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Small-Molecule Inhibitor Drugs in Neurodegenerative Diseases

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ASTRACT

Neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), are progressive disorders characterized by neuronal dysfunction and loss, resulting in cognitive, motor, and neurological decline. AD is primarily associated with the accumulation of β-amyloid plaques and hyperphosphorylated tau neurofibrillary tangles, along with oxidative stress, neuroinflammation, synaptic dysfunction, and neuronal loss. In PD, progressive degeneration of dopaminergic neurons is associated with α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, impaired autophagy–lysosomal pathways, and neuroinflammation. Although current treatments provide symptomatic relief, they do not effectively halt or reverse the underlying neurodegenerative processes, emphasizing the need for disease-modifying therapeutic strategies. Small-molecule inhibitors (SMIs) have emerged as promising therapeutic candidates because of their ability to selectively modulate disease-associated proteins and molecular pathways. This review discusses the classification and mechanisms of SMIs targeting amyloidogenic processing, tau phosphorylation and aggregation, cholinergic dysfunction, α-synuclein aggregation, kinase activity, oxidative stress, neuroinflammation, mitochondrial dysfunction, and autophagy–lysosomal pathways, and evaluates the clinical evidence for their use as disease-modifying treatments (DMTs) in AD and PD. Although SMIs have theoretical advantages over biologic therapies, such as intracellular access and lower production costs, their clinical translation has been limited: only a small number of symptomatic SMIs are FDA-approved, and most disease-modifying candidates have failed to show significant clinical benefit despite successfully engaging their molecular targets. But there are obstacles such as target specificity, blood–brain barrier penetration, toxicity, and limited clinical translation that are significant to their successful development.

Keywords: *Small-molecule inhibitors; Alzheimer's disease; Parkinson's disease; Disease-modifying therapy.*

1. INTRODUCTION

Neurodegenerative diseases are disorders in which neurons in the brain progressively lose function over time and ultimately die. The decline of neurons is caused by worsening symptoms as the diseases advance (Katsuno et al., 2018). There are a variety of neurodegenerative diseases, including Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Amyotrophic lateral sclerosis, and Multiple Sclerosis. All of the following diseases are examples of age-related diseases that have an increased onset with aging.

Given the increased lifespan of humans globally, there is an urgent need to treat these diseases, given their prevalence (Niccoli & Partridge, 2012). The prevalence rate for Parkinson's disease is ~15.63 per 100,000 population (Li et al., 2025). Currently, in the United States of America, more than six million Americans are living with Alzheimer's disease (Waziry & Williams, 2023). Currently, there are no treatments that have cured any of these diseases; therefore, there is a crucial need for therapeutic inventions.

There are many reasons why no cures have been found for these diseases, such as their complexity. Across each neurodegenerative disease, there are many pathological or biological processes involved in the decline of neuroactivity; therefore, it can be difficult to target a single pathway or treatment. In addition to the complexity, many patients with these diseases are unaware of their condition and are diagnosed in later stages. By the time the symptoms are noticeable, large amounts of neuronal loss have already occurred. This lack of awareness leads to irreversible death caused by the degeneration of unique brain regions of neurons. Since neurons are essentially irreplaceable, their loss can lead to numerous issues in the structure and function of the human body. Side effects of a treatment also play a role in the lack of cures for neurodegenerative diseases; treatments like inhibitors may affect other necessary proteins vital for life. Lastly, since these are very large-scale diseases, it is more challenging to produce outcomes due to high costs. However, some therapies are being actively researched, such as antibody therapeutics, recombinant proteins, peptides, nucleic acids, genetic intervention, and small-molecule inhibitors.

One specific avenue of therapeutic intervention is the use of small-molecule inhibitors, organic compounds that typically weigh less than 900 daltons. An SMI is designed to reduce or block the function of a biological target, often by binding to it. Specific to ND's, SMIs can target intracellular processes that antibodies may not reach. An advantage in therapeutic development is that it is cheaper and easier to manufacture and can target separate pathological processes in neurodegenerative diseases such as AD or PD, with the assistance of a single or several agents. Overall, the development of SMIs is useful as it can reduce overactive pathological processes before they cause irreversible damage. This review paper aims to discuss SMIs targeting the molecular pathways underlying AD and PD and to evaluate their potential as disease-modifying treatments (DMTs).

