ARTICLE OPEN ACCESS

What to Test in Parkinson Disease Prevention Trials?

Repurposed, Low-Risk, and Gene-Targeted Drugs

Grace F. Crotty, MBBChBAO, MD, and Michael A. Schwarzschild, MD, PhD

Neurology® 2022;99:S34-S41. doi:10.1212/WNL.0000000000200238

Correspondence
Dr. Crotty
grace.crotty@mgh.harvard.edu

Abstract

Despite the sound epidemiologic and basic science rationales underpinning numerous "disease modification" trials in manifest Parkinson disease (PD), none has convincingly demonstrated that a treatment slows progression. Rapidly expanding knowledge of the genetic determinants and prodromal features of PD now allows realistic planning of prevention trials with initiation of putatively neuroprotective therapies earlier in the disease. In this article, we outline the principles of drug selection for PD prevention trials, focused on proof-of-concept opportunities that will help establish a methodological foundation for this fledgling field. We describe prototypical, relatively low-risk drug candidates for such trials (e.g., albuterol, ambroxol, caffeine, ibuprofen), tailored to specific at-risk populations ranging from pathogenic *LRRK2* or *GBA* gene variant carriers to those defined by prodromal PD and α-synucleinopathy. Finally, we review gene-targeted approaches currently in development targeting clinically manifest PD for their potential in future prevention trials.

From the Department of Neurology, Massachusetts General Hospital, Boston.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

AD = Alzheimer disease; **ASO** = antisense oligonucleotide; **GCase** = glucocerebrosidase; **GBA** = glucocerebrosidase A; **LCC** = LRRK2 Cohort Consortium; **LRRK2** = leucine-rich repeat kinase 2; **NSAID** = nonsteroidal anti-inflammatory drug; **OR** = odds ratio; **PD** = Parkinson disease; **RBD** = REM sleep behavior disorder.

The adage, "An ounce of prevention is worth a pound of cure," attributed to Benjamin Franklin not only encapsulates the premise for pursuing prevention for Parkinson disease (PD) but it also hints at what treatments may achieve this laudable goal. He describes the intervention as a dosage in units, even if premetric that suggests a medicinal supplement or drug administered to stave off illness. Perhaps more prescient, at least metaphorically, was the purpose for which Mr. Franklin penned his timeless point. He used it to underscore the message of his 1735 writing entitled, "On Protection of Towns from Fire" (The Pennsylvania Gazette), in which he proposes multiple anti-inflammatory strategies to lessen the risk that fireplace embers and flammable material can combine to ignite a house. He drew particular attention to the importance of sweeping out chimneys, which can accumulate dangerous deposits that block their function. Although his wisdom is fabled, he of course was not thinking of nonsteroidal anti-inflammatory drug (NSAID) benefits or α-synuclein aggregate removal. Nevertheless, with his broader insight in mind, we present here our perspective on what might be the first drugs to be tested for their potential to prevent PD. Our article complements that of Janssen Daalen et al.,[1] which focuses on compelling nonpharmacologic strategies ripe for testing in PD prevention trials. Together, these 2 articles broadly consider the question of what interventions may be ready now or soon for early prevention trials in PD.

Principles of Drug Selection for PD Prevention Trials

General Strategies for Disease Modification

Overall, the principles that should be invoked in deciding what drugs to select for PD prevention trials should mirror those traditionally used in selecting candidate therapeutics for disease modification trials in manifest PD. To date, candidate neuroprotective therapeutics have been selected for clinical development based on increasingly compelling integration of evidence derived from PD genetics, epidemiology, and on biomarker and pathology studies in humans, as well as on preclinical modeling of PD.[2] Moreover, their disease-modifying potential has been evaluated through incrementally more innovative large randomized, placebo-controlled clinical trials over the past 3 decades—from DATATOP[3] to SURE-PD3.[4] Nevertheless, none of these have proven to favorably affect the course of the disease,[2] prompting a reassessment not only of the drugs selected but of trial designs used to test them. Investigating PD pathophysiology at earlier, prediagnostic stage of the disease has recently shifted from an aspiration to an opportunity to improve trial design for disease modification and is the focus of this supplemental issue of *Neurology*®.

Of interest, rationales for drug selection for prior PD protection trials may actually be stronger for prevention trials because they have typically been based on risk data and relied on the assumption that determinants of risk can be extrapolated to progression. For example, most "PD genes" have been established as such based on pathogenic variants that increase the risk of developing PD and not necessarily a faster progression. Similarly, for most trials of putative neuroprotectant molecules that have been justified in part based on their epidemiologic links to reduced PD risk, there has been little or conflicting evidence of links to PD progression (e.g., nicotine in NIC-PD [NCT01560754],[5] a calcium-channel blocker in STEADY-PD [NCT02168842],[6] caffeine in Café-PD [NCT01738178],[7] and simvastatin in PD STAT [NCT02787590]).[8] Thus, any true protective effect of these agents would more likely manifest in PD prevention than in its progression after diagnosis. This drug selection caveat for progression trials has understandably received little attention to date given the prior implausibility of PD prevention trials. Accordingly, the disease modification hypotheses tested to date are arguably stronger when applied to protective benefits before disease diagnosis. This point bolsters the more commonly cited "before-the-horse-is-out-of-the-barn" argument for intervention as feasible pre-PD diagnosis, which is well known to occur at a relatively advanced anatomic and biochemical stage of neurodegeneration when some 30%–50% of nigral dopaminergic neurons and some 50%–80% of striatal dopamine have already been lost.[9]

