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Review

Pharmacotherapy for Disease Modification in Early Parkinson's Disease: How Early Should We Be?

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Abstract. Slowing or halting progression continues to be a major unmet medical need in Parkinson's disease (PD). Numerous trials over the past decades have tested a broad range of interventions without ultimate success. There are many potential reasons for this failure and much debate has focused on the need to test 'disease-modifying' candidate drugs in the earliest stages of disease. While generally accepted as a rational approach, it is also associated with significant challenges around the selection of trial populations as well as trial outcomes and durations. From a health care perspective, intervening even earlier and before at-risk subjects have gone on to develop overt clinical disease is at the heart of preventive medicine. Recent attempts to develop a framework for a biological definition of PD are aiming to enable 'preclinical' and subtype-specific diagnostic approaches. The present review addresses past efforts towards disease-modification, including drug targets and reasons for failure, as well as novel targets that are currently being explored in disease-modification trials in early established PD. The new biological definitions of PD may offer new opportunities to intervene even earlier. We critically discuss the potential and challenges around planning 'disease-prevention' trials in subjects with biologically defined 'preclinical' or prodromal PD.

Keywords: Parkinson's disease (PD), prodromal PD, preclinical PD, neuroprotection, disease-prevention, disease-modification, biological definition of PD

INTRODUCTION

Parkinson's disease (PD) is unique among the neurodegenerative diseases for the availability of highly effective symptomatic therapies. The clinical efficacy of levodopa and other dopaminergic drugs is striking and, in many cases, able to almost completely control the cardinal motor features of the disease [1–4]. However, none of the available drugs to treat the symptoms of PD are able to slow the underlying progression of the disease and the increase in overall disability. The latter is driven by a combination of motor and non-motor features that characterize advanced PD and include levodopa-related response fluctuations and drug-induced dyskinesias, the emergence of drug resistant motor symptoms like freezing of gait and falls, as well as a plethora of increasingly severe non-motor problems including cognitive decline, dysautonomia and sleep-wake dysregulation [5]. Despite symptomatic therapy 50% of PD patients have been shown to meet pre-defined disability milestones and 22% are functionally dependent after only

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5 years of disease [6, 7]. After 10–15 years more than >50% have developed hallucinations and/or dementia and >40% require institutional care [8, 9].

Disease-modification defined by preventing or delaying the progression of disability beyond symptomatic treatment effects is, thus, generally accepted as a key unmet need in the treatment of PD. From a regulatory perspective evidence for 'disease-modification' requires demonstration of effects of an intervention not only on clinical progression but also on underlying pathophysiological disease mechanisms, although it has been argued that demonstration of delay or prevention of clinical decline should be the prime anchor of definitions of disease-modification [10, 11] (see Panel).

The history of disease-modification trials in PD now spans about three decades during which a large number of well-designed and often large studies have used a broad range of drugs targeting different pathways potentially or definitely involved in the molecular pathology of the disease [12, 13] (Table 1). With the exception of two phase 2 trials of GLP1 agonists [14, 15], all of these efforts have yielded negative or, as in the case of the ADAGIO trial of the MAO-B inhibitor rasagilin [16], inconclusive results. Here we review potential reasons why so far almost all drug trials aiming to show disease-modification have failed, with a focus on novel targets and emerging perspectives of intervening at the earliest stages of disease.

Panel: Glossary of terms surrounding early disease-modification in Parkinson's disease (PD)

– *Preclinical PD*

A phase of disease where biochemical and pathological changes are present, but not have yet led to any clinical manifestations. This phase can only be identified through biomarkers.

– *Premotor PD*

A phase of the disease prior to the emergence of disease-related motor symptoms, may overlap with 'preclinical PD' and 'Prodromal PD'.

– *Prodromal PD*

A phase of disease characterized by the presence of disease-related nonmotor and subtle motor symptoms that are subthreshold to the current definition of '*clinical PD*' (see [18] for the MDS research diagnostic criteria for prodromal PD).

– *Clinical PD*

A phase of disease characterized by presence of the cardinal motor features as defined by current diagnostic criteria [17]. The term '*early PD*' refers to newly diagnosed patients are not yet on medication or on stable dopaminergic medication and without functional impact of the disease.

– *Disease-modification*

Any therapy that alters the clinical course ('*natural history*') of a disease can be regarded as '*disease-modifying*'. Such a broad definition would also include symptomatic therapies for PD as they reduce the severity and functional impact of motor and non-motor symptoms and, thus, positively influence the progression of disability. However, in regulatory science, the term disease-modification is used in a narrower sense, i.e., for a therapy that is capable of positively influencing the course of the disease by biological mechanisms that revert disease-specific pathophysiological changes [13,19].

