 496 participants, a relatively large sample size for a phase II trial.[25] This may imply that this drug might have shown significant benefits or promise, leading researchers to invest in a larger trial.

Anle138b: Anle138b, just like UCB0599, prevents oligomeric aggregates from clumping. While UCB0599 was screened for anti-ASYN properties, Anle138b was screened for anti-prion properties, specifically DPP-related compounds. Upon binding to ASYN, Anle138b reduces the intermolecular hydrogen bonds in oligomers, turning them back into monomers (Figure 4). It also prevents the formation of oligomer pores in membranes. It stops the prion-like spread of ASYN.[26]

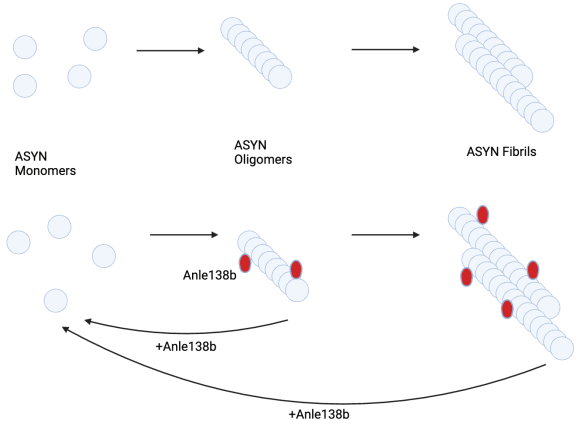

Figure 4: The mechanism of action for Anle138b: Anle138b is a small molecule that binds to the hydrogen bonds in ASYN oligomers and reverts them into nontoxic forms of ASYN.

Previously, Anle138b demonstrated efficacy in mice models of Parkinson's disease. Upon treatment with Anle138b, the mice showed improved motor performance and lowered levels of aggregated ASYN. The Rotarod performance scores of untreated PD mice were between 20 and 25, whereas the scores of PD mice receiving the treatment were between 25 and 30, showing a statistically significant increase in motor performance. Further, with a SIFT assay, it was demonstrated that Anle138b's effect on iron-induced ASYN oligomer formation decreased in a dose-dependent manner, with no treatment having 100% high control of aggregate signaling, 80% for 1 microliter of treatment, around 50% for 3 microliters of treatment, and around 30% for 10 microliters of the drug administered. Pore formation in lipid bilayers by ASYN also decreased significantly, with a pore insertion percentage of around 65% in the control group and 30% in the treatment group.[26]

Anle138b had a high oral bioavailability and good blood-brain barrier penetration. Compared to intraperitoneal administration, oral administration consistently resulted in around 50 percent AUC (Area under the curve) values. Additionally, as the dosage of Anle138b increased, so did its concentrations in the brain. The drug levels in the brain were also consistently three times greater than in the serum.[26]

With these promising results in mice models, a phase I trial was conducted with Anle138b to determine the drug's safety, tolerability, and pharmacokinetics in PD patients. It was found to have excellent safety and tolerability within patients, with no compound-related side effects and only a few minor adverse events.[27] Despite these promising findings, no current phase II study for Anle138b exists.

UCB0599 and Anle138 show great promise in being developed as disease-modifying therapies. Small-molecule drugs have many benefits, as they can be taken orally, have excellent blood-barrier penetration, and can make their way into a cell, which antibody drugs cannot do. However, small-molecule drugs tend to be less specific; thus, further research is necessary to prove their safety with their interactions in the human body.

Small Molecule (ASYN mRNA Transcription Inhibitor):

Buntanetap: Buntanetap is an ASYN-targeting drug currently in its phase III trial. This drug was first developed when researchers noticed similarities between the 5'UTR regions of two very different proteins - amyloid precursor protein and ASYN. Pathogenic proteins implicated in neurodegenerative diseases, such as tau and ASYN, also have the same atypical iron response element (IRE) in the 5 UTR regions of the mRNA. In a low-iron environment, an iron regulatory protein 1 (IRP1) binds to the IRE to prevent the mRNAs from being translated through ribosomes. When the intracellular iron level is high, which is common in many neurodegenerative diseases, IRP1 is released from the IRE, allowing for the translation of ASYN.[28,29] Buntanetap mimics a low intracellular iron environment by keeping the IRP1 bound to the IRE, thereby preventing the ribosomes from accessing the mRNA and thus inhibiting the translation of ASYN or other neurotoxic proteins. Notably, halting the transcription of ASYN does not eliminate existing aggregates but merely prevents more from being produced.[30] Therefore, if effective, this therapy would be best suited for individuals with early-stage PD (Figure 5).