Also noteworthy is that epidemiologic studies have thus far identified a far greater number of inverse risk factors that constitute plausible neuroprotective molecules in PD than they have in other neurodegenerative diseases. For example, caffeine, calcium-channel blockers, dairy products, ibuprofen, nicotine (and other tobacco components), NSAIDs, statins, urate, and other nongenetic factors have all been repeatedly linked to reduced risk of PD.[10,11] By contrast, fewer modifiable molecular exposures (e.g., possibly vitamin E) have been linked to a reduced risk of Alzheimer disease (AD),[12] despite its far greater incidence than that of PD. Similarly, less is known about protective exposures linked to a reduced risk or later age at onset of amyotrophic lateral sclerosis[13] or Huntington disease, although their relative rarity compared with PD let alone AD may account for their dearth of such determinants.

Prevention-Specific Strategies for Disease Modification

Among several drug selection determinants that distinguish those for PD prevention trials, particularly the first such trials, is safety. By definition, participants in prevention trials are healthy and unaffected regarding PD, and so the balance between potential for risk vs benefit must be tilted to lessen the likelihood for harm in offsetting the inherently lesser burden from an affliction that has not occurred. Moreover, even those at the highest risk for PD because of a common genetic factor (*LRRK2* G2019S variant, with a life-long penetrance of approximately 30%) or a prodromal feature (REM sleep behavior disorder [RBD]) are still on average unlikely to develop PD for years, if at all. Accordingly, agents that have favorable and well-established safety profiles, such as repurposed over-the-counter drugs or dietary factors, are naturally preferable candidates compared with new chemical entities (i.e., with unproven safety) or prescription drugs with established substantial toxicity or invasiveness. Thus, safety risk is a major organizing principle in the prioritization of candidates for the first PD prevention trials as illustrated in Figure.

Conversely, candidate neuroprotectants entering clinical trials as new chemical or biological entities with no prior human safety track record, which is typical of most therapeutics targeting specific PD genes, are higher risk (Figure, lower rows) and not well-suited for prevention trials in healthy participants. It is conceivable that higher risk would be acceptable from treatments once they have been demonstrated to be effective at slowing or halting progression in people with manifest disease but alas as above none yet exists. For now, the relative abundance of inverse risk factors with protective properties in PD compared with other neurodegenerative diseases adds a trove of relatively safe candidates to consider in early, proof-of-concept prevention trials.

Beyond safety, another important determinant of what treatment to select for the first trials of drugs for PD prevention is the nature of the at-risk population to be enrolled (i.e., who will be targeted). Because the emerging prospects for conducting PD prevention trials have been driven by the identification and characterization of distinct at-risk populations in recent years (see supplement articles by Molsberry et al.,[14] Postuma,[15] and Niotis et al.[16]), their unique pathophysiologic features will guide selection of agents that target them rather than a "one-size-fits all" approach. Thus, genetically defined at-risk cohorts (e.g., comprising carriers of pathogenic variants in leucine-rich repeat kinase 2 [*LRRK2*] or glucocerebrosidase A [*GBA*] gene) may be

Figure Drug Candidates and Their Rationales for PD Prevention Trials

Risk	Agent	Proximal mechanism	At-risk target population (e.g.)	Key evidence		
				Genetic	Epidemiologic	Models
Lower — repurposed	caffeine[26]	adenosine A_{2A} antagonism	LRRK2	[+]	+++ (PD) ++ (LRRK2 PD)	✔
	ibuprofen[39]	NSAID (PPAR-γ, COX)	LRRK2	[+]	++ (PD) ++ (LRRK2 PD)	✔
	albuterol (ER)[41,a]	β2 adrenergic agonism	ProPD	[++]	++ (PD)	✔
	ambroxol[46]	GCase inhibitory chaperone	GBA	++	-	✔
	terazosin[b,c]	phosphoglycerate kinase 1 activator	ProPD	-	+ (PD)	✔
	metformin[43]	multiple, incl. ↓ αSyn aggreg.	RBD	[+]	+ (PD)	✔
	inosine[4]	urate, antioxidant	LRRK2	-	+++ (PD) ++ (LRRK2 PD)	✔
Higher — novel	αSyn antibodies[49,d]	↓ extracellular αSyn	RBD	++	[+]	✔
	αSyn disaggregators[e,f,g]	↓ aggregated αSyn	RBD	++	[+]	✔
	cAbl inhibitors[h]	↓ cAbl → ↓ αSyn	RBD	[+]	-	✔
	LRRK2 inhibitors or ASOs[47]	↓ LRRK2 activity	LRRK2	+++	[+]	✔
	GCase activators, *GBA* gene[i,j]	↑ GCase activity	GBA	+++	[+]	✔