2. METHODOLOGY

This literature review was conducted using sources from PubMed, Google Scholar, and The Lancet, searching for articles published within the last 20 years to identify research studies on the molecular pathology of Alzheimer's disease (AD) and Parkinson's disease (PD) and on small-molecule inhibitors (SMIs) targeting these pathways. Search terms included "small-molecule inhibitor," "kinase inhibitor neurodegeneration," "α-synuclein aggregation inhibitor," "tau aggregation inhibitor," and "Nrf2 activator neurodegeneration," in addition to the AD-genetics terms used in the earlier search. Articles were included if they were published in a peer-reviewed journal, defined a molecular target relevant to AD or PD, and reported in vitro, preclinical, or clinical efficacy data; non-peer-reviewed papers and articles that did not focus on a specific SMI mechanism were excluded; and non-free full-text articles were excluded.

Titles and abstracts were first screened for relevance to SMI classification, mechanism, or clinical outcome, and then the full text of the remaining articles was reviewed to verify usefulness. Studies were prioritized if they described a defined molecular target, reported *in vitro*, preclinical, or clinical efficacy data, and were published in peer-reviewed journals. Reviews were used to identify mechanistic classes of SMIs, while primary research articles were used to support specific claims about individual compounds. Additional sources were identified through reference tracking of selected articles. This screening process yielded approximately 40 sources for inclusion in the final manuscript.

3. DISCUSSION

3.1 Pathology of AD

Alzheimer's disease (AD) is the most prevalent progressive neurological disorder that slowly deteriorates memory, thinking, and functioning. Patients with AD have characteristic deficits which lead to a loss of memory for recent events, problems planning and solving, and disorientation for time and place. These deficits also progress with the progression of the disease. Patients have problems with language, confusion, mood swings, lack of motivation, behaviour problems, and ultimately lack of basic bodily functions. As of 2024, 6.9 million people are living with Alzheimer's disease (AD), and by 2060, approximately 13.8 million individuals will be diagnosed with AD ("2024 Alzheimer's Disease Facts and Figures," 2024). With the increase in the number of diseases, the economic burden was approximately $321 billion in healthcare in 2022, which could exceed $1 trillion by 2050 (SkariaAnita, 2022). The trends highlight the importance of research and development of effective treatments to slow or prevent the progression of AD.

Pathology of AD may be grouped into two main categories: genetic and sporadic. Genetic causes of AD include familial and early-onset AD, which may occur before age 65. But only 1-5% of people with AD have familial AD. Mutations in genes such as APP (amyloid precursor protein), PSEN1 (presenilin 1), and PSEN2 (presenilin 2) disrupt Aβ peptide processing, a primary factor in early-onset disease pathology (Andrade-Guerrero et al., 2023). Over 300 mutations have been identified in the PSEN1 gene and approximately 80 in the PSEN2 gene.PSEN gene mutations include missense mutations, small insertions and deletions, and, in the case of PSEN1, genomic deletions. Mutations in PSEN1 are completely penetrant and can affect the age of onset as early as 25 years. By contrast, mutations in PSEN2, which are associated with incomplete penetrance and are often missense, usually occur at a much later age than PSEN1 mutations (Andrade-Guerrero et al., 2023).

Eventually, missense mutations result in an increase in altered proteins, which change APP processing and may interfere with the formation of the γ-secretase complex. APP processing may result in a marked rise in the ratio of AB42/AB40. The APP gene encodes the protein, which contains a total of 17 exons, 3 of which are relevant to AD, and two exons (16 and 17) code for the AB fragment following proteolytic processing.

Another type of AD is called sporadic AD. It is the most frequent variant of AD, and risk factors include age and environmental factors (Andrade-Guerrero et al., 2023). The most significant genetic risk factor for sporadic AD is the presence of a polymorphism of the apolipoprotein E gene (APOE ε4), especially when the gene is present as the APOE*ε4 allele, which is a significant risk factor for the disease. Clinical evidence indicates that amyloid pathology in the brains of APOE4 carriers is a key mechanism by which APOE4 raises the risk of AD. The number of pathways that are modulated by APOE isoforms is increasing, including both AB-dependent and AB-independent pathways (Yamazaki et al., 2019).

