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Digest

Current approaches to the treatment of Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) is the second most common neurodegenerative disorder. Clinical approaches to manage PD include symptomatic therapies, serving to compensate for the effects of dopaminergic neuronal deficits, as well as more recently a move toward disease modification, with the goal of slowing or stopping disease progression. This perspective surveys the approved therapies for PD treatment as well as provides a view of the ongoing clinical approaches aimed at improving outcomes for PD patients.

Parkinson's Disease (PD) is a chronic, neurodegenerative disorder second only to Alzheimer's Disease (AD) in prevalence and affects ~1% of the population over age 60.[1] Risk of developing PD appears to be increased by a combination of genetic and environmental factors. Clinical pathology and diagnosis is driven by progressive premature death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the observation of abnormal protein aggregates termed Lewy bodies, which contain α-synuclein, via post-mortem analysis.[2] The deficit in dopaminergic neurons impedes a number of motor functions, manifesting in rigidity, tremor, bradykinesia, and postural instability. A number of non-motor symptoms may also be present including olfactory and/or autonomic dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, pain, and fatigue. The heterogeneity in onset of disease and variable presence of symptoms complicates diagnosis as well as design of the therapeutic regimen for PD treatment. Further, there are related neurodegenerative disorders, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB), which further complicate stratification of patients into the appropriate diagnosis.[2]

To date, approved therapies for PD have focused on compensatory approaches targeting treatment of clinical symptoms (Fig. 1). This perspective will describe the approved and ongoing clinical pharmaceutical approaches to manage PD.[3] As will be detailed, there is an ongoing shift in the clinical landscape, as more research and development organizations focus on modification of PD to slow or stop disease progression, rather than temporary symptomatic relief.[2,4] This article will not describe alternative interventions used in the treatment of PD including surgical deep-brain stimulation and gene therapy.

Due to the slow progression of PD, measuring clinical progress toward PD modification has been particularly challenging. Specifically, the endpoint used for clinical registration to date has been the Unified Parkinson's Disease Rating Scale (UPDRS), which combines objective and subjective data including mood, self-evaluation of daily life activities, and motor evaluation.[5] To facilitate future clinical development, longitudinal studies have been undertaken to correlate imaging data (e.g. (DAT) SPECT) to UDPRS changes, which may allow quantitative, objective measures of impact on pharmacodynamic and biomarker endpoints related to impact on PD progression.[6]

Currently approved oral PD therapies

As previously described, degeneration of SNpc dopaminergic neurons and resultant loss of dopamine (**1**) activity in the striatum is the key driver for PD motor dysfunction (Fig. 2). All currently approved therapies for the treatment of PD aim to increase striatal dopamine levels to ameliorate associated motor deficits. Unfortunately, these approaches do not represent a long-term solution, as each loses efficacy as dopaminergic neurodegeneration progresses over time. The following therapies represent the mecha-

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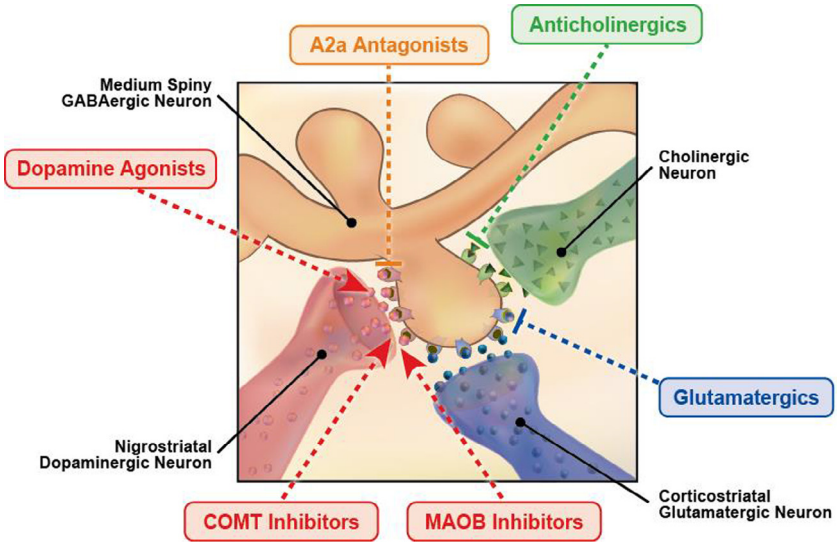


Fig. 1. Schematic of various methods for PD treatment.

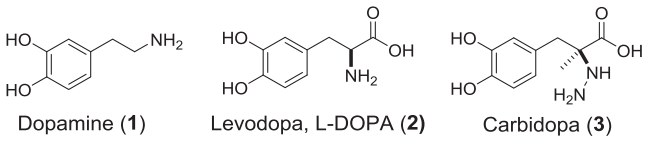


Fig. 2. Dopamine precursor approaches to PD treatment.

nisms of action that are currently leveraged to modulate dopamine levels for the symptomatic treatment of PD.