– *Neuroprotection*

The term '*neuroprotection*' was introduced to capture beneficial (protective) effects of an intervention on neuronal survival and function. While such neuroprotective effects can be expected to translate into clinically detectable disease-modification, the presumed underlying biological effect on neuronal survival cannot be proven during lifetime without validated biomarkers that are closely linked to the disease-specific neuronal pathology. In the context of PD, such biomarkers are currently largely lacking. While alpha-synuclein imaging is still under development, presynaptic dopaminergic imaging has been used as a surrogate for such effects in some of the randomized controlled trials outlined in Table 1.

– *Disease-prevention*

The term '*disease-prevention*' is tempting to use in the context of trials in presymptomatic or prodromal cohorts, as prevention of clinically established PD can be seen as the ultimate goal of disease-modifying interventions in such subjects. However, there are conceptual problems even here, given that presymptomatic or prodromal disease stages are, by definition, already a disease state. Nonetheless, in a broader sense, the term can be used to describe effects of an intervention that forestall the development of clinically overt PD.

– *Regulatory definitions of disease-modification in PD*

The European Medical Agency requires a two-step procedure to demonstrate disease-modification in PD—first a delay in clinical measures of disease progression should be shown and second an effect on the underlying pathophysiological process which correlates to a meaningful, and persistent changes in clinical function [20]. The Food and Drug Administration (FDA) has not published guidance related to PD. However, in their latest guidance related to drug development in early Alzheimer's disease, the term 'disease-modifying' has been replaced by 'persistent effect on disease course' that should be accompanied by a 'direct effect on the underlying disease pathophysiology' [21].

Table 1
Completed disease-modification trials in Parkinson's disease (non-exhaustive list)

Trial [Reference]	Year	Trial design	Intervention	Patient population	Trial duration	Primary Endpoint	Result (with regard to disease-modification)
DATATOP [66]	1993	2 X 2 factorial, double-blind	Selegiline and tocopherol	Early, untreated PD	24 months	Time to need for levodopa	Negative
ELLDOPA [67]	2004	Two-arm double-blind	Levodopa	Early, untreated PD	40 (+2) weeks	UPDRS after 2-week washout	Negative
ADAGIO [16]	2009	Phase III; two-arm double-blind delayed-start	Rasagiline	Early, untreated PD	72 weeks	three hierarchical end points*	Conflicting results (1 mg dose positive, 2 mg dose negative)
PROUD [68]	2013	Phase IV; two-arm double-blind delayed-start	Pramipexole	Early, untreated PD	15 months	UPDRS change	Negative (DAT-SPECT substudy negative)
NET-PD [69]	2015	Phase III; double-blind, parallel-group, placebo-controlled	Creatine	Early, treated PD	5 years	Clinical decline on global statistical test	Negative
FS-ZONE [70]	2015	Phase II; double-blind, placebo-controlled, parallel group	Pioglitazone	Early, untreated PD	44 weeks	Change in total UPDRS	Negative
EXENATIDE-PD [14]	2017	Phase II; two-arm double-blind	Exenatide	Moderately advanced PD (H&Y<3)	48 (+12) weeks	UPDRS after 12-week washout	3.5 points benefit on MDS-UPDRS III, but secondary outcomes not supportive
LEAP [71]	2019	two-arm double-blind delayed-start	Levodopa	Early, untreated PD	80 weeks	Change in UPDRS	Negative
STEADY-PD-III [72]	2020	Phase III; parallel-group, double-blind, placebo-controlled	Isradipine	Early, untreated PD	36 months	Change in UPDRS parts I to III score on medication	Negative
SURE-PD3 [73]	2021	Phase III; two-arm double-blind	Inosine	Early, untreated PD	24 (+3) months	Annualized change in MDS-UPDRS III; DAT-Scan substudy	Negative (DAT-Scan substudy negative)
NILO-PD [74]	2021	Phase IIa; parallel-group, double-blind, placebo-controlled	Nilotinib	Moderately advanced PD (H&Y 2.5–3, disease duration >5y)	6 (+2) months	Safety and Tolerability; change in MDS-UPDRS as secondary endpoint (2 months washout)	Negative (low CSF penetration, lack of biomarkers effect, and change in MDS-UPDRS trending in the negative direction)
PD STAT [75]	2022		Simvastatin	Moderately advanced PD (H&Y<4) with wearing OFFs	24 months (+2 months washout)	24-month OFF medication MDS-UPDRS part III scores	Negative (primary outcome indicated faster deterioration with simvastatin)

(*Continued*)

Table 1
(*Continued*)