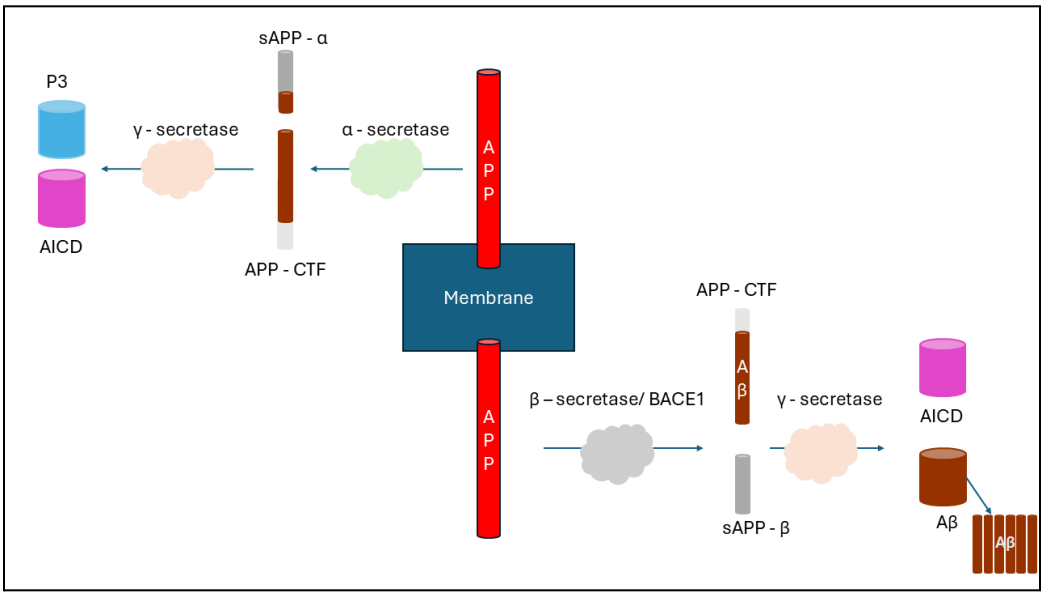


Figure 1. Amyloidogenic and non-amyloidogenic APP processing. Schematic depicting the two processing pathways for the APP protein. APP = amyloid precursor protein; CTF = C-terminal fragment; AICD = APP intracellular C-terminal domain; sAPP-beta = soluble APPbeta. Original figure created by author.

3.2 Small-Molecule Inhibitors in AD

Given the multifactorial pathology of AD, small-molecule inhibitors (SMIs) are a flexible therapeutic approach. Multiple classes of SMIs target different steps in the pathological cascade. β-secretase (BACE1) inhibitors target the first step in Aβ production by preventing APP cleavage (**Figure 1**). These drugs had strong amyloid lowering in early studies, but the majority of BACE1 inhibitors have failed in late-stage clinical trials due to lack of efficacy or cognitive side effects (Bazzari & Bazzari, 2022). γ-secretase modulators target the enzyme complex responsible for the last step of Aβ production with the goal of reducing pathogenic Aβ species while minimizing off-target effects. Tau-targeting SMIs inhibit tau aggregation or hyperphosphorylation. While some have shown promising results in preclinical models, human translation has been limited due to safety and brain penetration to reduce oxidative stress simultaneously. Tau-targeting SMIs also aim to simultaneously reduce oxidative stress, inflammation,

mitochondrial dysfunction, and impaired proteostasis (Yao et al., 2022). In summary, SMIs represent a flexible approach to early intervention, targeting both intracellular and extracellular pathological processes and synergistically combining protective mechanisms, although there has been limited clinical success. Of these strategies, only BACE1 inhibitors have been tested extensively in large phase 3 trials, and yet none of them have demonstrated disease modification; γ-secretase modulators and tau-targeting SMIs remain largely preclinical or early-phase, so whether they can translate into meaningful clinical benefit is still unproven (Table 1, Section 3.7).