Partial listing of plausibly neuroprotective potential therapeutic agents, organized by their relative safety risk into low and high, which corresponds to their status as repurposable drugs (for which there are extensive safety data) and novel drugs (for which there is little or no human safety data). Proximal mechanisms of putative neuroprotective action are listed, along with the at-risk population most rationally targeted at this point based on multiple lines of evidence (broken out to human genetic, epidemiologic, and preclinical models). The number of + signs indicates authors' subjective impression of the strength of evidence in a given category, with brackets reflecting more indirect evidence. ✔ indicates supportive evidence in toxin and/or genetic preclinical models of PD. Citations for most recent study (see text for reference) or associated clinical trial associated with proposed agents (a = ACTRN12620000560998, b = NCT03905811, c = NCT04386317, d = NCT04777331, e = NCT02606682, f = NCT04685265, g = NCT04483479, h = NCT03655236, i = NCT04127578, j = Trial NL7061 [NTR7299]]). αSyn = alpha-synuclein; ASO = antisense oligonucleotide; COX = cyclooxygenase; ER = extended release; GCase = glucocerebrosidase; NSAID = nonsteroidal anti-inflammatory drug; PD = Parkinson disease; PPAR-γ = peroxisome proliferator–activated receptor gamma; ProPD = prodromal PD; RBD = REM sleep behavior disorder.

best matched to drugs that specifically target the putative molecular dysfunction underlying their pathogenicity (e.g., an inhibitor of LRRK2 kinase activity or an activator of glucocerebrosidase activity, respectively; Figure). Alternatively, prodromally defined at-risk cohorts may be best matched to generalized PD mechanisms (oxidative, anti-inflammatory, excitotoxic, etc.) or those associated with a specific prodromal feature (e.g., synucleinopathic in RBD).[17]

Similarly, how prevention is measured could also affect the specific intervention selected. Rapidly evolving smartphone or wearable sensor technology may facilitate detection and tracking of subtler earlier parkinsonian deficits before diagnosis and may allow for prevention of prodromal progression rather than of phenoconversion to PD assessed through traditional in-person clinician-based diagnostic evaluations. Such methodological advances may support larger-scale, decentralized trials of putative protectants that are less resource-intensive or burdensome. Such remotely conducted trials would not only favor safer agents but those that are logistically simpler to distribute, administer, and monitor, such as some over-the-counter drugs, vitamins, or dietary supplements.

Prototypic Drug Candidates for Early PD Prevention Trials

Multiple key design elements of a PD prevention trial are just now beginning to come into focus, as reflected in the first convening of an international conference on planning for such trials this year.[18] Nevertheless, early pharmacologic candidates may now be reasonably proposed for testing based on the above principles. Not only do they offer realistic prospects for slowing the pathophysiology of PD before diagnosis but proceeding with their testing may also be of great value in establishing proof-of-concept and a methodological foundation for future prevention trials. For example, the first PD prevention trials will provide the first practical experience addressing challenges of recruiting and retaining individuals to a long-term treatment trial when they are at risk for but not diagnosed with PD.

In this study, we describe several emerging examples of plausibly protective, repurposable, oral agents with relatively low risk of serious side effects. Their candidacies illustrate how epidemiologic links of common exposures to a reduced risk of idiopathic PD (caffeine, ibuprofen, and albuterol) may extend to a PD subtype associated with a specific population at risk for the disease (e.g., carriers of pathogenic *LRRK2* or *GBA* variant or people with RBD).

Caffeine

The commonly consumed psychostimulant caffeine has been established as one of the most robust inverse risk factors (i.e., associations with "reduced risk") for PD, with dozens of epidemiologic studies reproducibly finding caffeine intake predictive of a lower risk of developing the disease (in prospective cohort studies) or likelihood of having it (in case-control studies).[10,19,20] In addition, the biological plausibility that caffeine may be a mediator and a marker of reduced PD risk has been demonstrated consistently in various preclinical animal models of PD neurodegeneration, ranging from mitochondrial toxin to genetic (α-synuclein) models and from invertebrate to rodent models.[19] Although its proximal mechanism of neuroprotective action is likely through its potent antagonism of endogenous adenosine at A_{2A} receptors (Figure),[21] this blockade may in turn disrupt several pathways underlying PD pathophysiology, including mitochondrial dysfunction, excitotoxicity, inflammation, autophagy, and other α-synuclein toxicities.[19,22]

Based on these convergent epidemiologic and laboratory data, caffeine has long been prioritized among candidates for disease modification trials in idiopathic PD[23] and remains so particularly among repurposable compounds.[24] Although trials of caffeine and a more specific adenosine A_{2A} antagonist (preladenant) have been initiated using a delayed-start trial design (which can gauge effects on disease progression by addressing the potential confound of putative symptomatic benefits), these components were eliminated with the trials' yielding negative results in their primary tests for symptomatic benefit.[7,19,25] Hence, while another A_{2A} antagonist (istradefylline) has received regulatory approvals for clinical use to improve the motor symptoms of PD,[19] as yet caffeine and adenosine A_{2A} antagonism remain untested for their potential impact on the course of idiopathic PD.

Although the case for caffeine in a PD progression trial continues to be made,[19,24] a more compelling argument is emerging for its assessment in PD prevention[19,24,26] for several reasons. First, caffeine's well-established and favorable safety profile is an especially important asset for prevention trials (Figure). As their enrollees, while at risk for PD, are unaffected and may remain so, clinical equipoise warrants a much higher threshold for accepting even a modest risk of toxicity in prevention trials compared with those enrolling people diagnosed with PD. Second, as above, the epidemiology links to PD are stronger and more consistent for PD risk[10,11,19] than for its progression.[19,27-29]

Third, epidemiologic links for specific at-risk populations are emerging and strengthening the case for the testing of caffeine in PD prevention, particularly for those whose risk results from a pathogenic *LRRK2* variant. A case-control study reported that the odds of having PD were 5-fold lower for caffeine users compared with nonusers among carriers of a pathogenic *LRRK2* variant more common in Asian populations (R1628P) and only 2-fold greater among noncarriers, with a significant interaction between genotype and exposure.[30] Although a small study, its main finding—that the well-established association between caffeine use and resistance to PD may be actually greater for LRRK2 PD—was replicated in a larger Western cohort, the LRRK2 Cohort Consortium (LCC), in which G2019S was the predominant *LRRK2* variant contributing to PD.[26] In this study, we and our colleagues found that people with PD consumed significantly less caffeine than those without PD only among pathogenic *LRRK2* variant carriers, as recorded on dietary questionnaires.