Trial [Reference]	Year	Trial design	Intervention	Patient population	Trial duration	Primary Endpoint	Result (with regard to disease-modification)
FAIRPARK-II [76]	2022	Phase II; parallel-group, double-blind, placebo-controlled	Deferiprone	Early, untreated PD	36 weeks	change in MDS-UPDRS at 36 weeks (and after 4 weeks washout)	Negative (worse clinical outcome with deferiprone); In MRI substudy nigrostriatal iron content decreased more with deferiprone; in DAT-Scan Substudy no difference between groups
PASADENA [22]	2022	Phase II; double-blind, placebo-controlled	Prasinezumab	Early, untreated PD (or MAO-B inhibitor only)	52 weeks	Change from baseline to week 52 in the MDS-UPDRS total score	Negative (DAT-SPECT substudy negative)
SPARK [23]	2022	Phase II; double-blind, placebo-controlled	Cinpanemab	Early, untreated PD	52 and 72 weeks	Change from baseline to week 52 (and 72 for the active-treatment dose-blinded extension phase) in the MDS-UPDRS total score	Negative (DAT-SPECT substudy negative
NCT02953665 [77]	2022	Phase II; double-blind, placebo-controlled	Liraglutide	Early, treated PD	54 weeks	Change from baseline to week 54 in the MDS-UPDRS III, Non-Motor Symptoms Scale (NMSS), and Mattis Dementia Rating Scale (MADRS-2)	Positive regarding change in the NMSS and the MDS-UPDRS II (secondary outcome), but negative regarding change in the MDS-UPDRS III and MADRS-2
MOVES-PD [26]	2023	Phase II; parallel-group, double-blind, placebo-controlled	Venglustat	Early PD with pathogenic GBA1 variants	52 weeks	Change from baseline to week 52 in the MDS-UPDRS parts II and III combined score in the practically defined OFF condition	Negative
LIXIPARK NCT03439943 [15]	2023	Phase II; double-blind, placebo-controlled	Lixisenatide	Early PD (<3 years) on stable symptomatic medications	12 months, followed by a 2-month wash-out period	Primary: change over 12 month in the MDS-UPDRS III ON scores; Secondary: mean MDS-UPDRS III OFF scores at month-14 (end of wash-out)	Both primary and secondary endpoints positive

*Superiority to placebo in the rate of change in the UPDRS score between weeks 12 and 36, superiority to delayed-start treatment in the change in the score between baseline and week 72, and noninferiority to delayed-start treatment in the rate of change in the score between weeks 48 and 72. DAT, dopamine transporter; *GBA1*, glucocerebrosidase gene; H&Y, Hoehn and Yahr stage; MDS, Movement Disorder Society; PD, Parkinson's disease; UPDRS, Unified Parkinson's disease rating scale; MAO-B, monoamine oxidase Type B.

Table 2
Challenges for disease-modification trials in Parkinson's disease

Obstacles	Main problem
Drug target selection	
– Multiple pathways involved in PD pathogenesis – Differentiating upstream vs. downstream event in pathogenetic cascades – Single vs. multiple targets	Imperfect animal models to test targets, difficult to prioritize among agents, largely unknown safety profiles for new drugs
Candidate drug	
– Demonstration target engagement – Dose selection – Single drug vs. combinations	Lack of reliable biomarkers
Target Population	
– Early vs. later disease stage	Difficulty demonstrating clinically meaningful effects in early disease, neuropathology may be too far advanced in later stages
– Selecting disease subtypes (e.g., genetic PD)	Large cohorts of genetic PD hard to recruit, may not be representative for sporadic PD
Trial Design	
– Sample size	Variability in outcomes demands large samples
– Trial duration	Slow progression in PD requires long duration to show clinically meaningful effects
– Outcome measures	Outcomes should be clinically meaningful

DISEASE MODIFICATION TRIALS IN PD: WHICH PATIENTS TO TARGET WITH WHAT INTERVENTION?

Numerous articles over the past decade have reviewed obstacles to demonstrate 'neuroprotection' or 'disease-modification' and potential reasons for the fact that no trial has yet led to the approval of a disease-modifying drug for PD [10–13, 17–21]. These include limitations in the translatability of preclinical findings of neuroprotection into the human disease, lack of reliable biomarkers for target engagement in early phase clinical development, challenges around selecting the right dose in clinical trials, as well as multiple trial design issues (see Table 2).

Foremost among the latter are the selection of the right target population in a stage of disease that seems most accessible to disease-modification as well as the challenge of achieving sufficient trial durations required to detect clinically meaningful effects on disease progression.

Target populations for disease-modification trials in PD: early vs. later stages

With very few exceptions all trials of potentially disease-modifying agents have been conducted in newly diagnosed patients with disease durations of less than 2 to 3 years since the time of diagnosis with or without symptomatic drug therapy who were free of functional impairments (Table 1). This type of population is commonly referred to as 'early' PD as opposed to patients on treatment with levodopa plus other agents who have developed motor complications and are classified as 'advanced' PD.