Dopamine precursors

Levodopa (L-DOPA, **2**), which is biosynthetically transformed to dopamine via aromatic L-amino acid decarboxylase (AADC), is commonly given to augment dopamine levels in PD patients (Fig. 2). Since its introduction in 1967, levodopa has persisted as the gold standard for the treatment of PD symptoms and is an integral component of combination therapies.[7] Levodopa tends to lose efficacy over time, with greater than 80% of patients on therapy for longer than 10 years experiencing dyskinesia and "on-off" periods.[8] Carbidopa (**3**) is often given in combination to reduce systemic metabolism of L-DOPA and increase central exposure, allowing lower doses of L-DOPA to maintain efficacy while reducing side effects such as nausea.

Dopamine agonists

There are five types of dopamine receptors in the brain, D_1–D_5. D_1 and D_5 (D_1-like) are GPCRs coupled to $G_{s\alpha}$ leading to activation of adenylyl cyclase and increasing cyclic adenosine monophosphate (cAMP).[9] D_2, D_3, and D_4 (D_2-like) are coupled to $G_{i\alpha}$ inhibiting adenylyl cyclase with a commensurate reduction in formation of cAMP. Dopamine agonists act on dopamine receptors to amplify the effects of dopamine. Approved therapies that agonize dopamine receptors and are prescribed for the treatment of PD include apomorphine (**4**), bromocriptine (**5**), ropinirole (**6**), pramipexole (**7**), and rotigotine (**8**, Figure 3).[10] Each of these molecules are most potent as agonists of D_2-like receptors with several also possessing some balance of D_1-like agonism and 5-HT, α-adrenergic and β-adrenergic antagonism.

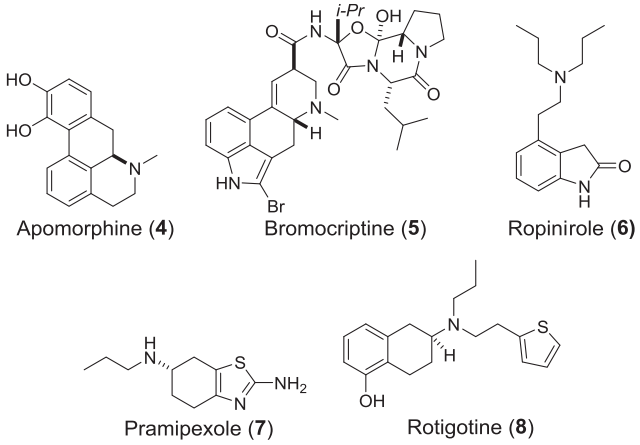


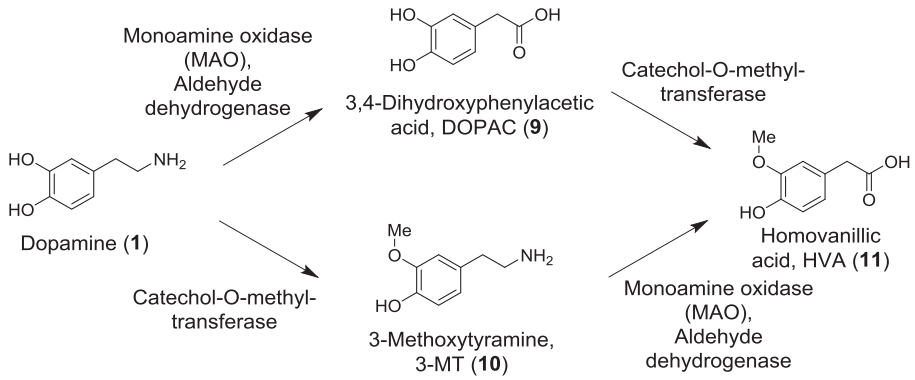
Fig. 3. Approved D_2-like Dopamine agonists.

MAO-B inhibitors

Monoamine oxidase B (MAO-B) is an enzyme involved in the metabolism of dopamine forming 3,4-dihydroxyphenylacetic acid (DOPAC, **9**) which is eventually transformed (by catechol-*O*-methyltransferase (COMT)) into homovanillic acid (HVA, **11**) (Scheme 1).[11] MAO-B inhibitors have been incorporated into the therapeutic regimen for PD treatment to decrease dopamine metabolism and thereby increase dopamine concentrations in the brain leading to a reduction in motor symptoms. Approved MAO-B inhibitors include selegiline (**12**) and rasagiline (**13**, Fig. 4), which are both irreversible inhibitors.[10]

COMT inhibitors

Catechol-*O*-methyl transferase (COMT) is an enzyme that catalyzes a parallel metabolic pathway transforming dopamine into 3-methoxytyramine (3-MT, **10**), which is subsequently oxidized by MAO-B to produce homovanillic acid.[12] Similar to MAO-B, inhibition of COMT leads to an increase of brain dopamine levels, reducing motor symptoms, and has been added to PD treatment over the past two decades as a combination therapy. Entacapone



Scheme 1. Dopamine metabolism via MAO-B and COMT.