Moreover, in this same LCC study, a large metabolomics survey was conducted to identify molecular correlates of *LRRK2* variant penetrance, which averages approximately 30% by age 80 years. Strikingly, of 282 analytes measured in plasma and CSF in 368 LCC participants, caffeine and related analytes (e.g., demethylation metabolites)—more so than any other measured metabolites—distinguished PD from unaffected controls (i.e., lower levels in PD vs controls), and that difference was significantly greater among pathogenic *LRRK2* variant carriers compared with noncarriers.[26] These exposure and biomarker data together with caffeine's protective properties in multiple PD models support caffeine's candidacy in PD prevention trials, particularly among those genetically at substantial risk because of a pathogenic *LRRK2* variant. Alternatively, these epidemiologic data are also consistent with an effect of early PD or its determinants on caffeine use, although pathogenic *LRRK2* variant do not seem to reduce caffeine use or caffeine levels.

The neuroprotective potential of caffeine together with its established safety profile support its consideration as a treatment candidate in PD prevention trials, particularly among those genetically at risk because of a pathogenic *LRRK2* variant. The design of such a trial with caffeine would however need to address several potential practical challenges. First, because caffeine use is so common, with adults in the United States consuming ~175 mg daily,[31] eligibility criteria may have to exclude a significant fraction of otherwise eligible candidates. However, including those habitually consuming >200 mg/d would accommodate the majority and would allow for a substantial active-arm increment in caffeine exposure over baseline intake if a study were designed to dose caffeine at 200 mg twice daily. This treatment regimen matches prior long-term dosing in PD trials[7,32] and squares with regulatory guidance that 400 mg/d is generally safe in adults and with over-the-counter medication labeling of caffeine (to be taken in doses up to 200 mg at least 3 hours apart). Second, caffeine may produce adverse effects (e.g., nervousness, insomnia), which may be intolerable or result in unblinding to caffeine treatment. However, in the above-mentioned phase 2/3 trials of caffeine in PD, adverse event rates did not significantly differ between those randomized to 200 mg twice daily and matching placebo, and blinding (which was assessed at the end each trial) seemed largely preserved.[7,32]

Finally, developing caffeine as a therapeutic without a clear commercial incentive may limit investment in the substantial resources required for a rigorous prevention trial. However, particularly at this early stage of prevention trial development, there may be sufficient public and philanthropic interest to warrant government and foundation support. Moreover, prototypic prevention trials may engender collective industry backing if viewed as instructive, proof-of-concept studies in a precompetitive space. The knowledge gained from such trials could greatly facilitate the testing of future commercial products, and their rapid transition from a PD progression to a PD prevention indication.

Ibuprofen

Immune system defenses in general and inflammation in particular have long been postulated as critical mediators of PD pathophysiology.[33] A cornerstone of this reasoning has been the epidemiologic evidence that anti-inflammatory medication use can predict a reduced risk of developing PD.[34] However, this association has been inconsistently observed, and in some studies, the link between NSAIDs and reduced odds or risk of PD has been driven by a subset of NSAIDs, generally nonaspirin NSAIDs and ibuprofen in particular.[10,11] In a meta-analysis of the only 5 prospective cohort studies of PD risk by use of ibuprofen, its regular intake was associated with reduced incidence of subsequent diagnosis of PD by 27% (95% CI 15%–37% relative risk reduction, $p < 0.0001$), whereas use of other NSAIDs was not linked to developing PD.[35]

Preclinical studies are also supportive of neuroprotective potential of ibuprofen in multiple PD models, and to a greater extent than other NSAIDs, in parallel with the differential epidemiologic associations of NSAIDs with PD.[35] Mechanistically, distinctive features of ibuprofen that may contribute to a greater potential efficacy in PD among NSAIDs include its relatively high CNS penetrance[36] and its properties as a peroxisome proliferator–activated receptor γ ligand and activator[37] in addition to its actions blocking cyclooxygenase and other proinflammatory pathways.[38]

Recently, a case-control study investigated whether ibuprofen and other NSAIDs may contribute to the incomplete penetrance of the PD-pathogenic or risk variants of the *LRRK2* gene.[39] They studied 2 international *LRRK2* variant-enriched cohorts, inquiring retrospectively over regular use (2+ pills per week) of specific or overall NSAIDs by nearly 600 *LRRK2* variant carriers, half with PD and half without PD. After adjusting for differences in potential confounding factors including age, sex, and smoking status, they found that regular ibuprofen use was associated with 5-fold lower odds of having LRRK2 PD (odds ratio [OR] 0.19; 95% CI 0.07–0.50), whereas more modest reductions were observed for aspirin (OR 0.51; 95% CI 0.28–0.91) or NSAIDs overall (OR 0.34; 95% CI 0.21–0.57).