3.3 Pathology of PD

Parkinson's disease (PD) is a neurological disorder characterized by progressive loss of dopamine-producing neurones in the substantia nigra pars compacta. It may result in motor and non-motor symptoms. Motor symptoms are resting tremor, bradykinesia (slowness of movement), rigidity, and postural instability, while non-motor symptoms include sleep disturbances, autonomic dysfunction, mood disorders, loss of smell (anosmia), and cognitive decline. The prevalence of PD is significantly higher in older age, and approximately 11.77 million people worldwide are affected by PD (Luo et al., 2025). In North America, incidence rates for people over 45 range between 47–77 per 100,000, while rates for those over 65 reach 108–212 per 100,000 (Willis et al., 2022).

PD is primarily sporadic, but there are also monogenic forms that are caused by mutations in genes like SNCA, LRRK2, and PARK family genes. The buildup of misfolded α-synuclein in Lewy bodies and Lewy neurites, mitochondrial failure, oxidative stress, lysosomal and autophagic impairment, and neuroinflammation are the neuropathological characteristics of Parkinson's disease. These processes culminate in the death of dopaminergic neurons and the resulting dopamine deficiency, which accounts for the motor deficits of PD.

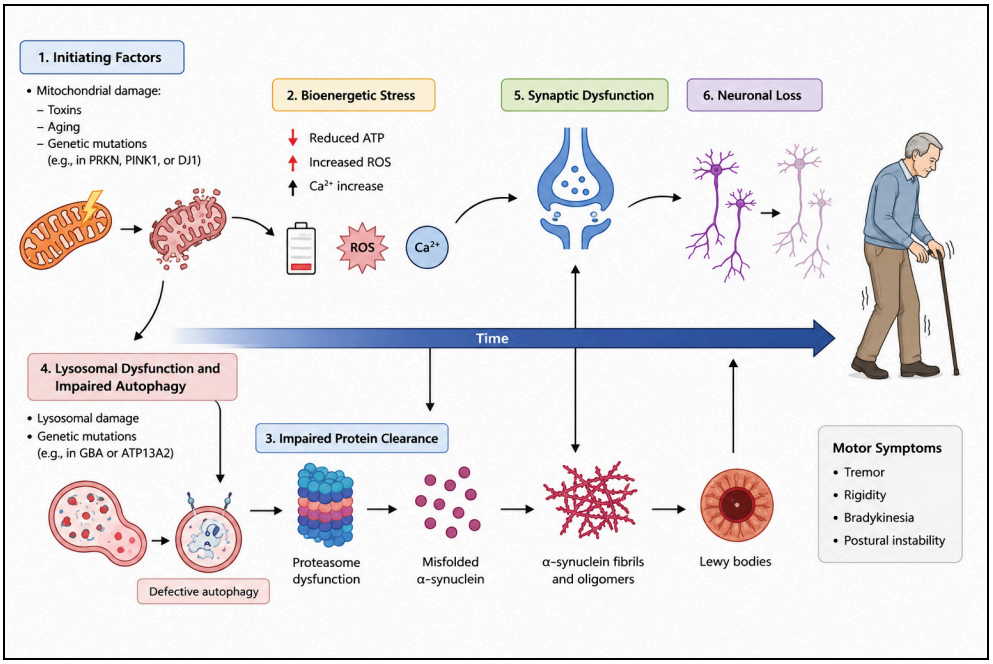


Figure 2: Pathogenesis of Parkinson's disease: Molecular and cellular mechanisms contributing to synaptic dysfunction and neuronal loss. (Adapted from The Pathogenesis of Parkinson's Disease (Morris et al., 2024).

3.4 SMI in PD

Small-molecule inhibitors (SMIs) in PD target enzymes, kinases, or signaling pathways that contribute to neurodegeneration. MAO-B inhibitors block monoamine oxidase B, reducing dopamine breakdown and alleviating motor symptoms, particularly in early-stage PD. They can be used alone or as supplements to levodopa therapy to extend "on" time and improve motor control. LRRK2 kinase inhibitors target the leucine-rich repeat kinase 2, one of the most common genetic contributors to familial PD. These inhibitors aim to reduce pathological kinase activity, prevent α-synuclein accumulation, and mitigate neuroinflammation.