Selecting subjects with early untreated PD has been accepted as a plausible strategy to ensure that the underlying pathology has not progressed too far for the respective pharmacological agent to still exert meaningful effects and at the same time allow for clinical comparisons with a placebo arm that are not confounded by effects of symptomatic therapies. One major reason why this approach has failed most of the time could be related to the slow progression of the severity of motor as well as non-motor symptoms in early PD. This leads to sensitivity issues of the 'gold-standard' scales that have been developed to assess symptom severity as well as functional impact. Most trials have used a primary endpoint of worsening of motor symptoms as measured by the UPDRS or MDS-UPDRS, which, because of its slow decline in early untreated PD, may be not sufficiently sensitive to detect statistically significant differences between active and placebo arms in this type of populations. Recent examples are the passive anti-synuclein immunotherapy trials of the monoclonal antibodies prasinezumab and cinpanemab, which failed to meet their primary endpoints of significant differences in progression of combined MDS-UPDRS parts I, II, and III scores over one year to 18 months [22, 23]. Over follow-up periods of 1 to 2 years the motor examination section of the MDS-UPDRS (part III) seems to be more sensitive compared to the patient report-based 'motor experiences of daily living' sec-

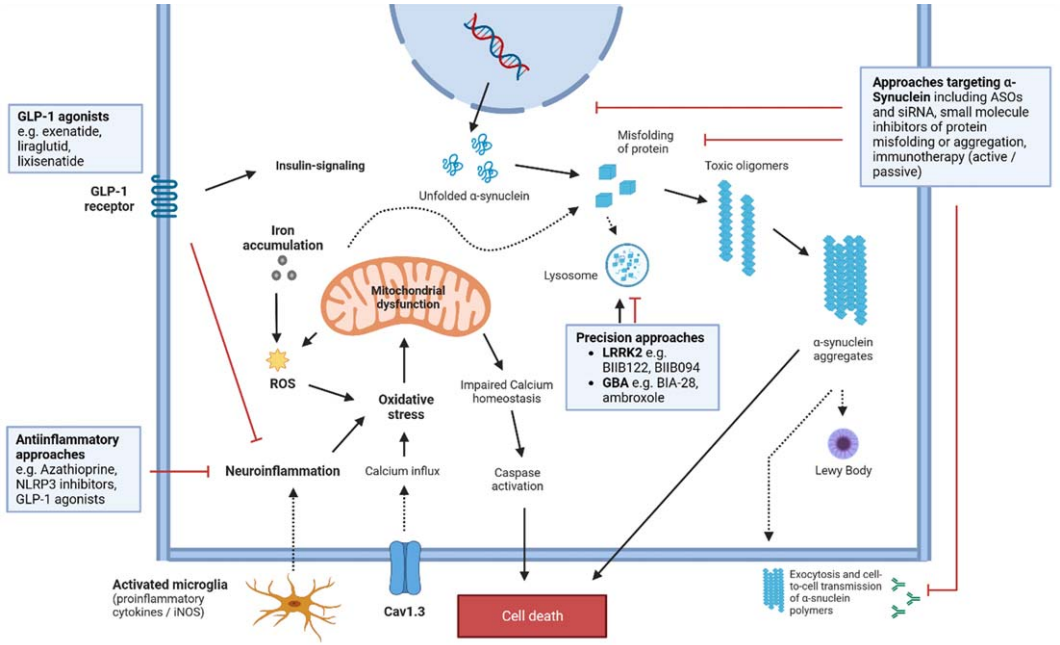

Fig. 1. Mechanisms in the pathophysiological cascade of PD and potential treatment targets. See text and Table 3 for more details regarding drug candidates. ASO, antisense oligonucleotide; Cav1.3, Calcium channel, voltage-dependent; GBA, gene encoding for Glucocerebrosidase; GLP-1, Glucagon-like peptide-1; iNOS, Nitric oxide synthases; LRRK2, Leucine rich repeat kinase 2; ROS, reactive oxygen species; siRNA, small interfering RNAs.

tion (part II). This has been observed in several of the trials listed in Table 1 including the Prasinezumab trial, where progression of part III but not of part II scores (or combined part I, II, and III scores) was reduced in the active arms as compared to placebo [22].

Recent trials have moved into target populations with more advanced disease and recruited treated subjects with disease durations of up to 3 years or even beyond (see Table 1). Two of these assessing the efficacy and safety of the GLP-1 agonists exenatide [14] and lixisenatide [15] have indeed been positive showing significant differences in favor of active drug on a primary endpoint of motor worsening over 12 months as assessed by the MDS-UPDRS part III (as opposed to part II).

