

## **Success Stories: Translating insights from genetic analyses in painful small fiber neuropathy into pharmacological practice – Lacosamide**

Small fiber neuropathy (SFN) is a peripheral neuropathy of the thinly myelinated A $\delta$ -fibers and unmyelinated C-fibers, and is associated with multiple underlying conditions. Gain-of-function mutations in voltage-gated sodium channels (NaVs) have been reported in around 15% of patients with SFN. Nav1.7, Nav1.8 and Nav1.9, encoded by the genes SCN9A, SCN10A, and SCN11A, respectively, are preferentially expressed in dorsal root ganglion (DRG) neurons and their peripheral axons.

Lacosamide is a functionalized amino acid which binds to fast-inactivated Nav1.7 with slower kinetics than classical sodium channel blockers. Since pain in SFN is produced by inappropriate firing of DRG neurons, the NaV channels in these neurons would be expected to be in at least a partially inactivated state, so that lacosamide would be expected to bind with and inhibit these channels, thus attenuating the firing of DRG neurons.

Based on this information a randomized, placebo-controlled, double-blind, crossover-design study was performed in 24 patients with Nav1.7-related SFN. Lacosamide had a significant effect on pain, general well-being, and sleep quality.

As a next step, voltage-clamp recordings were used to evaluate the effects of lacosamide on five Nav1.7 variants from patients who were responsive or non-responsive to treatment. It was demonstrated that lacosamide acts as a potent sodium channel inhibitor of Nav1.7 variants carried by responsive patients, via a hyperpolarizing shift of voltage-dependence of both fast and slow inactivation and enhancement of use-dependent inhibition. By contrast, the effects of lacosamide on slow inactivation and use-dependence in Nav1.7 variants from non-responsive patients were less robust. Importantly, we found that lacosamide selectively enhances fast inactivation only in variants from responders.

In conclusion, the finding of Nav1.7 gain of function mutations in patients with small fiber neuropathy has led to the development of a new treatment option, and more importantly, may serve as an example for future drug development and clinical trials.