Other SMIs in development address mitochondrial dysfunction, oxidative stress, and protein aggregation. By modulating these interconnected pathological pathways, SMIs aim to slow neurodegeneration and provide disease-modifying benefits beyond symptomatic relief. Although clinical trials for PD SMIs are still ongoing, preclinical evidence indicates that multi-target strategies may improve neuronal survival and quality of life in PD patients. Among these, only MAO-B inhibitors and levodopa therapies are FDA-approved, and they address symptoms rather than neurodegeneration directly. LRRK2 inhibitors and other disease-modifying therapies are currently in early-phase clinical testing (Table 1, Section 3.7).

3.5. Small-Molecule Inhibitors: Classification and Mechanisms

The SMIs that target AD and PD can be categorized according to the molecular process they disrupt: signaling (kinases), catalytic activity (enzymes), protein misfolding (aggregation), gene expression (epigenetics), immune activation (neuroinflammation), and redox balance (oxidative stress). In reality, these categories may overlap; for example, the same pathological trigger (e.g., protein accumulation) can activate multiple of these processes simultaneously.

Additionally, not every SMI discussed in this review functions strictly as an inhibitor. For example, Nrf2-targeting compounds activate an antioxidant transcriptional pathway rather than blocking a single pathological target, and are therefore more accurately described as pathway activators or modulators rather than inhibitors. The term "SMI", in this review paper, is used broadly to refer to any small molecule that modulates a disease-associated pathway.

3.5.1 Kinase Inhibitors

Kinases are enzymes that phosphorylate proteins, and some of these directly participate in the disease process of AD and PD. Tau hyperphosphorylation is a key event in the process of tangle formation, neuron loss, and dementia in AD, and SMIs that inhibit GSK3β have been investigated as a means to lower hyperphosphorylation of tau (Liu et al., 2023). c-Abl is a tyrosine kinase that, like LRRK2, has been associated with dopaminergic neuron death in PD and is being investigated for its neuroprotective effects (Abushouk et al., 2017), as is LRRK2 kinase inhibition, which attenuates gliosis and cytotoxicity after intracerebral injection of amyloid-beta and α-synuclein fibrils (Mutti et al., 2023). The broad participation of kinases in normal cell signaling makes them attractive targets for drugs but also makes them susceptible to off-target effects.

3.5.2 Enzyme Inhibitors

Enzyme inhibitors are inhibitors of catalytic proteins directly involved in the production or degradation of pathological molecules. In AD, BACE1 and γ-secretase inhibitors inhibit the enzymatic processes that produce amyloid-beta (Das & Yan, 2019; Lebois et al., 2025), and acetylcholinesterase inhibitors inhibit the enzymatic degradation of acetylcholine, which has a symptomatic effect (Mehta et al., 2011). In PD, MAO-B inhibitors inhibit the enzyme that degrades dopamine, increasing the amount of dopamine and relieving motor symptoms (Schapira, 2011). Enzyme inhibitors are well characterized pharmacologically as their targets are known to have a single defined catalytic function, although as noted above, enzyme inhibition at the biomarker level (such as decreasing amyloid-beta) does not always lead to clinical benefit.

3.5.3 Protein Aggregation Inhibitors

These SMIs directly interact with misfolded proteins to inhibit their ability to form toxic oligomers and fibrils. In PD, compounds like SynuClean-D (Pujols et al., 2018) and ZPD-2 (Peña-Díaz et al., 2019) inhibit the aggregation of both WT and familial variants of α-synuclein at substoichiometric ratios, and

some inhibit the seeded polymerization of various strains of α-synuclein. Other small molecules, such as flavonoids and structurally designed molecules, do so by binding to fibril ends and physically preventing further growth, sometimes referred to as "capping" (Sedov & Khaibrakhmanova, 2022). Similar inhibitors are used in AD to inhibit tau and amyloid-beta aggregation. Since aggregation inhibitors act on the misfolded protein, not on an upstream enzyme, they could be effective later in the course of the disease, but their effectiveness is highly dependent on achieving adequate brain levels.

