Beta-blockers associated with delayed onset and decreased progression of Huntington's disease

A well-studied, widely used class of drugs for heart health may have benefits for Huntington's disease. A new paper associated beta-blocker use with delayed onset and slower disease progression. Should you ask your doctor for a new prescription?

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Research led by Dr. Peg Nopoulos from the University of Iowa used the Enroll-HD database to answer a key question: "How does beta-blocker use influence motor-diagnosis onset and progression rates in premanifest and early motor-manifest Huntington's disease (HD)?". They found beta-blocker use was associated with positive effects!

Subtle changes because of HD

While HD primarily affects the brain, people with HD have subtle changes to their nervous system that can also affect heart rate and blood pressure. The scientists who worked on this paper had previously shown that these subtle nervous system changes happen early in life, which could cause their effects to build over time.

Scientific studies, like those written about here, are only possible because of members of the Huntington's disease community that participate in observational studies like Enroll-HD. Together, we are the prescription for change!

They thought that medications used to treat these subtle changes, like those recommended for minor heart problems and small elevations in blood pressure, could potentially have global benefits for the nervous system, perhaps having a larger influence on HD symptoms overall.

LOLs for a calmer heart

The researchers were specifically interested in a class of medications called beta-blockers. You've likely heard of many of these medications - propranolol, metoprolol, and atenolol are 3 commonly prescribed beta-blockers. A trick for identifying them is that they end in the suffix -lol.

Beta-blockers are a routinely prescribed pill for managing various conditions, like high blood pressure, irregular heart rhythms, and anxiety. They work by blocking the effects of adrenaline and other stress hormones on the heart and blood vessels, helping to slow heart rate and reduce overall cardiovascular strain.

Beta-blockers have been widely used in clinical practice for over 50 years, with the first drug in this class, propranolol, approved by regulatory agencies in the 1960s. Since then, they have become a mainstay treatment for a range of cardiovascular conditions due to their proven safety and effectiveness.

Over decades of use, beta-blockers have demonstrated a strong safety profile, with side effects that are well understood and manageable in most patients, making them one of the most trusted types of drugs in medicine.

Enroll in action

To answer questions about the effect of beta-blockers on the onset and progression of HD, the researchers turned to the Enroll-HD database. Enroll-HD is the largest global observational study focused on HD, involving people from around the world. Over 20,000 people are currently part of Enroll-HD! No drug is given during the study; it's designed to simply watch people with HD as they live and age and see how that differs from people without HD.

> **"The major take home from this new study is that the use of beta-blockers is associated with delayed motor diagnosis in people with premanifest HD and delayed disease progression in people with early motor symptoms. "**

During clinical visits for Enroll-HD, participants are asked questions by their neurologists, including current medication use. This information is then de-identified so no one can match clinical information to a specific person, and researchers across the globe are given access to that data. This allows leaders in HD research from around the world to dig into this data and ask and answer questions that will get us closer to a treatment.

Delay and decrease

Dr. Nopoulos' group used the Enroll-HD dataset to analyze the use of beta-blockers in people with the gene for HD who were not yet experiencing symptoms (premanifest HD) and those with early motor symptoms. The most common reasons people took these meds was because of high blood pressure, anxiety, depression, and heart problems like irregular heart rhythm or coronary artery disease.

For people in the premanifest HD group who were taking beta-blockers, the chance of being diagnosed with disease onset was decreased by 19% to 38%, depending on the specific medication. That's quite a bit! (The 38% decrease was seen for those taking propranolol.)

People with early motor symptoms who were taking beta-blockers showed improvements in several tests used to measure progression of HD symptoms, compared to people not taking beta-blockers. The beta-blocker users had slower progression in motor symptoms, slower decline in their ability to carry out day-to-day tasks, and a slower decline in thinking and memory tests.

However, when they got into the nitty gritty of the data for the early motor group, the type of medication seemed to matter. In looking at the 3 most common beta-blockers that were used in Enroll-HD - metoprolol, propranolol, and bisoprolol - only some of the meds influenced some of the tests. Only metoprolol affected motor symptoms, and only bisoprolol affected the ability to carry out day-to-day tasks and thinking and memory.