Selecting target populations in more advanced PD stages also improves chances to demonstrate clinical meaningfulness of effects from a putative disease-modifying intervention by using primary outcomes like time to development of functional disability or the occurrence of disability milestones in the motor or non-motor domains [13], although time-to event endpoints might require longer trial durations beyond the 12 to 24 months horizon of most previous trials (Table 1). An ongoing immunotherapy trial of prasinezumab in patients on stable symptomatic medication with disease duration of up to 3 years is using a primary outcome of time to a 5-point worsening of the MDS-UPDRS part III (NCT04777331).

One concern around testing disease-modifying agents in more advanced PD is related to the risk of the underlying pathology being too far advanced for the intervention to still exert clinical effects in spite of positive target engagement.

Selecting the right pharmacological targets

Identifying critical drug target within the pathogenetic cascade driving PD progression is another major challenge and the path to disease modification in PD is flanked by numerous failures of translation from preclinical proof-of-concept to clinical efficacy. Not least through the advances made in understanding the genetic architecture of PD multiple novel targets for disease-modifying pharmacological interventions have emerged and many of these are currently addressed in ongoing drug development programs [12, 13, 24] (Fig. 1 and Table 3).

Targeting specific pathogenetic pathways introduces the option of 'personalized' or 'precision-medicine' approaches to disease modification in PD,

Table 3
Candidate drugs currently tested for disease-modification in PD (non-exhaustive list)

Target	Drug	Mechanism	Stage of development	Outcome [REF]/registration number
Insulin signaling	Exenatide	GLP-1 agonist	Phase 3	Ongoing; NCT04232969
	NLY01	GLP-1 agonist	Phase 2	Ongoing; NCT04154072
	Liraglutid	GLP-1 agonist	Phase 2	Completed, see Table 1; NCT02953665
	Lixisenatide	GLP-1 agonist	Phase 2	Completed, see Table 1; NCT03439943
	Semaglutide	GLP-1 agonist	Phase 2	Ongoing; NCT03659682
α-Synuclein proteostasis	Antisense oligonucleotides (ASO) Small interfering RNAs (siRNAs)	Reducing α-synuclein production	Preclinical	[78]
	anle138b	Inhibition of α-synuclein aggregation	Phase 1	Ongoing; NCT04685265
	Radotinib	c-Abl tyrosin kinase inhibitor; Inhibition of α-synuclein aggregation	Phase 2	Ongoing; NCT04691661
	IkT-148009	c-Abl tyrosin kinase inhibitor	Phase 2	Ongoing; NCT05424276
	Buntanetap	Small molecule inhibitor of neurotoxic proteins	Phase 3	NCT05357989
	UCB0599	Small-molecule inhibitor of α-synuclein misfolding	Phase 2	Ongoing; NCT04658186, NCT05543252
	KM-819	Small molecule inhibitor of FAF1	Phase 2	NCT05670782
	Prasinezumab	Anti-α-synuclein antibody	Phase 2	Ongoing; NCT04777331 (PADOVA)
	Lu AF82422	Anti-α-synuclein antibody	Phase 1	Completed, results pending; NCT03611569
	MEDI1341	Anti-α-synuclein antibody	Phase 1	Completed, results pending; NCT03272165
Lysosomal function/LRRK2	DNL 201	LRRK2 inhibitor	Phase 1b	Favorable safety, biomarker evidence for target engagement in PD subjects; NCT03710707
	BIIB122 (DNL151)	LRRK2 inhibitor	Phase 2	Ongoing; NCT05348785 (LUMA)
	BIIB094	LRRK2 inhibitor (ASO; intrathecal administration)	Phase 1	Ongoing; NCT03976349

(*Continued*)

Table 3
(*Continued*)

Target	Drug	Mechanism	Stage of development	Outcome [REF]/registration number
Lysosomal function/β-Glucocerebrosidase	Ambroxole	Modulator of GCase activity	Phase 1 (published)	CSF penetration and biochemical effects demonstrated [79]
			Phase 2	Ongoing; NCT02914366
			Phase 3	Ongoing; NCT05778617, NCT05830396
	BIA-28	Modulator of GCase activity	Phase 2	Ongoing; NCT05819359
Mitochondrial function	Terazosin	alpha-1 antagonist; enhances glycolysis and ATP levels	Phase 2	Ongaoing; NCT05109364, NCT05855577
	Ursodeoxycholic acid	Naturally occurring bile acid; improves mitochondrial function	Phase 2	Completed; NCT03840005 Safe and well-tolerated, signals of target engagement on magnetic resonance spectroscopy; Phase III trials warranted [80]
Neuroinflammation (partially including GLP-1 agonists listed above)	Inzomelid (IZD174)	NLRP3 inhibitor	Phase 1	Completed, results pending; NCT04015076
	RO7486967	NLRP3 inhibitor	Phase 1	Ongoing; NCT05924243
	Sargramostim	Granulocyte macrophage colony-stimulating factor (GM-CSF)	Phase 1	Ongoing; NCT05677633 and NCT03790670
	Azathioprine	Immunosuppressant	Phase 2	EudraCT Number: Ongoing; 2018-003089-14