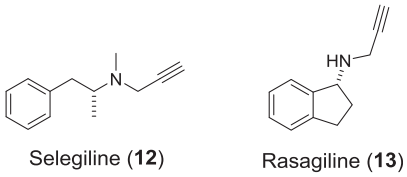


Fig. 4. Approved irreversible MAO-B inhibitors.

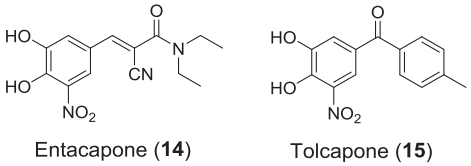


Fig. 5. Marketed COMT inhibitors.

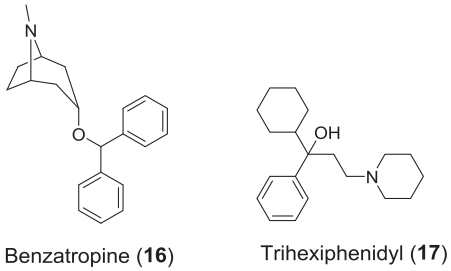


Fig. 6. Anticholinergics used in PD treatment.

(**14**) and tolcapone (**15**) are approved COMT-inhibitors now used as components of standard of care (Fig. 5).[10,13]

Anticholinergics

Anticholinergics do not act directly on the dopaminergic system, but instead modulate the activity of acetylcholine, which is involved in the regulation of movement, and can have beneficial impacts on tremor and dystonia in PD patients. Benzatropine (**16**) and trihexyphenidyl (**17**) are two approved antiparkinsonian therapies that decrease the activity of acetylcholine (Fig. 6).[10]

Miscellaneous approved therapies

There are several alternative mechanisms employed in the management of symptomatic PD manifestations. Amantadine (**18**) is an NMDA-type glutamate receptor antagonist that was historically used as an antiviral therapy and has been prescribed to mitigate dyskinesia in PD, though its efficacy has been questioned (Figure 7).[14] Droxidopa (**19**) is a prodrug of norepinephrine that was recently approved in the US for the management of neurogenic orthostatic hypotension in disorders such as PD, MSA, and pure autonomic failure. For the treatment of hallucinations, delusions, and psychosis associated with PD, pimavanserin (**20**), a 5-HT inverse agonist, has been prescribed. Additionally, rivastigmine (**21**), an acetylcholinesterase inhibitor, is used for the treatment of PD dementia.[10]

A variety of mechanisms and therapeutics described above are used in combination to enhance symptomatic benefit.[15] Substantial effort has been applied to novel formulations of these therapies that are prescribed at higher doses, as many PD patients suffer from dysphagia as the disease progresses. A number of efforts ongoing in the clinic are directed toward fixed-dose combinations

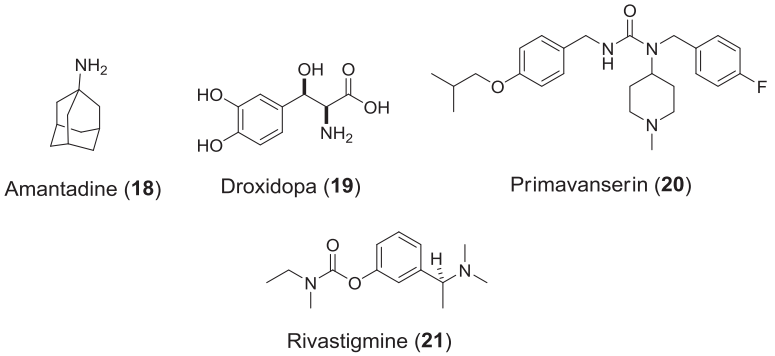


Fig. 7. Miscellaneous therapies for PD related symptoms.

of two or more therapeutics, novel formulations and methods of delivery (e.g. inhaled levodopa).

Ongoing clinical PD treatments and clinical trials

Dopamine modulators

The most active area of clinical research for symptomatic treatment of PD remains direct and indirect dopamine modulation. ACR 325 (orotidine, completed Phase 1,[16] structure unreported) and ACR343 (seridopidine, structure unreported) are dopamine stabilizers (D2 modulators) that were transferred in September 2016 to Saniona AB as Phase 2 ready for a PD trial.[17] Neurosearch led the early discovery efforts that originated these molecules, which are structural analogs of another Neurosearch dopamine stabilizer, pridopidine (**22**). Pridopidine (**22**) was licensed by Teva in 2012 and completed two Phase 3 Huntington Disease (HD) trials.[18] The FDA and EMA have assessed pridopidine (**22**) as unapprovable for HD based on the two existing Phase 3 trials, and it is unclear what impact this collection of D2 modulators may have in PD (Fig. 8).