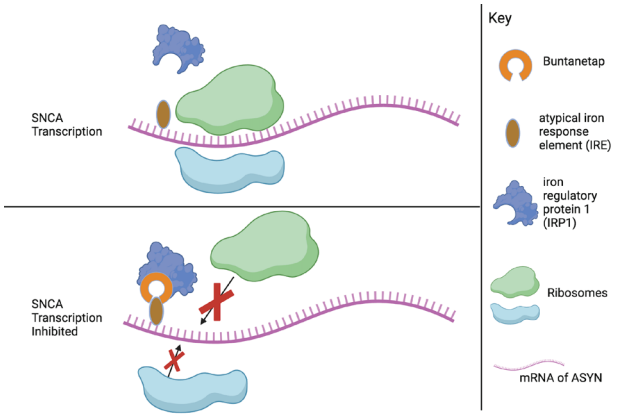

Figure 5: The mechanism of action for Buntanetap: Buntanetap inhibits the transcription of ASYN by increasing the binding of the iron regulatory protein 1 (IRP1) to an atypical iron response element (IRE), a characteristic found in neurodegenerative disease-causing proteins' mRNA. This prevents the ribosomes from binding to the mRNA and ultimately stops the transcription of ASYN.

In early phase I trials, buntanetap was tested in a single ascending dose (SAD), multiple ascending doses (MAD), and proof of concept trial (POC), all of which showed its safety and tolerability in patients.[30]

In another phase I/II trial, buntanetap was again tested for its safety and efficacy in 14 Alzheimer's disease and 54 PD patients. No adverse events occurred related to the drug itself. There were, however, some mild TEAEs, such as headaches, muscle spasms, and erythema, for Buntanetap and were noted as related. For 10 mg and 20 mg doses of buntanetap, the patients' MDS-UPDRS scores improved significantly (P-value < 0.05), with the placebo group having a score around -5 while the two treatments had scores of about -7 to -8, demonstrating improvement in motor functions such as rigidity and non-motor symptoms such as cognition. The WAIS coding score, which measures visual-motor dexterity, associative nonverbal learning, and nonverbal short-term memory, also improved for PD patients. The placebo group received scores of between -4 and -5, while the treatment groups all had scores of around 5, meaning that treatment groups scored higher on the cognitive test. Additionally, in the 14 PD patients who received the highest dosage (80 mg), there was a reduction in ASYN levels by nearly 50% in the cerebrospinal fluid (CSF) compared to the placebo group. Buntanetap also reduced inflammation, as shown by the reduced levels of inflammatory markers in the CSF. Neurofilament Light (NFL), a sensitive biomarker for neuroaxonal damage, was also measured to assess the drug's neuroprotective effects. NFL decreased from around 10% to nearly 0% from the placebo to the treatment group, indicating Buntanetap's potential in slowing neuronal death. Thus, the study showed that buntanetap was well tolerated in PD patients, with biomarkers supporting anti-inflammatory, neuroprotective, and ASYN-reducing properties.[30]

One objection could be that Buntanetap lacks specificity. Even though it binds to this region with a high affinity, with an IC50 of 3.2 nM, and does not bind to any canonical IRE loops, the atypical IRE could also be found in several other vital proteins' mRNA, potentially inhibiting their translations. However, since it was proven safe in patients, and the atypical IRE only seems to be present in neurotoxic proteins, Buntanetap remains a promising drug target for treating PD. Nevertheless, further studies should aim to test the long-term safety of the drug, as well as search for any other protein mRNAs with the same atypical IRE.

A phase II/III study involving 450 early-stage PD patients was completed on 12/4/23, but the results have not been posted yet.[31] The results of this study would be crucial in determining if stopping the overexpression of ASYN will be enough for a disease-modifying therapy and may give further insights into the drug's mechanisms.