It is difficult to compare these NSAID links to LRRK2 PD with those to idiopathic PD. The above mentioned study did not include idiopathic PD or controls without a *LRRK2* variant, and its OR results are not directly comparable with risk ratios derived from incidence studies noted above for idiopathic PD. Nevertheless, the 81% odds reduction for LRRK2 PD carriers with ibuprofen corresponds to a 75% risk reduction (assuming a nonexposed prevalence of 30%), which greatly exceeds the 27% risk reduction with ibuprofen noted above for idiopathic PD. The difference raises the possibility that if ibuprofen were a mediator and a marker of reduced PD risk, then its potential to prevent PD may be greater among those at risk for PD because of a pathogenic *LRRK2* variant compared with noncarriers.[39]

Thus, ibuprofen also represents a repurposable over-the-counter drug candidate for early PD prevention trials that target those at risk, particularly if genetically predisposed because of a pathogenic *LRRK2* variant. Design of such a trial must however carefully consider limitations of ibuprofen's candidacy. Although ibuprofen is widely available without a prescription based on its generally favorable safety profile, it is not without risks of well-established serious even if uncommon adverse effects, particularly gastrointestinal bleeding. Nevertheless, it has been dosed chronically in randomized controlled trials, for example, at 400 mg twice daily (taken with omeprazole as a gastroprotectant) vs placebo for 1 year in participants with AD (active arm n = 66), with few gastrointestinal adverse effects and fewer than in those on placebo.[40] An even lower dose of 200 mg ibuprofen twice daily may be adequate (based on the epidemiologic links to reduced risk on less than daily dosing)[35] and more appropriate for a PD prevention trial given that minimal risk should be assumed in healthy even if at-risk people. Eligibility criteria would reasonably include only those with a low risk of bleeding, who are not habitual ibuprofen users, and who are at-risk of PD because of a pathogenic *LRRK2* varian and other risk factors.

Albuterol

Albuterol (a.k.a. salbutamol) is another potential preventative for PD whose candidacy is similarly underpinned by its epidemiologic links to PD resistance. However, its recent candidacy originated out of a PD gene-based high throughput screen of a drug library—using an assay for reduced expression of the α-synuclein gene in neuronal cells.[41] In their tour de force study, the researchers not only identified β2-adrenoreceptor agonism as a strategy for suppression of α-synuclein gene expression but also provided biological and epidemiologic evidence in support of its potential to prevent PD. They found that β2-adrenoreceptor agonists including albuterol can confer protection in in vivo (MPTP-intoxicated mouse) and cellular (human α-synuclein–overexpressing induced pluripotent stem cell) models of PD.

In addition, they reported novel longitudinal epidemiologic data from a large Norwegian healthcare database in which use of albuterol was linked to a dose-dependent reduction in risk of incident PD cases. Conversely, the most commonly prescribed β2-adrenoreceptor antagonist propranolol was associated with a significantly increased risk of PD. However, the study could only partially address potential confounds by indication (for smoking-related respiratory illness and essential tremor, respectively), and subsequent epidemiologic studies produced weaker or inconsistent evidence for a protective effect of β2-adrenoreceptor activation.[42]

Nevertheless, albuterol has emerged as an attractive—repurposable, relatively safe, and plausibly protective—candidate for disease modification in PD. Indeed, it recently entered into a phase 2 randomized controlled platform trial of putatively protective, approved medications in manifest PD (ACTRN12620000560998). It is being dosed in a sustained-release formulation, which should reduce the tolerability if not the likelihood of well known, generally mild adverse effects of immediate-release oral or inhaled albuterol such as action tremor and nervousness.This side effect profile is similar to that of caffeine such that the inclusion of both in a multi-arm active drug trial could improve their effective blinding.

Given its "synuclein suppressant" properties, albuterol may be most rationally tested in an early trial for PD prevention that targets an at-risk population in the prodromal stages of synucleinopathy. Accordingly, it is one of a number of agents poised for repurposing (also including caffeine, ibuprofen, ambroxol, melatonin, and antidiabetic agents, such as metformin[43]) as candidate therapeutics in RBD trials evaluating progression to neurodegenerative parkinsonism and/or changes in relevant biomarkers of the underlying pathophysiology.[14]

Ambroxol

An oral mucolytic drug provides an example of a relatively low-risk, repurposable agent that also represents a potential personalized therapy for individuals carrying a pathogenic *GBA* variant. This drug has been available over-the-counter as a cough medicine since the 1970s. In 2009, it was identified through a high throughput library screen of FDA-approved drugs to act as a pharmacologic chaperone of glucocerebrosidase (GCase), increasing its activity and protein levels in lysosomes through a pH-dependent mechanism of action.[44] In PD and in particular *GBA* variant-mediated PD, there is interest in increasing GCase activity given its observed reciprocal relationship with α-synuclein levels,[45] with increasing GCase activity possibly reducing α-synuclein–mediated pathogenicity.