3.5.4 Oxidative Stress Inhibitors

Oxidative stress inhibitors work by boosting the brain's natural antioxidant defenses, most commonly through activation of Nrf2, a transcription factor that turns on antioxidant genes (Tejo & Quintanilla, 2021). The activation of Nrf2 has been shown to induce the expression of antioxidant enzymes that can prevent oxidative damage and mitochondrial impairment, both of which are involved in PD and AD (Tejo & Quintanilla, 2021; Brandes et al., 2021). Multiple compounds that activate Nrf2 are already approved by the FDA for other diseases, and clinical trials are currently ongoing for related neurodegenerative diseases, reducing the potential time required to repurpose them for AD and PD (Tejo & Quintanilla, 2021).

For example, dimethyl fumarate is an Nrf2 activator already FDA-approved for multiple sclerosis, and omaveloxolone is an Nrf2 activator approved for Friedreich's ataxia. Clinical trials repurposing these and related Nrf2-activating compounds for AD and PD are ongoing, which may reduce the time required for their development in neurodegenerative diseases (Tejo & Quintanilla, 2021).

Because oxidative stress compounds mitochondrial dysfunction and inflammation rather than acting alone, Nrf2 activators are often studied as part of multi-target strategies rather than standalone treatments (Arbo et al., 2022).

3.6 SMIs IN AD AND PD

3.6.1 Comparative analysis of SMIs in AD and PD

Although AD and PD share some pathogenic characteristics, such as protein misfolding, mitochondrial dysfunction, oxidative stress, and neuroinflammation, there are also clinical differences and primary neuropathologies. The major pathological hallmarks of AD are extracellular amyloid beta plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau, which are mainly involved in memory and cognition (Yao et al., 2022). In contrast, PD is linked to the build-up of α-synuclein in Lewy bodies and the death of dopaminergic neurons in the substantia nigra, causing motor dysfunction and subsequently cognitive impairment.

Nevertheless, the small molecule inhibitors (SMIs) in both diseases seek to intervene early in the pathological processes, decrease the amount of toxic proteins, and modulate the cellular stress responses. In AD, BACE1 and γ-secretase inhibitors are used to inhibit the production of amyloid-β, while in PD, LRRK2 kinase and MAO-B inhibitors are used to reduce the toxicity of α-synuclein and maintain

dopaminergic function (Bazzari & Bazzari, 2022). Both diseases highlight the need for multi-target therapies targeting oxidative stress, inflammation, and proteostasis. Comparative analysis highlights the potential of SMIs, but the differences in disease etiology and brain region vulnerability should inform drug design and therapeutic strategies. Table 1 (Section 3.7) summarizes these compounds from each drug class alongside their stage of development and evidence level, to make this comparison more explicit.

3.6.2 Mechanisms of Actions

The therapeutic efficacy is quite different for symptomatic SMIs and disease-modifying SMIs. Symptomatic agents (e.g., MAO-B inhibitors for PD, acetylcholinesterase inhibitors for AD) are effective at short-term symptom reduction, but do not prevent neuronal loss (Chopade et al., 2022; Zhao et al., 2018). Even if promising results were seen in preclinical studies, the results of disease-modifying SMIs in human trials have been much less consistent. The best example is verubecestat, a BACE1 inhibitor that has been studied in two different phase 3 trials. In the EPOCH trial, which included nearly 2,000 patients with mild-to-moderate AD, verubecestat reduced the amount of amyloid in the brain and CSF, but did not slow cognitive or functional decline, and the trial was terminated early because an interim analysis indicated that the drug was not effective (Egan et al., 2019). In patients with earlier, prodromal AD, a second trial, APECS, tested verubecestat on the premise that it would be more effective to treat before the onset of dementia symptoms. Rather, patients taking verubecestat developed dementia earlier than placebo patients, and this trial was also terminated early (Egan et al., 2019). Combined, these two trials demonstrate that reducing a pathological protein (biomarker-level efficacy) does not necessarily equate to a real clinical benefit with respect to memory or daily functioning (clinical-level efficacy), and in this instance, may have been detrimental. The same type of disparity is beginning to show up in PD. In a preliminary trial of the LRRK2 inhibitor BIIB122, the drug was shown to suppress LRRK2 kinase activity in the blood and CSF of trial participants by up to 98%, indicating that it does indeed reach and inhibit its target, but the study only lasted for 28 days and was not designed to determine whether BIIB122 can actually slow PD progression (Jennings et al., 2023). This raises the question of whether, by itself, targeting the intended molecular target is sufficient to provide a meaningful clinical benefit, a question already answered in the negative with verubecestat in AD.