Small Molecule (Neurotransmitter Regulators):

Neurotransmitter regulators are one method being explored in the effort to find a disease-modifying therapy for PD. Two drugs suggested targeting ASYN through neurotransmitter regulation—memantine and citalopram—are currently in Phase III and II clinical trials, respectively. Although they differ in their proposed mechanisms for reducing ASYN, both drugs may carry out their neuroprotective roles by regulating the level of neurotransmitters.

Memantine: Memantine is a drug initially used to target dementia in Alzheimer's disease. This drug aims to cater to Parkinson's patients with mild cognitive disorder (PD-MCI).[32]

Memantine may be neuroprotective by stopping neurons from dying from overstimulation by neurotransmitters. When too much glutamate is released from a neuron, the post-synaptic neuron dies through excitotoxicity. Memantine blocks the glutamine receptors (NMDA receptors) to stop the overstimulation. It is also hypothesized that memantine prevents ASYN endocytosis, decreasing ASYN levels by inhibiting its uptake (Figure 6).[32]

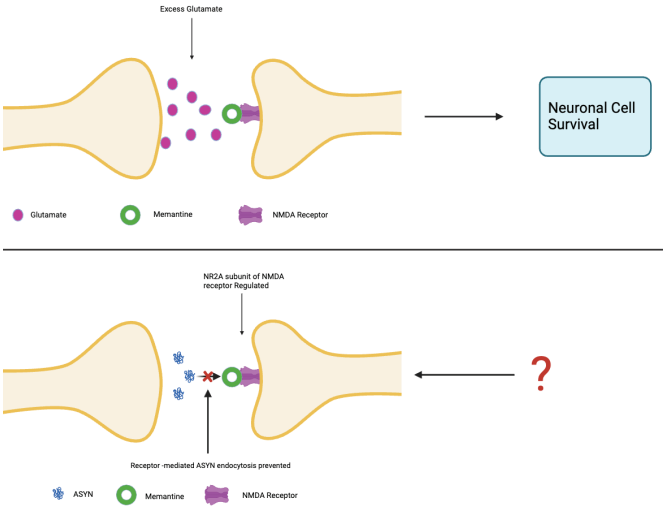

Figure 6: The mechanism of action for memantine: Memantine blocks the glutaminergic NMDA receptors. This promotes neuronal cell survival by avoiding excitotoxicity when too much glutamate is released. The exact pathway to how memantine may decrease ASYN levels or inhibit its spreading has yet to be elucidated. Memantine may affect NMDA receptors and their neuronal uptake of spreading-competent external ASYN.

An *in vitro* study of memantine's effects on interfering with ASYN transmission was published in 2021.[32] Using SH-SY5Y cells and mice, immortalized neuroblastoma cells were used to study neurodegeneration, and memantine's modulatory effect on ASYN's internalization was proposed to decrease the amount of internalized ASYN fibrils. The study also sought to investigate the neuroprotective effects of memantine in ASYN-enriched SH-SY5Y cells. The findings suggested that memantine inhibits cell-to-cell transmission of ASYN by regulating the NR2A subunit of NMDA receptors, thereby affecting receptor-mediated ASYN endocytosis and producing a pro-survival effect on neurons. Additionally, memantine reduced the expression of phosphorylated ASYN in the substantia nigra, leading to improved motor conditions, such as balance through a rotarod test, and a neuroprotective effect on dopaminergic enzymes.[32]

Thus, on a cellular level, memantine showed much potential: it inhibited cell-to-cell propagation and decreased the internalization of ASYN. Neurodegeneration occurs when aggregated ASYN, which is toxic, spreads from cell to cell. Containing this spread may be essential to the search for a disease-modi-

