

REPURPOSED THERAPIES IN PARKINSON'S DISEASE

What Patients and
Families Need to Know

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“Repurposing” — testing drugs often already approved by the U.S. Food and Drug Administration (FDA) for one disease to see whether they help people with another disease — can be an important strategy for speeding drug development.

But how do existing medicines come to be repurposed for Parkinson’s disease? And what should you be aware of if you or your loved one is considering taking a drug before it is approved for use in Parkinson’s?

The Bottom Line: Proceed with Caution

Repurposing, sometimes also referred to as repositioning, often means taking a drug that has already been FDA-approved to treat a given health condition, and using it to treat another. (Repurposing also can apply to drugs under investigation for other conditions and to over-the-counter supplements, which are not FDA-approved.) From the time a compound is discovered until it is developed into a medication that reaches the market, the development of a drug can take over a decade and cost \$1 to 2 billion or more. In the best-case scenarios, repurposing can significantly shorten this timeframe and reduce costs.

The Michael J. Fox Foundation’s mission is to leave no stone unturned as we seek to streamline every possible route to breakthroughs that can lead to new and better treatments. In a disease such as Parkinson’s, where patients lack a proven disease-modifying therapy and need better symptomatic therapies, a more efficient but still rigorous way to meet these goals is attractive. Repurposing is potentially an important strategy for speeding drug development, because it takes advantage of the time and financial resources previously invested in a therapy that may prove to benefit people with Parkinson’s disease (PD).

For patients and families, repurposing raises certain specific questions and issues that warrant thoughtful consideration and decision-making. For those living with the disease and their loved ones, of course new and better treatments can’t reach market soon enough. If you count yourself among those awaiting breakthroughs, you may understandably question why further testing is needed. Since existing drugs by definition are available at the pharmacy, you may be considering asking your doctor to prescribe a drug “off label” (i.e., prescribe it to you for your Parkinson’s rather than for the condition it is currently approved to treat).

Simply because a medication is FDA-approved for one condition doesn’t mean it’s safe, tolerable and efficacious for another. Rather, it must be put through rigorous and standardized testing for a full evaluation of these qualities. Even in perfect health, the human body is a complicated machine. When disease and individual intricacies enter the picture, it gets exponentially more complex. No one can predict which medications will prove to be safe and beneficial in Parkinson’s. (And it’s important to be skeptical of such claims in the absence of clinical trial data.)

This guide lays out high-level issues to help you educate yourself about repurposed drugs. However, if you’re contemplating off-label use of a repurposing drug candidate currently in Parkinson’s-specific testing, a thorough discussion with your physician and care team is a must. All drugs bring side effects and potential complications, which could include serious adverse effects and/or interactions with other drugs you may rely on. Only your doctor can provide a knowledgeable opinion on the potential implications for your personal health and care. And if, after proceeding with due caution in weighing pros and cons, you do choose to take a medication off label, regular monitoring to evaluate potential side effects is crucial.

How Therapies Are Repurposed

Out of the thousands of medications that line drugstore shelves, how do some come to be repurposed for use in Parkinson’s?

As in other aspects of drug development, many factors apply. In some cases, promising data may emerge from studies in small groups of people with PD. Or researchers investigating the basic biology of Parkinson’s (i.e., the underlying mechanisms that are thought to cause the disease) may realize that certain cellular biological events, pathways or structures overlap with the basic biology of another disease. Epidemiological studies, which seek insights through the study of large populations, also can



demonstrate links or associations that are clues for Parkinson's drug development. Here, researchers evaluate large numbers of people to determine if those on a certain medication are diagnosed with PD at lower rates.

Once clues are uncovered, investigators can search for basic science and/or pre-clinical evidence to support further inquiry, and narrow their search by focusing on Parkinson's-specific factors that would impact the likelihood of a drug benefiting people with Parkinson's. This might include, for example, whether a drug is able to enter the brain (not all medications can pass through the "blood brain barrier," which protects the brain from infection by keeping it separated from blood), if and how a drug's effectiveness can be measured, as well as its safety profile.