3.6.3 Therapeutic Efficiency and Limitations

There are several benefits of SMIs over biologics. They are small and can penetrate the plasma membrane and thus exert their effect within the cell, and are typically less expensive and simpler to produce than antibody-based therapies. SMIs can also be chemically engineered to simultaneously target multiple targets within a single molecule, which is increasingly being adopted to tackle the multifactorial nature of AD and PD (Thakur et al., 2026; Cavalli et al., 2008; Kumar et al., 2018). But SMIs have their own real constraints. Many are not effective because they do not cross the blood-brain barrier at a high enough concentration. Side effects may also occur, as in the case of BACE1 inhibitors, where the drug was also found to cause cognitive decline, albeit through off-target binding to structurally similar proteins that it was not designed to target (Bazzari & Bazzari, 2022). Furthermore, SMIs are typically based on a single

hypothesis, such as the amyloid cascade hypothesis, so they may not capture the entirety of the disease and thus be less effective in isolation (Chopade et al., 2022).

3.7 Comparative Summary of Representative Small-Molecule Inhibitors

To directly compare which SMI strategies have demonstrated real clinical benefit and which have failed, and which remain preclinical, Table 1 summarizes representative compounds discussed throughout this review, organized by disease, molecular target, mechanism, stage of development, evidence level, therapeutic effect, and major limitations.

Disease	Target	Compound	Mechanism	Stage	Evidence Level	Therapeutic Effect	Major Limitations
AD	BACE1 (β-secretase)	Verubecestat	Blocks APP cleavage to prevent Aβ production	Phase 3 (terminated early)	Clinical — negative	Lowered brain/CSF amyloid but no cognitive benefit	Did not slow decline; worsened outcomes in prodromal trial (Egan et al., 2019)
AD	γ-secretase complex	γ-secretase modulators (class)	Reduces pathogenic Aβ species, minimizes off-target cleavage	Preclinical / early clinical	Preclinical	Not established in humans	Off-target effects on other γ-secretase substrates
AD	Tau (GSK3β / DYRK1A)	Dual GSK3β/DYRK1A inhibitor	Reduces tau hyperphosphorylation	Preclinical	Preclinical	Reduced tau pathology in animal models	Limited BBB penetration and human safety data (Liu et al., 2023)
AD	Acetylcholinesterase	Acetylcholinesterase inhibitors	Increases synaptic acetylcholine	FDA-approved	Clinical — established	Symptomatic improvement only	Does not slow neurodegeneration (Mehta et al., 2011)
PD	MAO-B	MAO-B inhibitors	Reduces dopamine	FDA-approved	Clinical —	Symptomatic improvement	Does not slow neurodegenera

Disease	Target	Compound	Mechanism	Stage	Evidence Level	Therapeutic Effect	Major Limitations
			breakdown		established		tion (Schapira, 2011)
PD	LRRK2 kinase	BIIB122	Suppresses LRRK2 kinase activity	Phase 1/2	Clinical — target engagement only	Up to 98% kinase suppression in blood/CSF	28-day trial not designed to test disease progression (Jennings et al., 2023)
PD	α-synuclein aggregation	SynuClean-D / ZPD-2	Inhibits α-synuclein fibril formation	Preclinical	Preclinical	Reduced aggregation, protected dopaminergic neurons in models	Not yet tested in humans (Pujols et al., 2018; Peña-Díaz et al., 2019)
AD & PD	Nrf2 pathway	Dimethyl fumarate, omaveloxolone	Activates antioxidant gene expression	FDA-approved (other indications)	Clinical — other diseases only	Reduced oxidative stress in preclinical NDD models	Not yet validated for AD/PD; approved only for MS and Friedreich's ataxia (Tejo & Quintanilla, 2021)

Table 1. Representative small-molecule inhibitors and activators discussed in this review. “Evidence level” differentiates compounds with established clinical benefit (FDA-approved symptomatic agents) from those with only target engagement or biomarker-level clinical evidence (e.g. BIIB122) and those still confined to preclinical models (e.g., protein aggregation inhibitors. No compound in this table has yet demonstrated disease modification in a completed human trial.