GCase, β-Glucocerebrosidase; FAF1, Fas-associated factor 1; HV, healthy volunteers; LRRK2, Leucine-rich repeat kinase 2; PD, Parkinson's disease; PPAR γ, peroxisome proliferator-activated receptor; DAT, Dopamine transporter; *GBA1*, glucocerebrosidase gene; H&Y, Hoehn and Yahr stage; MDS, Movement Disorder Society; PD, Parkinson's disease; UPDRS, Unified Parkinson's disease rating scale; MAO-B, monoamine oxidase Type B.

exemplified by recent drug trials targeting GCase or LRRK2 activity in PD populations harboring mutations in these genes [25]. The first large disease-modification trial phase 2 study in a genetic PD subtype enrolled 221 participants with one or more GBA1 gene variants to test if venglustat, a brain penetrant glucosylceramide synthase inhibitor, could slow the progression of combined MDS-UPDRS part II and III scores over 52 weeks [26]—following the rationale of 'substrate-reduction' that is a standard therapy for people with Gaucher's disease and also been able to reduce α-synuclein pathology and behavioral deficits in rodent models. Patients were on dopaminergic therapy and had average disease durations of 4 to 5 years from time of diagnosis. The trial failed its primary endpoint and change from baseline to week 52 in combined MDS-UPDRS part II and II scorers was even numerically greater in the venglustat group, although there was target engagement with a 75% reduction of CSF glucosylceramide levels. While the negative results of this trial show that the principle of substrate-reduction for Gcase is unlikely to provide benefit in GBA-PD, it does not invalidate targeting Gcase activity directly by molecular chaperones. Several such agents are currently tested in phase 2 and 3 trials including ambroxol (NCT05778617, NCT05830396) and BIA-28 (NCT05819359).

LRRK2 inhibitors are another group of candidate drugs for a 'personalized' approach to disease-modification in PD. BIIB122 is an oral selective, brain penetrant inhibitor of LRRK2 for which safety and target engagement have been shown in both healthy volunteers and subjects with PD [27]. A phase 3 trial of this drug in PD patients carrying a pathogenic LRRK2 mutations was set up to measure effects on time to predefined worsening in the MDS-UPDRS II and III (NCT05418673) and a corresponding phase 2 trial is enrolling PD patients without mutation (NCT05348785).

DISEASE PREVENTION TRIALS IN PD: CHALLENGES AND FUTURE OPPORTUNITIES

Preventing or delaying 'phenoconversion' in subjects meeting criteria for 'prodromal' PD has been discussed as a new approach of 'disease-modification' trials that would conceptually become a type of 'disease-prevention' effort [10, 28].

Such target groups can now be defined by established multifactorial screening algorithms for prodromal PD such as the MDS criteria [29], although—despite their high specificity—their sensitivity and positive predictivity for early conversion in population-based cohorts seem suboptimal [30–32]. Other approaches to identify such individuals target single specific prodromal markers with subsequent enrichment steps like hyposmia followed by DAT-Scan as exemplified in the PARS study [33]. In idiopathic RBD, the strongest and most specific marker for PD and other α-synucleinopathies, conversion rates are only around 6% per year [34] and long-term series have reported median latencies from presumed RBD onset to clinically overt disease of 12–14 years and from diagnosis of idiopathic RBD to clinically overt disease of 6 years [35, 36]. These drawbacks of long delays to phenoconversion can potentially be overcome by enrichment strategies like adding further risk-markers such as hyposmia, subtle motor dysfunction, or subtle cognitive decline, which have all been shown to indicate higher conversion rates over shorter periods of time in subjects with idiopathic RBD [34, 37]. Despite these obstacles, prodromal cohorts are highly appealing as targets for disease-modification trials. On one hand the neurodegenerative process has already caused clinical symptoms that can be monitored for study purposes and that may also enhance motivation for individuals to participate in clinical trials. On the other hand, neurodegeneration may not have progressed too far to be modified by putatively neuroprotective interventions. All the approaches mentioned above in prodromal cohorts have yielded a maximum conversion rate of approximately 60% over 5 years or less [10, 33, 34]. Before inclusion of participants into disease-modification trials it would be desirable to have an additional highly specific and 'confirming' biomarker to further enhance likelihood of a true prodromal state and to homogenize groups of prodromal individuals. Evidence of pathogenic α-synuclein on SAA would lend itself to such a purpose as it shows presence of the pathological hallmarks of synucleinopathies and it is highly specific for these disorders. Indeed, in line with the overall conversion rates in idopathic RBD of >80%, positive SAAs from CSF have been detected in around 90% in different series of idiopathic RBD patients [38–41].