Some drugs currently under study for repurposing in Parkinson's disease — and how they were identified — are listed on pages 4 and 5.

The Realities of Repurposing

Repurposed drugs usually skip Phase I clinical trials as these first-in-human trials are primarily focused on demonstrating safety in healthy volunteers. In FDA-approved medications, this step (which alone can take years and cost hundreds of thousands to millions of dollars) has already been done and doesn't usually have to be repeated. Phase II and III clinical trials do, however, still have to be done, and these are long and expensive studies. These studies are focused on gathering critical safety and tolerability data in the target population (i.e., people with Parkinson's) and evaluating whether the treatment provides benefit to those with the disease.

These phases require hundreds of new volunteers, the collaboration of multiple clinical trial sites, and, typically, many years, specifically when looking at whether a drug changes disease course. So, while leveraging already-completed Phase I trials does save time, money and effort, many cost-, labor- and time-intensive steps remain necessary.

The last two stages of testing unfortunately eliminate a considerable number of therapies from the drug development pipeline. Across all indications, Phase II trials have a success rate of only 30 percent and Phase III's track record stands at 40 percent. While stark, these numbers illustrate why trials are an essential part of repurposing.

Repurposing also may not stimulate widespread industry interest or funding. When original drug patents have expired and generic substitutes are available (as often is the case with therapies up for repurposing), companies may lack incentive to invest in further development. (That's where government institutions and nonprofit organizations, with donor support, can help fill the gap.)

Pursuing Therapies Undergoing Clinical Testing: Reasons to Wait

Many people, when they hear about medications or supplements in clinical testing for repurposing, contemplate using them right away. After all, some argue, if it's FDA-approved or accessible over the

counter, why wait? This response is understandable, especially given Parkinson's patients' unmet needs for better treatment options and a disease-modifying therapy (one that would go beyond symptom alleviation to slow or stop the underlying progression of the disease). Yet there are critical reasons to proceed with caution. At the very least, using therapies prematurely could hurt your pocketbook (supplements aren't covered by insurance and drugs may not be). At the worst, it could harm your health.

The purpose of clinical trials for repurposed drugs is to test these drugs specifically in people with Parkinson's — individuals whose chemistry and biology is altered by PD, and whose responses and side effects can differ from those in whom the drug was originally tested and confirmed safe and efficacious. The overall population of people with PD also is older (the average age at diagnosis is 60), and age often brings concurrent medical illnesses and sometimes complex medication regimens that need to be considered.

The chronic nature of Parkinson's also must be taken into account — treatments are likely to be life-long and must be safe and tolerated for such time periods.

Given all these nuances, only when Phase II and III clinical trials positively demonstrate safety, tolerability and efficacy in people with Parkinson's will the FDA review and approve the therapy for PD. Until then, the drug's role in Parkinson's is unproven. Holding off ensures these treatments are evaluated for safety in Parkinson's and that you and your doctor have rigorous scientific evidence on which to base your treatment decisions and to hopefully avoid potential harmful effects and adverse health outcomes.

"Off-Label" Use

The reality is that some people will choose to pursue a treatment before testing is complete. This constitutes "off-label" use, which is a broad term to describe unapproved use of an approved medication. Based on clinical trial evidence, the FDA labels a drug with key information, including which conditions it is indicated to treat and how the drug should be administered and dosed. Any deviation from these instructions is considered off label. When medically appropriate, health care providers are allowed to (and often do) use drugs off label.

As with any medical treatment, off-label use must be weighed to determine if the potential benefit balances the risks. Your doctor wants to keep his or her oath to "do no harm" and maintain your well-being above all else. To do so, physicians rely on research evidence to inform their practice of medicine. Off-label use of a therapy can entail everything from a higher dose or different formulation than what is specified on a drug's label all the way to your provider prescribing the medication for a condition it is not approved to treat. (When limited or no options are available, such as with Parkinson's non-motor symptoms, the latter is somewhat common. Anti-psychotic medications were, and still are, frequently used to treat Parkinson's disease psychosis because there is only one approved medication to treat this condition.)