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fying therapy for PD. However, a pharmacological functional magnetic resonance imaging (fMRI) study published in 2022 showed no meaningful difference in most neuropsychological tests for cognitive performance and neuroimaging measures between placebo and treatment groups in PD patients.[33] There is one exception of a specific cognitive test, the trail-making test A, a test for visual attention and task switching, which showed a significant increase upon treatment. A further fMRI analysis revealed that memantine administration reduced brain activation in regions associated with visuospatial working memory. The right lingual gyrus and the left superior frontal gyrus had reduced activity. These results indicate that memantine may have no or potentially harmful effects on cognition and visuospatial memory in Parkinson's disease mild cognitive impairment (PD-MCI) patients.[33] Despite these negative results, many previous studies show the opposite. A study on memantine's impact on PD motor symptoms reported that memantine could improve Parkinsonian symptoms independently of dopaminergic drugs as patients had an improvement in their MDS-UPDRS score with a p-value of less than 0.003.[34]

A phase III study was completed on 7/1/23. Over 51 months, 50 patients and participants were followed. Although no results have yet been posted, researchers aim to explore whether memantine inhibited ASYN spread in PD patients.[35]

There are some potential limitations with how memantine may exert neuroprotective properties. PD patients usually develop the symptoms of dementia only when the disease has markedly progressed, i.e., over 50% of substantia nigra midbrain neurons are lost. Attempting to slow down neurodegeneration when a patient is already advanced into the disease, or even to stop it entirely, seems inefficient and perhaps ineffective. However, this drug was initially used for targeting dementia in Alzheimer's or Lewy Body dementia, which are similar to Parkinson's dementia. In both instances, neurodegeneration has spread to the cortex at the onset of dementia for PD patients.[36] Therefore, it should ideally be administered to maximize the drug's efficacy when PD hasn't progressed much. It might be refined to target specifically Parkinson's in the midbrain.

Citalopram: Citalopram, a drug used to alleviate depression, is a selective serotonin reuptake inhibitor (SSRI). It makes serotonin more available to postsynaptic neurons by increasing its presence in the synaptic cleft. More serotonin improves response inhibition, which is the ability to suppress automatic behaviors for more controlled decisions, and helps with impulsivity problems in PD. In addition to this symptomatic treatment, citalopram was proposed to decrease ASYN levels and, therefore, be disease-modifying. This possibility hinges on the proposed mechanism that elevated serotonin can reduce the amount of insoluble amyloid-beta (Abeta), the key peptide related to Alzheimer's disease progression, and indirectly decrease the amount of ASYN aggregation/accumulation (Figure 7).

However, the exact mechanism requires further elucidation, especially concerning how Abeta production is affected and how reducing or increasing Abeta would affect ASYN levels.[37-39]

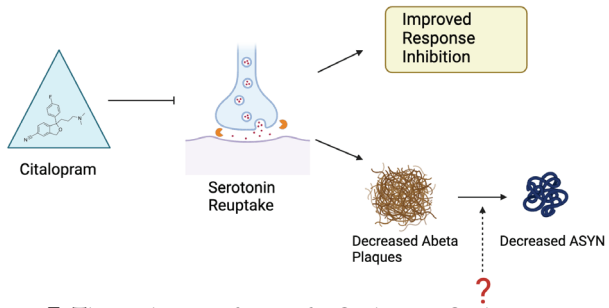

Figure 7: The mechanism of action for Citalopram: Citalopram is a small molecule that inhibits serotonin reuptake, improving response inhibition and possibly decreasing Abeta plaques and ASYN levels. The exact mechanisms still need to be determined.

Indeed, previous studies have shown that an increase in serotonin reduces Abeta and Abeta plaque levels in the brains of mice.[38] Other studies of mice with overexpressed tau, Abeta, and ASYN have shown that increasing insoluble Abeta correlates with Lewy body formation.[39]

A study on citalopram aimed to measure its effect on the impulsivity of PD patients. Impulsivity is a significant problem in PD, as it is marked by patients having difficulty stopping a response. The study showed that for participants with worse UPDRS-III scores (more severe motor problems), the reaction time (SSRT) improved linearly. Additionally, functional imaging showed that as UPDRS- III scores worsened, citalopram enabled greater activation of the right interior frontal cortical, the area involved in stop-related activation, which is the brain's role in inhibiting a response, particularly in situations where it is necessary to stop a behavior. Even though the mechanisms of Citalopram seem unclear, this study suggests that Citalopram can potentially improve stop-signaling reaction times.[37] Because this study focused on measuring the symptomatic benefits of citalopram, its effect on decreasing ASYN was not measured. For future work, researchers should better understand the drug's mechanism for reducing ASYN levels and look further into the relationship between ASYN and Abeta.