There are no epidemiologic data or associations between ambroxol use and risk or progression of PD or GBA-mediated PD. However, last year, the results of a single-center open-label noncontrolled clinical trial of ambroxol in participants with PD with and without pathogenic *GBA* variants were published.[46] This study of escalating oral ambroxol therapy, with doses previously found to be safe (even if 10 times greater than that used for mucus thinning), primarily investigated its CSF penetrance and the change in CSF GCase activity, along with other secondary outcomes, including safety, tolerability, CSF α-synuclein levels, other serum and CSF protein concentrations, and motor and nonmotor outcomes. In their primary analysis of 17 participants (8 with pathogenic *GBA1* variants and 9 without pathogenic *GBA1* variants), the authors observed increased CSF ambroxol levels (though 9-fold lower than in serum) and decreased CSF GCase activity (which may be explained by ambroxol's putative chaperone role), but no change in blood leukocyte GCase activity. Ambroxol was also found to be well-tolerated and safe with no serious adverse events in this small group. Other findings included increased CSF α-synuclein concentration, increased CSF GCase protein levels, and decreased mean scores on part 3 of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale when comparing assessments on day 0 with day 186.

These results are generally encouraging, but further investigation in a large randomized controlled trial is warranted.

Regardless of the population targeted or the outcome assessed, early PD prevention trials may be designed as phase 2 trials to evaluate multiple distinct candidate agents along with a placebo group to enhance recruitment, blinding (as above), efficiency, and prospects for positive results. At this stage, additional dosing groups may not be necessary given guidance available on efficacy from epidemiologic associations and on safety from extensive clinical experience with these agents. In addition, the practical knowledge gained from investing in the first PD prevention trials would improve the design and implementation of subsequent prevention trials and thus their potential for success.

Gene-Targeted Drugs

The increased knowledge of genetics in PD has expectedly resulted in interest regarding gene-targeted therapies and consideration of their utility in genetically at-risk individuals. As mentioned earlier, we feel that most of these therapies are not yet ready for early PD prevention trials because of greater risks from uncertain safety profiles and more invasive or onerous administration than those of the prototypical repurposable candidates discussed above. However, these treatments may be appropriate in the near future, either because of promising initial results in manifest PD or because of sufficient enthusiasm and resources to justify parallel clinical development in at-risk and manifest populations, as seen in Huntington disease with the PREQUEL and PRECREST trials in individuals with premanifesting disease and the 2CARE and CREST-E trials in individuals with manifesting HD, respectively.[18] Accordingly, we briefly review current early phase gene-targeted clinical trials for individuals with pathogenic *LRRK2* and *GBA* variants and for those against α-synuclein (Figure).

In pathogenic *LRRK2* variant carriers, there are presently 2 strategies being explored: (1) LRRK2 kinase inhibition using small molecules because of the observed toxic gain of function of the variant and (2) antisense oligonucleotides (ASOs) to reduce the expression of the mutated gene through blocking mRNA translation, inducing mRNA degradation, or promoting splicing around the variant. Currently, LRRK2 inhibition is being studied by Denali/Biogen, GSK, Genetech, and Pfizer, whereas ASOs are being explored by Biogen, with further details tabulated in this review.[47]

In pathogenic *GBA* variant carriers, the approach differs from that of pathogenic *LRRK2* variant carriers and instead focuses on (1) restoring cerebral GCase activity through intracisternal infusion of adeno-associated virus vectors delivering a gene encoding functional GCase, as under investigation by Prevail Therapeutics/Lilly with PR001 in the PROPEL study (NCT04127578); (2) administration of small molecule chaperones for GCase, such as ambroxol, as discussed above; or (3) use of a GCase activator, as being studied by BIAL with BIA 28-6156/LTI-291 (Trial NL7061 [NTR7299]). Another approach in pathogenic *GBA* variant carriers involved substrate reduction therapy: reducing glycosphingolipid using glucosylceramide synthase inhibitors. However, this approach failed to show benefit in Sanofi's recently completed MOVES-PD, phase 2 clinical trial (NCT02906020).

Targeted therapies against α-synuclein are of great interest given its role in disease pathogenesis,[48] and their consideration for prevention trials in at-risk cohorts would naturally focus on RBD, as an established synucleinopathy, possibly in combination with other prodromal PD features. Recent trials include means to reduce extracellular α-synuclein levels through active immunization against the protein, the AFFITOPE trial by AFFiRiS, [49] or passive immunotherapy, as being studied in the phase 2 PADOVA trial by Roche/Prothena (NCT04777331). Alternative strategies include administration of small molecules targeting the misfolded or aggregated α-synuclein with NPT200-11 (NCT02606682), ENT-01 (NCT04483479), anle138b (NCT04685265), and Nilotinib (NCT03205488) or use of CRISPR-dCas9 epigenome-editing approach.[50]

Gene-targeted research is an exciting area of active research. Outstanding questions for this approach include those surrounding safety, tolerability, potency or degree of inhibition or restoration required for efficacy, selectivity of agent for the CNS, and appropriate mode of delivery for CNS penetrance.

To conclude, the question of what therapeutic agents to evaluate in early PD prevention trials has many plausible answers, ranging from repurposed, low-risk agents to gene-targeted therapeutics. Given the rapidly expanding knowledge of at-risk populations, we feel that a personalized trial, tailored to specific populations may be most fruitful, that is, individuals carrying a pathogenic *LRRK2* or *GBA* variant or those otherwise at high risk for synuclein-mediated disease because of RBD or a combination of prodromal features. Based on currently available data and the fact that some individuals at-risk will never develop PD, we lean toward the assessment of repurposed, low-risk agents in the first PD prevention trials. In addition to maximizing safety and testing rational candidates, such proof-of-concept trials could leverage philanthropic, government, and/or precompetitive industry investment to lay the groundwork for promising future interventions with the now plausible goal of ending suffering from PD by preventing it.