When considering off-label drug use for a potential disease-modifying benefit, the focus of many of the therapies in testing for repurposing, the implications of use and potential safety risks deserve even more attention.

Dietary supplements (e.g., inosine) also may be repurposed. As these can be purchased over the counter, they don't require strict authorization from your medical provider. Even so, your physician should know about all supplements as well as over-the-counter and complementary and alternative therapies you plan to use. The "natural" feel of supplements may be appealing, but this doesn't necessarily equal "safe" nor does it mean supplements are free from potential side effects or drug interactions. In addition, the potentially effective dose and amount of active product contained within unproven supplements often is unknown. (Note that although supplements are not subject to FDA review prior to marketing, the FDA can remove them from the market due to safety concerns.)

Regardless of which drug or supplement you are considering, it is vital to talk with your physician, who can help you decide together what's right for your situation. You'll want to discuss:

- » Potential risks, side effects and benefits of the therapy, as well as off-label medication use in general
- » Your medical conditions, medications and supplements, and any possible drug interactions with the therapy in question
- » Cost of the therapy and if health insurance will cover it
- » Whether alternatives to the therapy in question exist
- » Available scientific evidence in support of this therapy
- » Ongoing research on this therapy and the option of clinical trial participation

If, after thorough discussion, you and your provider move forward with the off-label use of the therapy, you'll need ongoing monitoring, which may include both examinations and lab tests, while you're on the drug. Regular follow-up is especially important if you start a medication for a condition you don't have (i.e., you take a drug for diabetes or high blood pressure when you have neither of these conditions).

What if, on the other hand, you do have one of these conditions? Should you switch to a diabetes or blood pressure medication that's in clinical trials for PD instead of the one you're on? Maybe, but there is likely a specific reason your doctor selected the medication you're currently taking. You may be unable to change diabetes drugs because of potential side effects or drug interactions, or you might need a certain blood pressure medication that regulates heart rate or protects your kidneys. Sometimes, these other medications may be more expensive or not covered by insurance.

Another Route to Experimental Treatments: Enroll in Clinical Trials

One way to access repurposed therapies as they undergo testing is to volunteer for clinical trials. This isn't for everyone, but it's an

option for those who wish to advance Parkinson's research and are eligible for the specific clinical trial testing the therapy of interest. It's worth pointing out that trial participation might not guarantee the therapy, though — when trials are "placebo-controlled," half of the volunteers are randomly selected to get placebo and the other half to take the therapy. Clinical trials are crucial to evaluating whether a drug works in PD, and they can't happen without volunteers. If everyone took a therapy outside of a clinical trial (i.e., with a prescription from their doctor or over the counter), researchers would never be able to collect the necessary data to determine whether these medications could be repurposed.

Drugs Currently Being Studied for Potential Repurposing in Parkinson's Disease

Several therapies that are now in mid to late phases of clinical trial testing began with population observations.

» Inosine

This dietary supplement raises blood levels of the antioxidant urate. Researchers saw that people with higher levels of urate tended toward lower PD risk and that in those with Parkinson's who had higher urate, symptoms progressed more slowly. Inosine is now in a Phase III trial to evaluate whether it can slow progression of disease.

» Nicotine patches

Across large numbers of people, researchers saw that current cigarette smokers seemed to have a lower incidence of Parkinson's compared to those who never smoked. Nicotine affects cells that respond to acetylcholine, an important signaling chemical in the brain and throughout the body. These epidemiological observations led to speculation that nicotine could be protective against PD, so scientists studied its effects on dopamine-producing brain cells in Parkinson's cellular and pre-clinical models. Positive results in this realm led to a Phase II trial evaluating whether nicotine smoking cessation patches could slow PD progression, and results from this trial are now being analyzed.

Observing smaller groups of patients also can provide insights to potential repurposing candidates for both disease-modifying and symptomatic treatments. A treating physician may notice a pattern in his or her patients (e.g., their disease advances more slowly than expected or certain symptoms show a marked and otherwise unanticipated improvement) and find that they are all taking the same therapy for another condition. Or, when using medications off label to treat Parkinson's symptoms (as is the case with non-motor symptoms that do not have approved treatments), patients and physicians may notice a promising signal that is deemed worthy of additional investigation.