Lu AE04621 is a prodrug of catecholamine acting as a D1/D2 agonist that has been part of Lundbeck's neurodegeneration portfolio since at least 2010.[19] A 15 patient Phase 1 trial in PD patients was completed in 2016. Neither the results of this trial nor the structure of Lu AC04621 have been disclosed to date. The chemotype may be related to a bioactivation prodrug concept first described by investigators from the University of Groningen and University of Göteborg in 2002 based upon recent Lundbeck patent activity (Scheme 2).[20,21]

Pfizer has an ongoing program studying D1 agonists for the treatment of PD. They have pursued an integrated approach to more systematically characterize disease course in PD patients. PF-06649751 is their lead candidate currently being studied in a Phase 2 trial in PD patients with motor fluctuations that commenced in 2016.[22] The structure of this molecule has not been disclosed, nor has a predecessor D1 agonist, PF-06412562 that completed Phase 1 in 2014 but no longer appears on the company's pipeline chart.[23] To pair with their small molecule modulator, Pfizer has partnered with IBM to develop infrastructure leveraging sensors and wearable technology in a controlled environment to advance quantification of PD symptoms. Specifically, a facility with a network of connected sensors in New York that can house PD patients and non-PD control subjects is being utilized to monitor symptoms and behavior in real time with the intent of providing novel insights into disease activity and intervention.[24] Pfizer is planning to leverage this information and these technologies in their Phase 3 trial with PF-06649751 in 2019 should their Phase 2 data support progression.

Integrated Research Laboratories has initiated a 2016 Phase 1b trial in PD patients in Sweden to test their D2 agonist with undisclosed structure, IRL-790, described as a psychomotor stabilizer to treat L-DOPA induced dyskinesia.[25]

Eli Lilly has an ongoing Phase 1 trial in PD patients studying the progressability of LY3154207.[26] Their pipeline chart lists a Phase 1 D1 potentiator being assessed for the treatment of dementia, which may be the same new molecular entity. No additional information about this compound's structure or specific pharmacology has been reported to date, though Eli Lilly has disclosed pharmacological characterization of an allosteric dopamine D1 potentiator tool molecule.[27,28]

Clera Inc. has studied a D2-specific agonist, CLR4001, for the treatment of PD in a Phase 2a clinical trial.[29] Neither the results of this study nor the structure of CLR4001 have been disclosed.

Seelos Therapeutics licensed aplindore (SLS-006, **23**) in late 2016, a D2/D3 partial agonist originally discovered by Wyeth prior to the company's acquisition by Pfizer (Fig. 8). Upon the acquisition, Seelos described SLS-006 as "a Phase 3 ready and clinically-validated partial dopamine agonist".[30] There are currently no active clinical trials listed for SLS-006.

Reviva Pharmaceuticals is developing a dopamine-serotonin system stabilizer, RP-5063 (also known as RP-5000) with polypharmacology, acting as a partial agonist on D2, D3, D4, serotonin 5-HT_{1A}, and 5-HT_{2A} receptors, as well as antagonist effects on the serotonin 5-HT_6 and 5-HT_7 receptors.[31] The focus of their clinical efforts to date have centered on memory deficits related to schizophrenia, with positive Phase 2 data in hand, but they also list PD as an indication of interest for this molecule.[32] No structural information has been disclosed thus far.

Kissei Pharmaceuticals features a D2 agonist, KDT3594, on their pipeline chart in Phase 1 for PD.[33] The structure has not been published, and there are no current US clinical trials listed.

MAO-B inhibitors

MAO-B inhibition continues to be studied, though the pharmacological approaches to this pathway have evolved. Dart Neurosciences is investigating the utility of reversible MAO-B inhibitors, a mechanistically differentiated approach to the currently approved irreversible inhibitors selegiline (**12**) and rasagiline (**13**). HT-3951 (structure unreported), which was originated by Helicon Therapeutics, entered into a Phase 2 trial for ischemic stroke in 2016. Both HT-3951 and its discontinued predecessor HT-1067 have been described as potential approaches to PD management,[34] though there are no ongoing trials reported exploring HT-3951 in this indication.

