

## Treatments For GoF (Gain of Function):

1. Memantine: This drug has been widely used for Alzheimer's disease, but its effect on GRIN children varies from patient to patient. Sometimes the beneficial effects of memantine are temporary, but long-time effect has also been reported.

<https://www.frontiersin.org/articles/10.3389/fphar.2021.773455/full>

2. Perampanel: This is an anti-epileptic drug that acts on the AMPA receptor (which interacts with NMDA) and has been used in a clinical case of a child with GRIN1 GoF.

<https://pubmed.ncbi.nlm.nih.gov/33403508/>

3. Radiprodil: This is a drug for which a phase 1 clinical trial is currently being conducted in Europe and in the US. Outside of these clinical trials, radiprodil is, unfortunately, not yet approved for use in patients with GRIN. The effect of Radiprodil is directed to the GRIN2B protein, although it is expected to work on other GoF GRIN genes as well.

Radiprodil is expected to have a positive effect on the control of epilepsy and behavioural problems in GoF GRIN disorders. It is important to know that memantine and radiprodil have different modes of action on the NMDA neuroreceptor, broadening their use in different GRIN GoF mutations.

<https://onlinelibrary.wiley.com/doi/10.1002/acn3.50998>

<https://www.sciencedirect.com/science/article/pii/S0028390817302290?via%3Dihub>

4. Dextromethorphan: This is the active ingredient in over-the-counter cough medications. Anecdotally, it has had a positive but transient effect in GoF patients.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8283169/>

5. Ketamine – This drug is generally used as an anesthetic, and has only been tested at the cellular level, meaning in the laboratory but not in GRIN patients. It is a highly controlled substance, because of its recreational use. It should be used with extreme caution in GRIN children as it can have serious side effects.

<https://onlinelibrary.wiley.com/doi/10.1002/acn3.51406>

Other Ketamine-like drug derivatives are currently being developed for depression. We hope that in the future these drugs will be considered for the treatment of GRIN disorders.