» Amantadine

Some patients are surprised to find that the Parkinson's medication amantadine, which works on the dopamine and



glutamate brain chemical pathways, also fights the flu virus and originally was introduced for this indication in the late 1960s. Some years later a Parkinson's patient noticed an improvement in her PD symptoms while she was on amantadine for the flu, and this serendipitous observation was then confirmed in others with the disease. Fast forward through clinical trials and amantadine was approved for the treatment of Parkinson's. The drug is now prescribed either alone to treat mild symptoms in early Parkinson's or, more commonly, to target dyskinesia (involuntary, uncontrolled movements) in mid or later stages. Given that amantadine was found to be particularly effective for dyskinesia, it has now been reformulated into a longer acting, or "chrono-synchronous," preparation that was approved by the FDA in August 2017. It is the first and only medication specifically designated to treat dyskinesia.

» **Buspirone**

This medication, which impacts the serotonin and dopamine brain chemical systems, is approved to treat anxiety in the general population, but its safety and efficacy has never been tested in Parkinson's. Given that it works on the brain and it could interact with common PD medications, further study is important. An ongoing Phase II trial is evaluating tolerability.

Like many Parkinson's non-motor symptoms, anxiety does not yet have an approved medication. If this (or other non-motor symptoms) is interfering with quality of life and the management of other PD motor or non-motor symptoms, it should be treated. Treatment may include non-pharmaceutical options (e.g., cognitive behavioral therapy, counseling, exercise) but, because no alternatives exist, it also may involve off-label medication use.

Just as with completely novel therapies, the "aha" moments of repurposing discoveries may occur at the lab bench. As researchers delve into the underlying pathways that lead to PD, they may realize that a currently available drug could correct an abnormal process or prevent damage.

» **Isradipine**

Isradipine works to lower blood pressure by blocking specific calcium channels on blood vessels. These same calcium channels are present on dopamine-producing brain cells that are lost in PD. Pre-clinical work demonstrated that blocking brain cell calcium channels slowed PD progression, and population studies suggested a lower risk of Parkinson's among individuals taking isradipine. Based on this evidence, isradipine is currently in a Phase III clinical trial to determine if it can slow Parkinson's progression.

» **Exenatide**

This injectable drug, known as a glucagon-like peptide-1 (GLP-1) agonist, is used to treat type 2 diabetes. It stimulates insulin release from the pancreas by binding to a receptor called GLP-1. Researchers found this same GLP-1 receptor on brain cells, and pre-clinical studies showed exenatide is effective in protecting against Parkinson's and slowing progression of disease. A Phase II trial evaluating exenatide's safety and benefit for Parkinson's motor symptoms demonstrated potential, but additional investigations are necessary to fully define the drug's effect. (Similar diabetes drugs — liraglutide and lixisenatide — also are undergoing Phase II testing to determine safety and efficacy in PD.)

» **Nilotinib**

Nilotinib targets a form of blood cancer called chronic myelogenous leukemia. Several Phase II clinical trials are either currently or soon will be underway to test this therapy for PD, and this can be traced back to basic science findings. Nilotinib inhibits a protein called c-Abl, which, when elevated, may lead to clumping of the protein alpha-synuclein (the "sticky" protein thought to be responsible for death or damage of brain cells in PD) and/or interfere with dopamine signaling between brain cells. Pre-clinical studies showed neuroprotective effects and a small open-label clinical trial of 12 patients demonstrated promising signs deserving of more rigorous testing through larger, randomized, placebo-controlled and blinded (i.e., neither patients nor researchers know who is taking placebo vs. nilotinib) clinical trials. These Phase II trials are now in the recruiting or planning phases.

INFORMATION IN THIS GUIDE WAS ACCURATE WHEN IT WAS PUBLISHED IN JUNE 2017. FOR THE LATEST UPDATES ON REPURPOSED THERAPIES, VISIT MICHAELJFOX.ORG.

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