



## National Tay-Sachs & Allied Diseases Association

### **Enzyme Enhancement Therapy/Pharmacological Chaperone Therapy**

#### **What is enzyme enhancement therapy (EET)/pharmacological chaperone therapy (PCT)?**

Our genes provide specific instructions to make proteins, which carry out essential functions in our bodies. An enzyme is a type of protein whose function is to break down specific substances (substrates) in our body to produce one or more products. If a gene has a harmful change (i.e., pathogenic variant), it may not provide correct instructions to produce functional enzymes. Deficiencies in certain enzymes can lead to a toxic accumulation of substances in the body. This is what happens with GM2 gangliosidosis (Tay-Sachs and Sandhoff), GM1 gangliosidosis, and Canavan disease due to genetic changes causing reduced or absent activity in the HexA, HexB, GLB1, and ASPA enzymes, respectively.

**EET/PCT is a treatment approach that aims to rescue and improve the function of deficient enzymes in the body.**

#### **How does EET/PCT work?**

In GM2 gangliosidosis, GM1 gangliosidosis, and Canavan disease, certain types of variants (missense variants) change the protein in a way that leads to reduced enzyme activity. The reason can be that the protein is being produced at a lower rate, or it is not folding or being transported properly (PMID: 12459725). Null variants (also known as nonsense, frameshift, deletion, or insertion variants) lead to complete absence of the protein and therefore no enzyme activity at all.

EET/PCT uses types of small molecules, often called ‘pharmaceutical chaperones,’ to help the enzyme fold properly, allowing it to function more efficiently. Pharmaceutical chaperones can bind to and stabilize the enzymes, possibly correcting the folding process and improving the transportation of these enzymes in the body (PMID: 24236974). Because EET/PCT requires the presence of enzymes, it is not a therapeutic option for individuals

with no enzyme activity produced, and thus it is dependent on the presence of a particular variant (mutation) and its chaperone responsiveness.

Migalastat and Ambroxol are examples of pharmaceutical chaperones used to treat Fabry and Gaucher disease, respectively (PMID: 35865957). In late-onset GM2 gangliosidosis, pyrimethamine was explored as a potential chaperone. However, when given to patients with Tay-Sachs disease, HexA enzyme activity was only temporarily increased and significant improvements in symptoms was not seen (PMID: 35865957; 37627292). Higher drug doses administered in one trial also showed negative side effects, including immune responses in patients (PMID: 20926324). In GM1 gangliosidosis, several types of pharmaceutical chaperones, including carbasugar and DGJ-related molecules, have been explored in molecular studies (PMID: 34816592). Additional types of pharmaceutical chaperones are being studied, which may identify more promising chaperones for GM2 and GM1 gangliosidosis in the future (PMID: 35865957). In Canavan disease, studies are also focused on identifying and developing pharmaceutical chaperones that will stabilize the mutated ASPA enzyme (PMID: 39128657).

EET/PCT is seen as a potential treatment option because the molecules used can pass through the blood-brain barrier (BBB) (PMID: 17073517, 30524313). It is also viewed favorably due to the convenience of oral administration, lower manufacturing costs, and lower immunogenicity compared to other therapies like enzyme replacement therapy.

### **What are the limitations of EET/PCT?**

**Requires enzyme activity:** EET/PCT is not beneficial for individuals who have no enzyme due to certain types of variants like null variants (PMID: 31940970), and it is also dependent on the biochemical responsiveness of a particular variant (PMID: 32023956).

**Immune responses:** Patients may have an immune response against delivering small molecules into the body, although this response is less likely compared to other methods like enzyme replacement therapy.

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To access the literature reference, enter the PMID number into the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) search box or Google “PMID XXXXXXXX”, replacing the “X’s” with the appropriate number.

Data is current as of August 2024