Acknowledgment

This study received grant support from The Farmer Family Foundation Parkinson's Research Initiative, NIH R01NS110879, the Melvin Yahr Early Career Award in Movement Disorders Research, and grant no. PF-MET-2011 from the Parkinson's Foundation.

Study Funding

Supported in part by Award ID PF-MET-2011 from the Parkinson's Foundation.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 15, 2021. Accepted in final form January 18, 2022.

Appendix Authors

Name	Location	Contribution
Grace F. Crotty, MD	Department of Neurology, Massachusetts General Hospital, Boston	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Michael A. Schwarzschild, MD, PhD	Department of Neurology, Massachusetts General Hospital, Boston	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

References

1. Janssen Daalen JM, Schootemeijer S, Richard E, Darweesh S.K.L., Bloem B.R. Lifestyle interventions for the prevention of Parkinson disease: a recipe for action. *Neurology*. 2022;99(7 Suppl):S42-S51.
2. Lungu C, Cedarbaum JM, Dawson TM, et al. Seeking progress in disease modification in Parkinson disease. *Parkinsonism Relat Disord*. 2021;90:134-141.
3. Parkinson Study G. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1993;328(3):176-183.
4. Parkinson Study Group S-PDI, Schwarzschild MA, Ascherio A, et al. Effect of urate-elevating inosine on early Parkinson disease progression: the SURE-PD3 randomized clinical trial. *JAMA*. 2021;326(10):926-939.
5. Ma C, Liu Y, Neumann S, Gao X. Nicotine from cigarette smoking and diet and Parkinson disease: a review. *Transl Neurodegener*. 2017;6:18.
6. Parkinson Study Group S-PDIIII. Isradipine versus placebo in early Parkinson disease: a randomized trial. *Ann Intern Med*. 2020;172(9):591-598.
7. Postuma RB, Anang J, Pelletier A, et al. Caffeine as symptomatic treatment for Parkinson disease (Cafe-PD): a randomized trial. *Neurology*. 2017;89(17):1795-1803.
8. Carroll CB, Webb D, Stevens KN, et al. Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): protocol for a double-blind, randomised, placebo-controlled futility study. *BMJ Open*. 2019;9(10):e029740.
9. Cheng HC, Ulane CM, Burke RE. Clinical progression in Parkinson disease and the neurobiology of axons. *Ann Neurol*. 2010;67(6):715-725.
10. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol*. 2016;15(12):1257-1272.
11. Chen Y, Sun X, Lin Y, Zhang Z, Gao Y, Wu IXY. Non-genetic risk factors for Parkinson's disease: an overview of 46 systematic reviews. *J Parkinsons Dis*. 2021;11(3):919-935.
12. Ashley S, Bradburn S, Murgatroyd C. A meta-analysis of peripheral tocopherol levels in age-related cognitive decline and Alzheimer's disease. *Nutr Neurosci*. 2021;24(10):795-809.
13. Wang MD, Little J, Gomes J, Cashman NR, Krewski D. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. *Neurotoxicology*. 2017;61:101-130.
14. Molsberry SA, Hughes KC, Schwarzschild MA, Ascherio A. Who to enroll in Parkinson disease prevention trials? The case for composite prodromal cohorts. *Neurology*. 2022;99(7 Suppl):S26-S33.
15. Postuma RB. Neuroprotective trials in REM sleep behavior disorder: the way forward becomes clearer. *Neurology*. 2022;99(7 Suppl):S19-S25.
16. Niotis K, West AB, Saunders-Pullman R. Who to enroll in Parkinson disease prevention trials? The case for genetically at-risk cohorts. *Neurology*. 2022;99(7 Suppl):S10-S18.
17. Videnovic A, Ju YS, Arnulf I, et al. Clinical trials in REM sleep behavioural disorder: challenges and opportunities. *J Neurol Neurosurg Psychiatry*. 2020;91(7):740-749.
18. Crotty GF, Keavney JL, Alcalay RN, et al. Planning for prevention of Parkinson disease: now is the time. *Neurology*. 2022;99(7 Suppl):S1-S9.
19. Chen JF, Schwarzschild MA. Do caffeine and more selective adenosine A2A receptor antagonists protect against dopaminergic neurodegeneration in Parkinson's disease? *Parkinsonism Relat Disord*. 2020;80(suppl 1):S45-S53.
20. Hong CT, Chan L, Bai CH. The effect of caffeine on the risk and progression of Parkinson's disease: a meta-analysis. *Nutrients*. 2020;12(6):1860.
21. Xu K, Di Luca DG, Orru M, Xu Y, Chen JF, Schwarzschild MA. Neuroprotection by caffeine in the MPTP model of Parkinson's disease and its dependence on adenosine A2A receptors. *Neuroscience*. 2016;322:129-137.
22. Yan R, Zhang J, Park HJ, et al. Synergistic neuroprotection by coffee components eicosanoyl-5-hydroxytryptamide and caffeine in models of Parkinson's disease and DLB. *Proc Natl Acad Sci USA*. 2018;115(51):E12053-E12062.
23. Ravina BM, Fagan SC, Hart RG, et al. Neuroprotective agents for clinical trials in Parkinson's disease: a systematic assessment. *Neurology*. 2003;60(8):1234-1240.