Small Molecule (Cell Death Inhibitor):

Cell death inhibitor therapies are a unique method for modifying the progression of PD as they aim to slow down neuronal deaths by inhibiting apoptosis.

KM-819: KM-819 is a small-molecule drug developed to target the protein FAF1. Faf1 is associated with the Fas death-inducing signaling complex (DISC) and enhances apoptosis. KM-819 inhibits FAF1 and prevents the accumulation of ASYB by promoting its degradation through autophagy restoration.[40]

The ubiquitin-proteasome system (UPS) or the autophagy-lysosome pathway (ALP) degrades many protein aggregates. ALP removes aggregated proteins, while UPS primarily degrades monomeric proteins.[41-44] FAF1 is a protein that prevents the ALP from degrading the aggregated ASYN in PD.

KM-819, therefore, targets FAF1 and hinders its ability to inhibit the ALP from breaking down aggregated ASYN.[40] This helps to preserve mitochondrial functions and prevent neuronal cell death (Figure 8).

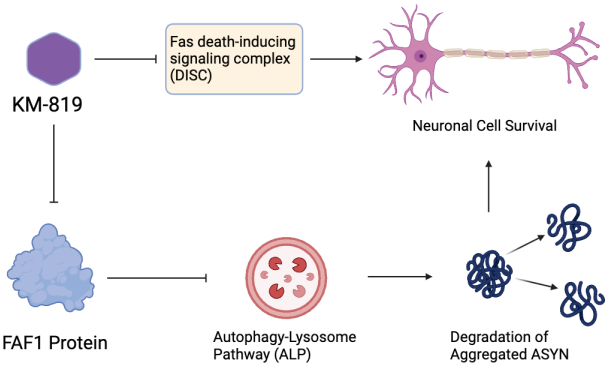

Figure 8: The mechanism of action for KM-819: KM-819 first inhibits DISC from promoting neuronal cell survival. In addition, it inhibits the FAF1 protein's inhibition on the autophagy-lysosome pathway (ALP) to enable the ALP to degrade ASYN.

A study using SH-SY5Y cells and mouse PD models tested KM-819's safety and efficacy. The results showed that KM-819 effectively reduced ASYN aggregation, thus preventing mitochondrial dysfunction and apoptosis induced by FAF1-mediated ASYN accumulation. KM-819 was also found to dose-dependently reduce mtROS (mitochondrial reactive oxygen species) production and mitochondrial depolarization, with EC50 values of 3.98 ± 0.05 nM and 5.39 ± 0.56 nM, respectively.[40]

The drug has shown promising overall safety results, with phase I trials revealing that PD patients tolerate it well and show no treatment-related side effects.[45] Ongoing phase II trials, which aim to further assess its safety and effectiveness in humans, are set to be completed on 11/13/25.[46]

Neuroinflammatory Kinase Inhibitor:

Currently, only one drug in development aims to inhibit neuroinflammatory kinases to reduce ASYN levels. However, this drug is closely related to targeting neuroinflammation, which is hypothesized to impact ASYN levels indirectly.

Hypoestoxide: Hypoestoxide (HE), derived from the shrub Hypoestes rosea, is a natural diterpene that targets neuroinflammation by regulating the activity of NF-κB, which is a transcription factor that plays an important role in the pro-inflammatory regulation pathway. In PD, neuroinflammation is a problem that causes further neuronal cell death. When HE obstructs NF-κB through IκB kinase inhibition, neuronal cell survival is promoted through preventing neuroinflammation.[34] Specifically, IκB kinase inactivates NF-κB, inhibiting pro-inflammatory gene transcription. However, the exact mechanism of how this might decrease ASYN levels remains unclear (Figure 9).