YKP-10461 (also known as SKL-PD) from SK Biopharmaceuticals and Celerion has been classified as a non-propargylic amine containing reversible MAO-B inhibitor that has completed a Phase 1 trial in healthy volunteers[35] and is seeking partnership for initiation of a trial in PD patients. The structure of YKP-10461 has not been disclosed to date, but pharmacokinetic and pharmacodynamic data in a dose ranging study testing 10–250 mg dose levels from the Phase 1 trial have been presented.[36]

COMT inhibitors

Limited efforts at COMT inhibition in the clinical space are represented by an ongoing Phase 2 trial sponsored by Orion Pharma. Orion is testing a carbidopa, levodopa combination with their purportedly improved COMT inhibitor ODM-104 (structure undis-

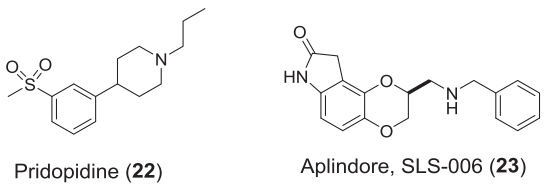
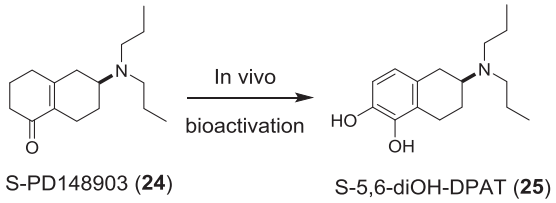


Fig. 8. Dopamine agonists undergoing clinical trials.



Scheme 2. Prodrug approach to Dopamine agonism.

closed). Their crossover study is designed to test the head to head efficacy of ODM-104 versus standard of care COMT inhibitor entacapone.[37]

GABA modulators

Gamma-aminobutyric acid (GABA) modulation has been proposed as a novel approach to PD treatment,[38] based on potential impact on motor activity observed when PD patients were treated with zolpidem.[39] Sage Therapeutics launched in 2010 to explore the utility of GABA and NMDA receptor modulators for the treatment of CNS disorders. SAGE-217 (**26**), an orally bioavailable steroidal derived $GABA_A$ positive allosteric modulator has ongoing Phase 2 trials in PD,[40] postpartum depression, major depressive disorder, and essential tremor (Fig. 9). For PD, SAGE-217 is being tested in combination with Levodopa versus Levodopa monotherapy.[41]

Additionally, ODM-106 from Orion Pharma is a $GABA_B$ receptor positive allosteric modulator that has completed a Phase 1 trial in healthy volunteers.[42] No additional clinical activity has been reported since early 2016, and the structure of this molecule has not been disclosed to date.

A2A antagonists

A number of pharmaceutical companies have pursued $Adenosine_{2A}$ (A2A) antagonists for the treatment of PD. A2a receptors are predominately localized to striatopallidal neurons where they are co-localized with D2 receptors. Antagonism of A2a receptors is thought to exert anti-parkinsonian effects by reducing overactivity of striatal pallidal output neurons however clinical evaluation of this mechanism has been met with mixed results. Kyowa Hakko Kirin reported top line results in December 2016 from a Phase 3 trial with their A2a antagonist Istradefylline (KW-6002, **27**, Fig. 10), which was previously approved as an adjunctive PD therapy in Japan.[43] Unfortunately, this molecule failed to achieve a statistically significant difference vs. placebo for the endpoint of "off time" in its most recent United States clinical trial, though there was a trend toward an improvement with both dose levels.[44] This result is akin to the findings with Merck's previous A2a antagonist, preladenant (**28**), which was discontinued after failing to show positive differentiation from placebo in 2013 as either an adjunctive therapy with L-Dopa or as a monotherapy in patients with early PD (Fig. 10).[45,46] It should be noted however that in the preladenant trials (adjunctive and monotherapy), the active control Rasagiline also failed to separate from placebo on the primary endpoints, making it difficult to reach definitive conclusions regarding the potential efficacy of preladenant.

Kyowoa Hakko Kirin has another A2A antagonist, KW-6356 (undisclosed structure), currently in Phase 2 in Japan for early PD.[47] KW-6356 has been partnered with Lundbeck for other markets. It is unclear what impact the istradefylline (**27**) results may have on KW-6356's future development.