24. Belvisi D, Pellicciari R, Fabbrini G, Tinazzi M, Berardelli A, Defazio G. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: what do prospective studies suggest? *Neurobiol Dis*. 2020;134:104671.
25. Stocchi F, Rascol O, Hauser RA, et al. Randomized trial of preladenant, given as monotherapy, in patients with early Parkinson disease. *Neurology*. 2017;88(23):2198-2206.
26. Crotty GF, Maciuca R, Macklin EA, et al. Association of caffeine and related analytes with resistance to Parkinson disease among LRRK2 mutation carriers: a metabolomic study. *Neurology*. 2020;95(24):e3428-e3437.
27. Simon DK, Swearingen CJ, Hauser RA, et al. Caffeine and progression of Parkinson disease. *Clin Neuropharmacol*. 2008;31(4):189-196.
28. Simon DK, Wu C, Tilley BC, et al. Caffeine and progression of Parkinson disease: a deleterious interaction with creatine. *Clin Neuropharmacol*. 2015;38(5):163-169.
29. Moccia M, Erro R, Picillo M, et al. Caffeine consumption and the 4-year progression of de novo Parkinson's disease. *Parkinsonism Relat Disord*. 2016;32:116-119.
30. Kumar PM, Paing SS, Li H, et al. Differential effect of caffeine intake in subjects with genetic susceptibility to Parkinson's disease. *Sci Rep*. 2015;5:15492.
31. Drewnowski A, Rehm CD. Sources of caffeine in diets of US children and adults: trends by beverage type and purchase location. *Nutrients*. 2016;8(3):154.
32. Postuma RB, Lang AE, Munhoz RP, et al. Caffeine for treatment of Parkinson disease: a randomized controlled trial. *Neurology*. 2012;79(7):651-658.
33. Schonhoff AM, Williams GP, Wallen ZD, Standaert DG, Harms AS. Innate and adaptive immune responses in Parkinson's disease. *Prog Brain Res*. 2020;252:169-216.
34. Hirsch EC, Standaert DG. Ten unsolved questions about neuroinflammation in Parkinson's disease. *Mov Disord*. 2021;36(1):16-24.
35. Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. *Neurology*. 2011;76(10):863-869.
36. Kokki H, Kumpulainen E, Lehtonen M, et al. Cerebrospinal fluid distribution of ibuprofen after intravenous administration in children. *Pediatrics*. 2007;120(4):e1002-1008.
37. Tsuji T, Asanuma M, Miyazaki I, Miyoshi K, Ogawa N. Reduction of nuclear peroxisome proliferator-activated receptor gamma expression in methamphetamine-induced neurotoxicity and neuroprotective effects of ibuprofen. *Neurochem Res*. 2009;34(4):764-774.
38. Singh A, Tripathi P, Singh S. Neuroinflammatory responses in Parkinson's disease: relevance of Ibuprofen in therapeutics. *Inflammopharmacology*. 2021;29(1):5-14.
39. San Luciano M, Tanner CM, Meng C, et al. Nonsteroidal anti-inflammatory use and LRRK2 Parkinson's disease penetrance. *Mov Disord*. 2020;35(10):1755-1764.
40. Pasqualetti P, Bonomini C, Dal Forno G, et al. A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease. *Aging Clin Exp Res*. 2009;21(2):102-110.
41. Mittal S, Bjornevik K, Im DS, et al. beta2-Adrenoreceptor is a regulator of the alpha-synuclein gene driving risk of Parkinson's disease. *Science*. 2017;357(6354):891-898.
42. Hopfner F, Hoglinger GU, Kuhlenbaumer G, et al. beta-adrenoreceptors and the risk of Parkinson's disease. *Lancet Neurol*. 2020;19(3):247-254.
43. Sportelli C, Urso D, Jenner P, Chaudhuri KR. Metformin as a potential neuroprotective agent in prodromal Parkinson's disease-viewpoint. *Front Neurol*. 2020;11:556.
44. Maegawa GH, Tropak MB, Buttner JD, et al. Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease. *J Biol Chem*. 2009;284(35):23502-23516.
45. Barkhuizen M, Anderson DG, Grobler AF. Advances in GBA-associated Parkinson's disease—pathology, presentation and therapies. *Neurochem Int*. 2016;93:6-25.
46. Mullin S, Smith L, Lee K, et al. Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a nonrandomized, noncontrolled trial. *JAMA Neurol*. 2020;77(4):427-434.
47. Schneider SA, Hizli B, Alcalay RN. Emerging targeted therapeutics for genetic subtypes of parkinsonism. *Neurotherapeutics*. 2020;17(4):1378-1392.
48. McFarthing K, Simuni T. Clinical trial highlights: targetting alpha-synuclein. *J Parkinsons Dis*. 2019;9(1):5-16.
49. Volc D, Poewe W, Kutzelnigg A, et al. Safety and immunogenicity of the alpha-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial. *Lancet Neurol*. 2020;19(7):591-600.
50. Kantor B, Tagliafierro L, Gu J, et al. Downregulation of SNCA expression by targeted editing of DNA methylation: a potential strategy for precision therapy in PD. *Mol Ther*. 2018;26(11):2638-2649.

What to Test in Parkinson Disease Prevention Trials?: Repurposed, Low-Risk, and Gene-Targeted Drugs

Grace F. Crotty and Michael A. Schwarzschild

Neurology 2022;99;34-41
DOI 10.1212/WNL.0000000000200238