3.8 Blood-Brain Barrier

The blood-brain barrier (BBB) is one of the biggest obstacles to the development of effective SMIs for AD and PD. The majority of therapeutic medicines, including numerous small compounds, cannot cross the BBB's highly selective barrier in large enough quantities to be efficacious (Sweeney et al., 2018). The smaller size of SMIs makes them more likely to cross the BBB than large biologics, but chemical properties such as lipophilicity, molecular weight, and the presence of efflux transporters like P-glycoprotein play a role in successful BBB crossing (Trippier, 2016; Mikitsh & Chacko, 2014). When

they don't pass BBB permeability testing, many promising SMI candidates are given up, despite their success in previous lab tests. The situation is even more complicated when BBB dysfunction occurs, as it does in both AD and PD, because a dysfunctional BBB does not necessarily allow more of the drug to penetrate, as researchers previously thought. Consequently, in the design of SMI, penetration of the BBB has become one of the initial concerns, instead of a concern that is tackled later.

3.8 Disease-Modifying Therapy

A major difficulty in the development of SMI is the distinction between symptomatic treatment and actual disease modification. A disease-modifying therapy (DMT) should modify the underlying course of neurodegeneration, rather than simply mask its symptoms (Castellani & Perry, 2012). This distinction is hard to prove in a clinical trial because it would involve lengthy and costly studies with sensitive biomarkers that would be able to measure a slower decline, not merely short-term symptom improvement (Yiannopoulou et al., 2019; McGhee et al., 2016). The majority of AD SMI trials, such as BACE1 and γ-secretase inhibitors, have not met this DMT standard. One of the challenges is that treatment is often given after extensive damage to the neurons has occurred. The other issue is that many trials have been conducted with outcome measures that are more sensitive to symptom changes than to disease modification (Yiannopoulou et al., 2019). The same is true for PD: while symptomatic dopaminergic treatments are effective, no SMI has been shown to slow the neurodegenerative process.

3.9 Clinical Trial Limitations

Clinical trial design presents extra challenges which are more structural than biological. Research on the AD drug pipeline has shown extremely poor success rates for trials progressing through each phase, and hundreds of programs have been discontinued in the last 20 years (Yiannopoulou et al., 2019; Oxford et al., 2020; Cummings et al., 2014). Common issues are poor patient selection, with patients with a wide spectrum of disease severity being included in the same trial; lack of reliable biomarkers to ensure that the drug is actually reaching its target; and the duration of trials may be too short to establish a real disease-modifying effect, particularly when the diseases are slow to progress. Cost is another important consideration, as larger patient numbers and extended follow-up periods are needed for CNS trials compared to other treatment areas, making the prospect of continued investment less attractive after early failures (Chopade et al., 2022). The challenges are similar for both the development of AD and PD SMI, indicating that a large number of failures are not necessarily due to the biology of the diseases themselves, but also due to the way in which the trials are conducted.

4. CONCLUSION

Alzheimer's disease and Parkinson's disease are still major public health problems, and their prevalence is increasing at a rapid rate, along with the economic costs. Complex pathogenic mechanisms, including protein aggregation, neuroinflammation, and mitochondrial dysfunction, characterize both diseases. Small-molecule inhibitors offer a flexible route to inhibit pathogenic mechanisms of both diseases, while also reaching intracellular targets that biologics cannot access. Although clinical success has been

limited, there is hope for more effective interventions through ongoing research and multi-target strategies. In the near future, a better understanding of molecular mechanisms, early diagnosis, and precision-targeted therapies will be crucial to reduce the effect of neurodegenerative diseases (Yao et al., 2022).

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