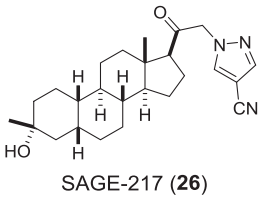
Tozadenant (sYN-115, **29**), originally discovered by Roche and currently being developed by Biotie Therapies as a subsidiary of Acorda Therapeutics, is being assessed at doses of 60 mg BID and 120 mg BID in a Phase 3 PD trial that is expected to deliver results by the end of 2017 (Fig. 10).[48,49]

Recently, some investigations of A2a antagonists have shifted from PD to potential applications in immuno-oncology.[50] Several examples include CPI-444 (previously V-81444 from Vernalis, undisclosed structure) from Corvus currently in Phase 1b[51] in combination with atezolizumab (Roche's PD-L1 monoclonal antibody), PBF-509 licensed from Palobiofarma by Novartis (undisclosed structure) and being studied in combination with Novartis's PD-1 antibody, PDR001, in non-small cell lung cancer,[52] and AZD-4635 (formerly HTL-1071 from Heptares, undisclosed structure) being tested in combination with durvalumab (AstraZeneca's PD-L1 monoclonal antibody) for the treatment of advanced solid malignancies.[53]

Additional miscellaneous ongoing clinical approaches to PD treatment

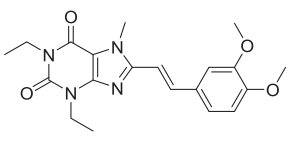
Eltoprazine (**30**) is an agonist of serotonin $5\text{-}HT_{1A}$ and $5\text{-}HT_{1B}$ and an antagonist of $5\text{-}HT_{2C}$[54] that has received orphan designation and is being studied in a Phase 2 trial[55] for Levodopa induced dyskinesia (Fig. 11). This molecule previously demonstrated efficacy in a small (18 patient) trial funded by the Michael J Fox Foundation to investigate efficacy in this endpoint.[56]

Landipirdine (sYN-120, **31**) is a dual $5\text{-}HT_6$ and $5\text{-}HT_{2A}$ antagonist being developed by Biotie Therapies, a subsidiary of Acorda Therapeutics, for the treatment of PD-related dementia (Fig. 11). There is an ongoing Phase 2 trial[57] that has received funding from

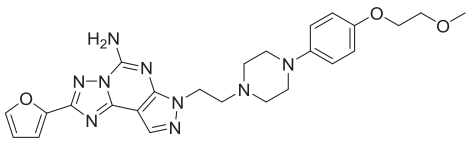


SAGE-217 (**26**)

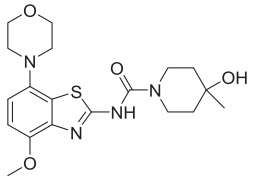
Fig. 9. SAGE-217, a GABA modulator under study in a Phase 2 PD trial.



Istradefylline (**27**)



Preladenant (**28**)



Tozadenant (**29**)

Fig. 10. A2A antagonists that have been studied for utility in PD.

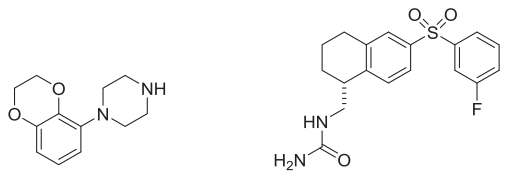


Fig. 11. Miscellaneous molecules under clinical study for PD related symptoms.

the Michael J Fox Foundation and should complete in the first half of 2018.[58,59]

Prexton Therapeutics is developing PXT 002331 (Foliglurax), a metabotropic glutamate receptor 4 (mGluR4) positive allosteric modulator (PAM), for the treatment of PD. A Phase 1 trial in 72 subjects given ascending doses of the molecule (structure undisclosed to date), administered orally showed that Foliglurax was safe and well-tolerated at doses above those that produce robust effects in preclinical non-human primate models of PD.[60] Following completion of a series B funding round, Prexton Therapeutics has confirmed that Foliglurax, will enter into a Phase 2 clinical trial in 2017.[61]

Disease modification approaches in clinical development

As previously discussed, all currently approved therapeutics for PD provide symptomatic benefit but none have been shown to slow or stop the progression of the disease. There have been clinical efforts to demonstrate PD modification, such as the ADAGIO trial testing the disease modifying potential of rasagiline (**13**).[62] The results of this trial showed a potential beneficial effect on UPDRS via early intervention with rasagiline at 1 mg/day, but lack of statistically significant impact at 2 mg/day. Currently, there are a number of additional therapeutic strategies in clinical development which are being evaluated for their disease modifying potential in PD. The major focus of these disease modifying therapies is on reducing α-synuclein toxicity either by reducing α-synuclein aggregates, increasing α-synuclein clearance or by preventing cell to cell spread of pathological α-synuclein. These therapeutic approaches are detailed in the sections below.

Small molecule disease modification approaches

NPT 200-11 is a novel small molecule with undisclosed structure that targets pathogenic α-synuclein by stabilizing conformations of α-synuclein rendering them incapable of assembling into toxic pore-like oligomers.[63] Neuropore Therapies in collaboration with UCB, completed a Phase I study assessing the safety, tolerability and pharmacokinetics of NPT 200-11 in healthy volunteers in 2016. Although results have not been made public, Neuropore has confirmed that UCB is proceeding with the development of this novel therapeutic candidate and awarded a progression milestone of $5 million.[64] Neuropore/UCB subsequently initiated a Phase 1 clinical trial in MSA in September 2016.