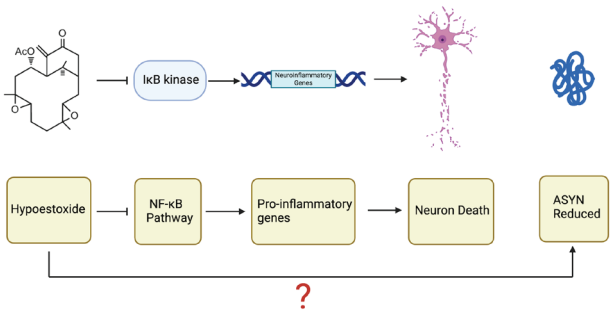

Figure 9: The mechanism of action for Hypoestoxide: Hypoestoxide is a natural compound that inhibits the IκB kinase. This disrupts the NF-κB, or transcription factors for pro-inflammatory genes. By inhibiting this pathway, HE prevents proinflammatory genes, promoting neuronal survival. However, how Hypoestoxide reduces ASYN levels remains unclear.

In LPS and ASYN-induced PD mouse models, HE treatment was shown to have considerably decreased IBA-positive cells. This suggests reduced neuroinflammation, as IBA is a marker for microglia associated with neuroinflammation. As for motor performances, round beam traversal tests showed that the vehicle group had over 1 error for 10 cm of the beam. In contrast, animals receiving the treatment had around 0.5 errors per 10 cm, a statistically significant decrease indicating that HE administration improved motor symptoms in PD mice. Additionally, an analysis of tyrosine hydroxylase, a marker for dopaminergic neurons, in the striatum showed an increase from the control group with 200 TH optical density to 300 TH in the treatment group. Though not necessarily a problem, such an increase in TH optical densities was not observed in the substantia nigra, which was unexpected. HE also decreased ASYN levels in the brain. The ASYN optical density was significantly reduced in the frontal cortex neuropils, striatum, and hippocampus, although not the frontal cortex neurons. The levels of insoluble ASYN were reduced considerably.[47]

These results of decreased neuroinflammatory markers, ASYN, and increased motor performances indicate that HE may decrease ASYN levels by inhibiting inflammation. However, the exact mechanism of HE is still unknown. While it is supposed to inhibit cell death by regulating NF-κB-induced neuroinflammation, its specific effects on ASYN still require further research.[47] A Phase I/II study started on 1/3/22 and was completed on 12/31/22, which tested for the effect of HE in PD patients. Despite the completion date, results have yet to be published, raising concerns that the study may have been negative or discontinued, in contrast to the promising results of mouse models of PD.[48]

Summary:

Although each therapy had varying levels of impact on ASYN levels, comparing the results by the magnitude of the effect would be ill-matched because the studies used different ways of measuring ASYN aggregate levels. Therefore, the plausibility of the drug working on the cellular level, as well as whether positive results for biomarkers or other tests regarding ASYN aggregation levels will be considered to determine which drug seems most promising.

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A significant obstacle to ASYN-targeted drug development is measuring ASYN pathology in PD patients. While there have been recent advances that improved detection, such as seeding amplification assays in CSF, neuroimaging biokarkers remain largely underdeveloped.[49] The challenge in measuring *in vivo* levels of ASYN aggregates complicates the process of evaluating a drug's efficacy and its ability to reduce ASYN accumulation.

Of the ten ASYN-targeting disease-modifying therapies, six were shown to have positive outcomes in a clinical setting. Buntanetap, KM-819, hypoestoxide, UCB0599, Anle138b, and citalopram showed safety, tolerability, and potential to reduce ASYN in the brain. UB-312 and UCB7853 were only tested for safety, meaning that the drugs' disease-modifying potential could not be measured. On the other hand, memantine and prasinezumab failed to show promising results, although other studies indicate that other long-term benefits or benefits for specific subpopulations may exist.

Developing ASYN-targeting therapies for Parkinson's disease has posed several key challenges. Many promising drugs, specifically antibody-based drugs such as UB-312 and UCB7853, have shown to have limited brain penetration. Because the blood-brain barrier prohibits most antibodies from coming into the brain, these drugs become less efficient in targeting the ASYN aggregates that reside primarily in the brain. Additionally, the mechanism of action for other therapies, such as KM-819 and Hypoestoxide, raise different concerns even with positive outcomes. Because they are not primarily focused on ASYN aggregates and use indirect means, such as inhibiting the FAF1 protein or neuroinflammatory kinase, these drugs may not have the desired or large enough impact on reducing ASYN levels with respect to other, more direct therapies.