Targeting asymptomatic or 'preclinical' disease stages could come even closer to an ultimate goal of 'disease-prevention' in the sense of completely preventing development of clinical disease in a subject's lifetime [42]. Genetic PD subtypes are of particular interest in relation to disease-prevention trials

for a number of reasons. First, these patients have defined molecular defects that are linked to the pathophysiology of their disease and thus allow for a precision-medicine approach to treatment [25]. In addition to reduced pathophysiological heterogeneity there is also less clinical heterogeneity in terms of disease progression in such cohorts [43]. Finally, asymptomatic individuals harboring mutations in PD genes are conceptualized as being in a 'preclinical' state of disease and intervening in this period could be more effective compared to later stages where pathology has progressed to override compensation and causes clinical symptoms [44]. Nonetheless, there are significant obstacles in the way of implementing disease-prevention trials in healthy carriers of PD-associated genes. These include the problem of recruitment of a trial population given that even GBA1 mutations, which represent the most common risk gene for PD, only affect around 5–10% of PD subjects globally and the overall carrier frequency of the G2019S mutation of the LRRK2 gene has been estimated at 0.5% [43, 45]. Reduced penetrance is another significant problem. As many as 70% of LRRK2 or 90% of GBA1 mutation carriers will never develop PD [43, 44] and for those who will the time to developing clinical symptoms is unknown. This would pose great difficulty in selecting meaningful outcome measures for trials in these types of target population and lead to long trial durations, which would also be true for the subsequent group of preclinical PD subjects.

Recent attempts to develop frameworks for a biological definition of PD may offer new opportunities to better define and enrich target populations for both disease-modification as well as 'disease-prevention' trials. Two recently published proposals both anchor the diagnosis of PD (subsumed under the term of 'Neuronal Synuclein Disease' (NSD) in one of them) on the presence of biomarkers independent of clinical symptoms. The proposed biological anchors rely on the demonstration of disease-specific alpha-synuclein pathology by seed amplification assays (SAAs) in the CSF, the presence of highly penetrant PD mutations, and evidence for dopaminergic neurodegeneration by molecular imaging [46, 47]. These approaches follow the example of biological diagnostic concepts initially put forward as the 'ATN' system for Alzheimer's disease [48] and allow for a PD or 'NSD' diagnosis in the earliest stages of disease, when affected individuals have not yet developed any clinical symptoms or signs. Asymptomatic individuals with positive a-synuclein SAAs are classified as 'Parkinson's type synucleinopathy' [46] or stage 1 NSD [47], while the appearance of 'prodromal' motor or non-motor signs with sufficient likelihood of being disease-related are classified as 'stage 2' in the NSD integrated staging system (NSD-ISS) proposed by Simuni and colleagues. Such biological diagnostic definitions would both allow for a more accurate diagnosis of 'prodromal' PD then is currently possible by using clinical features as the main anchors and would also offer an objectively measurable tool to detect preclinical disease. The latter, although conceptualized for a long time [49], has only recently become practically tangible – first by genetic markers and now through the availability of highly sensitive in-vivo assays to detect disease-specific α-synuclein pathology [50, 51]. A 'biological' definition of disease not only allows to detect preclinical disease but also has the potential to delineate pathogenetic subtypes and further reduce heterogeneity in future trial populations. The most attractive vision for the future use of these approaches relates to the prospect of implementing disease-prevention trials in populations of biomarker defined preclinical disease, i.e., people with 'Parkinson's type synucleinopathy' [46] or 'stage 1 NSD' [47]. The recruitment base for such trials would presumably be much larger than is the case for trials selecting mutation carriers (see above). However, there are considerable challenges to be addressed when trying to screen for and select individuals in the population for such efforts.

OUTLOOK: WILL DISEASE-PREVENTION TRIALS IN PRECLINICAL PD BECOME FEASIBLE?