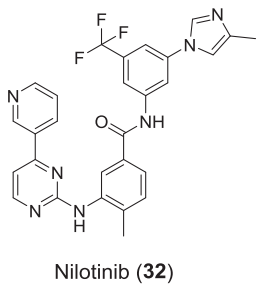


Fig. 12. Approved oncology agent undergoing evaluation for PD efficacy.

Inhibition of c-Abl, a tyrosine kinase, has been proposed as a mechanism to reduce α-synuclein aggregation based on preclinical evidence demonstrating that c-Abl overexpression enhances, while c-Abl deletion reduces, α-synuclein aggregation and neuropathology in vivo. Nilotinib (Tasigna®, AMN107, **32**), a c-Abl kinase inhibitor, approved in the US for the treatment of imatinib-resistant chronic myelogenous leukemia (CML) has recently been tested for safety in a small Phase 1 clinical trial in PD and DLB patients (Fig. 12).[65] The study, conducted by researchers at Georgetown University, indicated that nilotinib (150 mg and 300 mg), was safe and tolerable. Moreover, several of the patients on drug reported improvement in their clinical symptoms; however, it is important to note that this was an open label trial and there was no placebo arm. In early 2017 Georgetown University Medical Center announced the launch of a Phase 2, randomized, double-blind, placebo-controlled clinical trial to study the safety of nilotinib and its effects on clinical outcomes and biomarkers in patients with mid-stage PD.[66]

Increased degradation of α-synuclein is another potential mechanism explored in the clinic. Currently, the leading candidates for this approach center on modulating the activity of the Glucocerebrosidase (GBA) pathway. Mutations in GBA are the leading genetic risk factor for sporadic PD and reductions in GBA activity are thought to lead to an accumulation of α-synuclein. Lysosomal Therapeutics is currently developing a brain penetrant, small molecule enhancer of GBA activity called LTI-291 (structure not reported) which is expected to enter Phase 1 testing in 2017. Recently, the anti-mucolytic drug Ambroxol (**33**) was shown to enhance the levels and activity of GBA in fibroblasts from control and GBA mutation carriers.[67] As a result, the Cure Parkinson's Trust and the Van Andel Research Institute initiated a Phase 1 proof of principle trial to determine the CNS target engagement of Ambroxol (**33**) and its effect on GBA and α-synuclein in PD patients with and without GBA mutation.

An alternative mechanism in the GBA pathway to enhance the degradation of α-synuclein is through inhibition of glucosylceramide synthesis. Glucosylceramide is a glycolipid substrate of GBA that is hypothesized to stabilize α-synuclein oligomers. In preclinical models with a GBA mutation, Sanofi Genzyme has previously reported that the glucosylceramide synthase (GCS) inhibitor GZ667161 (**34**) slowed the accumulation of hippocampal aggregates of α-synuclein, ubiquitin, tau, and reduced associated memory deficits.[68] In December 2016, Sanofi Genzyme initiated a Phase 2 MOVES-PD study to evaluate efficacy, safety, pharmacokinetics and pharmacodynamics of ibiglustat (**35**), a brain penetrant GCS inhibitor, for the treatment of PD (Fig. 13).[69] The randomized, double blind, placebo-controlled trial is enrolling approximately 230 patients with early-stage PD carrying a GBA mutation or other pre-specified variant.

Immunotherapeutic approaches

AFFITOPE® PD01A is an α-synuclein vaccine being developed by AFFIRis AG. A Phase 1 safety trial showed once-monthly subcutaneous dosing with PD01A (15 and 75 μg) for 4 months to be well tolerated and ~50% of the patients developed α-synuclein antibodies in the serum and CSF[70] In a follow-up "booster" study, 86% of vaccinated patients generated an immune response; of these responders, 63% produced α-synuclein-specific antibodies.[71] Preliminary observations indicated that of the responders, eight subjects (42%) did not require an increase in dopaminergic PD medication during the study period and five of these eight subjects had stable UPDRS III scores at study conclusion. As this observa-

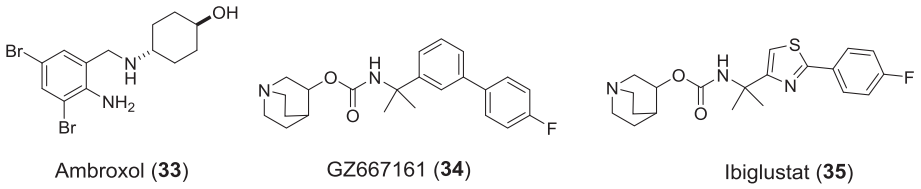


Fig. 13. Modulators of the GBA pathway with potential PD utility.