The therapies that have shown success during trials in lowering ASYN aggregates and having a viable cellular mechanism have been the small molecule drugs that directly target ASYN. These therapies have been shown to be able to cross the blood-brain barrier. However, one criticism is that these small molecules lack the specificity of the antibody. While there may be concerns about what else this small molecule could react to, the trials of UCB0599 or Anle-138b have shown no adverse effects after taking the medication among Parkinson's patients.

Given the complexity and multi-factorial nature of PD, a combination therapy approach may be necessary. For example, UCB0599 and UCB7853 were designed to be complimentary, with the UCB7853 being highly specific to ASYN aggregates and UCB0599 being able to easily cross the blood-brain barrier. This is similar to how the levodopa-carbidopa combination works well for managing symptoms. Being able to target many of the disease mechanisms, such as neuroinflammation, ASYN aggregation, and more, could prove to be the most effective strategy for slowing the progression of PD.

Despite many positive early results from the various trials, further research is required to improve the therapies' specificity, clinical efficiency, and more. UCB0599 and Anle-138b stand out as the more promising candidates given their strong early clinical data, but ongoing trials will determine each drug's true potential.

■ Conclusion

Overall, many of the small-molecule therapies were highly successful. This may be because they can be ingested orally and have good blood-brain barrier penetration. However, they lack specificity and may have unknown interactions and consequences with other bodily functions. Overall, the antibody therapies have been less successful. Although antibodies are highly effective and specific, they are limited from crossing the blood, which is problematic since pathologic ASYN aggregates to be targeted are primarily located in the brain.

All the drugs mentioned except for UCB0599 and Anle-138b have clinical limitations, including penetrating the blood-brain barrier and having a mechanism of action that is plausible on the cellular level. UCB0599 and Anle-138b have all these characteristics, making it the most promising alpha-synuclein-targeting disease-modifying therapy. Among all of the clinical trials, there have been discrepancies in the clinical populations of the studies, with citalopram and KM-819 having more early-stage PD patients and prasinezumab and memantine having late-stage PD patients. Because of the varying progression of Parkinson's patients for each clinical trial, certain populations have more neurodegeneration or ASYN aggregate levels, potentially influencing the differences among the results.

This analysis focused solely on whether positive results were shown, what might be the molecular mechanism, and if further studies were ongoing to test the drug. Due to the discrepancies between the units for measuring ASYN and neurodegeneration decrease between each trial, no direct comparisons were possible, as different readouts were used. Additionally, only ASYN-targeting disease-modifying drugs from Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update [14] were examined, meaning that additional or new therapies might not have been included in this review.

Based on the above trends, small molecule therapies seem to be the most promising treatment for Parkinson's disease. Therefore, researchers should focus more on increasing the specificity of small molecules to yield the best results. Additionally, the mechanisms of hypoestoxide, citalopram, and memantine and their relations to decreasing ASYN levels should be further studied to determine whether they may be viable methods for preventing neurodegeneration. Combination therapies should also be explored, such as taking UCB0599 for earlier stages of the disease and UCB78523 in later stages.

In general, small molecules showed more success than antibodies as they could better cross the blood-brain barrier, whereas antibodies, although more specific to ASYN aggregates, could not cross the barrier and make a meaningful impact on ASYN levels. Among the small molecule therapies, those specifically targeting ASYN production or oligomerization rather than those relying on indirect mechanisms such as utilizing neurotransmitters or decreasing the autophagic response were more successful in trials. These included UCB0599, Anle138b, and buntanetap, which all show the potential to be disease-modifying as they have sound theoretical pathways for reducing ASYN while demonstrating good safety

and tolerability. Anle138b needs a phase II study to test and understand the drug efficacy in persons with PD. At the same time, Buntantetap may prohibit ASYN translation but may have side effects due to inhibiting the translation of other proteins. Therefore, of the ten ASYN-targeting disease-modifying therapies explored in the Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update,[16] UCB0599 and Anle-138b seemed to be the most promising drugs for PD as of now due to their positive clinical results, viable cellular model, and ongoing therapeutic trials.

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