Using the newly proposed criteria for a biological disease definition there are two potential groups of preclinical subjects that could be recruited for disease-modification trials, those defined by harboring fully penetrant PD gene mutations or those with positive α-synuclein SAAs. Healthy subjects with such genetic variants are, however, very rare and recruitment for clinical trials would pose a major challenge. More common pathogenic mutations such as in the LRRK2 and GBA genes are associated with incomplete penetrance and much lower disease risk. Designing disease-prevention trials in healthy carriers of the latter group of mutations would require enrichment by additional molecular or imaging biomarkers for early conversion in order to arrive at sufficient endpoints in time frames that

are feasible for trials and relevant for patients. Similar problems around recruitment and outcomes have to be addressed when targeting preclinical subjects that are defined by a positive result on α-synuclein SAAs (corresponding to stage 1 NSD [47] or 'Parkinson's type synucleinopathy'[46]). Even if reliable large scale SAA testing became feasible through non-invasive sampling via plasma- or serum-based assays [52, 53], the significance of a positive test in the population is currently uncertain. There are no studies dedicated to the assessment of SAA in the elderly community and prevalence of positive SAAs as well as the risk for subsequent development of α-synucleinopthies are unknown. In addition, identifying such individuals is not trivial even if the rate of SAA positivity in healthy control groups was around 5% to a maximum of 10% across the different hospital-based cohorts [54]. This seems to be in line with earlier studies finding incidental Lewy bodies and nigral neuronal loss in more than 10% of individuals free of PD above age 60 in histopathological population-based cohorts [55, 56]. Based on these numbers trial screen failure rates of up to 20%, α-synuclein SAA screening would have to be performed in more than 7000 subjects to arrive at a total sample size of 300 subjects for a disease prevention trial. In addition, lag times to clinical symptoms and/or to markers of neurodegeneration such as striatal dopaminergic loss in preclinical SAA positive individuals are expected to be very long. For these reasons alone SAAs testing would make more sense in preselected individuals with prodromal features like RBD or hyposmia (see above), who may have α-synuclein SAA positivity rates of around 80%. Once such individuals are identified, there is a need for additional biomarkers that indicate early progression or conversion to clinical disease. Imaging evidence for neurodegeneration such as DAT-SPECT has been proposed for such purposes [46]. Enrichment strategies will be essential to reduce numbers needed for disease-modification trials and to avoid employing unnecessary interventions that may be associated to psychological stress in individuals that may never go on to develop clinically relevant disease.

Selecting *outcome measures* for disease-modification trials in preclinical target populations would also mean entering largely unchartered territory. Time to 'phenoconversion' has been previously discussed in relation to disease-modification trials in prodromal PD but its use in biologically defined asymptomatic individuals poses even greater challenge in the latter compared to the former (see above). Alternative outcomes like on composite scores of motor, cognitive and other non-motor progression combined with evidence for progression of neurodegeneration from imaging or molecular markers could be viable and powerful alternatives [10, 57–61]. Achieving quantification of α-synuclein SAAs or the introduction of α-synuclein PET-imaging and establishing correlations with such quantitative measures with clinical progression might have an impact for outcome measures in disease-prevention and disease-modification trials alike, although it is yet unclear whether disease-modifying compounds would or should indeed have an influence on such measures or not.

Selecting agents to be tested also raises additional issues in preclinical cohorts. Testing interventions in people free of any clinical signs of disease and disability requires a level of safety that would have to practically exclude any risk of serious adversity. While this appears feasible for non-pharmacological approaches like lifestyle interventions, e.g., structured physical activity or nutritional programs [62], it is a very high bar for agents other than repurposed drugs with very well-established safety profiles and almost precludes trials of new and experimental interventions in preclinical individuals. The uncertainty if and when subjects meeting criteria for biomarker-based 'preclinical' disease will develop early clinical disease with functional impairment means that the burden of any 'disease-preventing' intervention should be minimal in order to be acceptable to patients and authorities alike [42].

Apart from safety risks of experimental therapies there are important additional *ethical considerations* to be addressed [63]. One of these concerns the phenomenon of 'overdiagnosis', which is a well-known problem for controversial screening tests and refers to the detection of subclinical disease (sometimes called pseudodisease), which would not have become manifest clinically in someone's remaining life time (e.g., prostate cancer through prostate-specific antigen screening) [64]. 'False-positive' results of a screening procedure give rise to unnecessary further diagnostic tests and create worries of having a disease that may never manifest. Furthermore, depending on a given health care system, a positive screening result, e.g., a diagnosis of NSD, can have significant impact on the access to health care or life insurances [65]. Risk disclosure strategies should therefore take many factors into account, related to the screening test itself (e.g., its evidence, accuracy, reliability etc.) as well as to the subjects including education,

social background, comorbidities, age, cognitive status, etc. Studies or trials in presymptomatic PD should therefore offer careful individualized counseling of participants and an option for psychosocial support.

Despite of all these challenges defining disease by the detection of underlying molecular pathology ('biological definition') marks a major step forward for efforts to achieve a reliable prodromal or even preclinical diagnosis which will eventually open the door to prevention also in the field of PD.

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