tional study was not double blind, it is not known whether effects seen in the active groups are indicative of positive treatment effects. A "reboost" study, in which subjects are given a second boost vaccination to evaluate the long-term safety, immunologic and clinical response to PD01A is ongoing with results expected in mid-2017.[72]

PRX002 is humanized anti-α-synuclein antibody being developed by Prothena Biosciences Inc., in conjunction with Roche. In a Phase 1 study of 40 healthy subjects PRX002 was shown to be safe, well-tolerated and reduced free serum total α-synuclein levels up to 96%.[73] Data from a second Phase 1b trial of 80 PD patients was recently disclosed. In this six-month study, patients received three monthly doses of PRX002 or placebo followed by a 3 month observational period. No dose-limiting toxicities were observed and PRX002 demonstrated acceptable pharmacokinetic properties. CNS penetration was demonstrated by a dose-dependent increase in PRX002 levels in CSF (~0.3% relative to serum across all dose levels). PRX002 demonstrated a rapid, dose- and time-dependent reduction of free serum α-synuclein levels of up to 97% after a single dose and which were maintained following two additional monthly doses.[74] Based on the positive Phase 1 data, Prothena/Roche announced the initiation of PASADENA, a year-long phase 2 efficacy study of PRX002 in approximately 300 patients with early PD. The study is expected to start in the second quarter of 2017.

Biogen has also advanced a monoclonal antibody (BIIB054) against pathological forms of α-synuclein into the clinic. In a Phase 1 randomized, double-blind, placebo-controlled, single-ascending dose trial evaluating safety, tolerability, pharmacokinetics and immunogenicity in 48 healthy subjects BIIB054 exposure and C_{max} were dose proportional with a 28 day serum half-life and an average CSF-to-serum ratio of 0.2% across all tested doses. BIIB054 was safe and well-tolerated with the exception of the highest dose (135 mg/kg), where one serious adverse event was reported.[75] Based on this preliminary data Biogen plans to take BIIB054 into phase 2.

Select emerging preclinical approaches

A survey of recently disclosed preclinical presentations and publications via an analysis of patents, meeting abstracts, and the literature describing efforts toward PD treatment reveals an emphasis on genetically supported targets as well as a focus on disease modification rather than exclusively symptomatic therapeutic approaches. Some examples of recent preclinical disclosures targeting various biological pathways are detailed. AstraZeneca invented a myeloperoxidase (MPO) inhibitor AZD5904 (**36**) that has been considered for the treatment of PD based upon block of oxidative stress induced during neuroinflammation (Fig. 14).[76,77] A PET study with a structurally related thioxanthine AZD3241 (**37**) was conducted in PD patients providing support for further study of MPO inhibitors in neurodegenerative diseases.[78] G protein-coupled receptor 6 (GPR6) has been investigated by several pharmaceutical companies including Lundbeck for the treatment of PD.[79,80] GPR6 is an indirect dopamine pathway modulation approach to PD treatment. No clinical activity has been reported

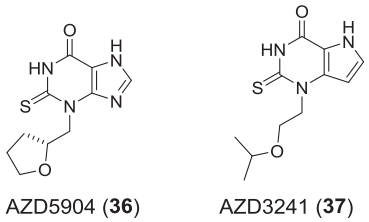


Fig. 14. Representative preclinical small molecule approaches under investigation for PD treatment.

to date for GPR6. Additionally, inhibitors of Leucine-rich repeat kinase 2 (LRRK2) are being pursued by numerous research organizations including Merck,[81] Pfizer, Lundbeck, Sanofi, and Denali. Mutations in LRRK2 are the most common autosomal dominant cause of PD and appear to increase kinase activity thus it has been hypothesized that lowering LRRK2 kinase activity may have disease modifying effects in PD. Despite disclosure of multiple chemotypes, a clinical LRRK2 kinase inhibitor candidate has yet to be identified.[82] This lack of progress is in part due to the challenge of developing a molecule with sufficient potency, selectivity, and brain penetration to drive a low human daily dose while avoiding off-target liabilities as patients will likely be on such a disease modifying treatment chronically. This is not an exhaustive list of recent preclinical efforts, but is intended to give a sense for the types of approaches that may emerge clinically in the foreseeable future.

Conclusions

As described in this perspective, there are a number of biological approaches aimed at addressing the unmet needs of PD patients. There are multiple symptomatic treatments available with additional options emerging in the clinical space. Further, there has not been success to date in demonstrating PD modification, though this continues to be an area of focus with intense effort ongoing preclinically and clinically to this end. It is likely that a combination approach will be most effective in managing PD symptoms and ultimately slowing or stopping disease progression. The next decade will feature interrogation of a number of novel pathways accompanied by data rich clinical trial designs with the goal of improving the lives of PD patients.

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