Process or prescription?

These results beg the question - is it the medication that's having the benefit or treatment of the underlying condition? To answer that question, the group also looked at another medication commonly prescribed for cardiovascular issues - ACE inhibitors.

We don't yet have data from a clinical trial to support prescribing beta-blockers for Huntington's disease. This study merely represents an association between their use and delayed onset and decreased progression.

While ACE inhibitors are frequently prescribed for similar health issues for which beta-blockers are given, ACE inhibitors did not have the same positive effect in this study. ACE inhibitors showed no positive association with HD onset and symptom progression. This suggests that there's something specific about beta-blockers, and not just treating these heart-related issues, that is having this beneficial effect.

Limitations

The largest limitation of this study, which is noted by the authors, is that they're looking at correlation, not causation. They can't say for sure if the positive changes in onset and progression are *caused* by beta-blockers. They can only say these positive changes are *associated* with beta-blockers.

Studies like Enroll-HD allow researchers to dig through lots of data and are very helpful for pulling out this type of association. But clinical trials are needed to draw firm conclusions about the effects drugs are having. However, once scientists know about positive associations, they can then do specific experiments to get at exactly what is driving the association, which can lead to the development of other drugs, and future clinical trials.

The data is also limited in that the Enroll-HD database has limitations for collecting data from disease progression biomarkers, like neurofilament light (NfL). NfL is a molecule that's released from damaged and dying brain cells. We know that NfL levels rise as HD progresses. However, we don't know if NfL levels change with beta-blocker use. The second iteration of Enroll, which is currently being rolled out, is designed to expand in ways that will improve collection of biomarkers, including NfL.

The fine print

In studies like this that can only generate associations, there's always some fine print. While we can't say for sure if beta-blockers are the *cause* of these improvements, we can call out a few of the confounding variables to try and understand what else could be at play here.

We know that beta-blockers are frequently prescribed for anxiety. We also know that unchecked anxiety can impact motor symptoms in people with HD and have major effects on one's ability to carry out day-to-day tasks. It's possible that beta-blockers used to suppress anxiety had a positive effect simply because they reduced overall worry and unease, leading to improved daily life.

> **"One thing that we learned unequivocally from this study is that the people participating in Enroll-HD are changing the face of HD research. "**

We know that HD causes vascular changes, particularly in the brain. We also know that treating low level hypertension with beta-blockers could have long-term benefits for vascular effects. So it's possible that managing vascular changes early could be leading to some of the positive changes noted in this study.

We also know, for sure, that living a healthy lifestyle is correlated with later disease onset and slower progression. It's likely that people going to the doctor for medical problems that would be treated by beta-blockers are more health forward, so they may exercise more frequently or eat healthier foods too. So it's possible that at least some of the positive benefits noted in this study could be because those taking beta-blockers are, overall, more health conscious people.

Prescription for change

The major take home from this new study is that the use of beta-blockers is associated with delayed motor diagnosis in people with premanifest HD and delayed disease progression in people with early motor symptoms. However the most effective beta-blocker is unclear since the exact drug that showed benefit varied by experiment. And notably, dose was not examined since it varies wildly based on medication and indication for which it is prescribed.

If this study has you wondering if you or a loved one should start taking a beta-blocker for HD, please reach out to your primary care physician or neurologist. While beta-blockers are generally safe, **there are contraindications** for these medications, such as low blood pressure, COPD, and circulatory problems.

One thing that we learned unequivocally from this study is that the people participating in Enroll-HD are changing the face of HD research. With their help, scientists are uncovering critical information to generate ideas that will lead to future clinical trials. The strength of the HD community and their participation in these large observational studies is the real prescription for change.

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

NfL biomarker of brain health

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

hormone Chemical messengers, produced by glands and released into the blood, that alter how other parts of the body behave

manifest after HD diagnosis, or when symptoms are already showing