Mechanism of Action for the IB-Stim

Functional abdominal pain associated with IBS is believed to involve abnormal processing of signals between the brain and the gut, otherwise known as the "brain-gut axis".

Pre-clinical studies have indicated the likely mechanism of action through which percutaneous electrical nerve field stimulation (PENFS) improves symptoms of functional abdominal pain associated with irritable bowel syndrome (IBS). PENFS targets the central nervous system through gentle electrical impulses applied to cranial nerve branches located just beneath the skin of the ear. Tracing studies have confirmed that these cranial nerve branches project centrally to the nucleus tractus solitarius (NTS). The NTS then projects to other brain structures involved in autonomic control and pain, including the RVM, hypothalamus and amygdala.

The amygdala is a key component of the CNS that links stress, fear, anxiety and pain from somatic and visceral structures. The amygdala integrates this information and facilitates the individual phenotypic responses. In fact, studies in subjects with IBS have already demonstrated abnormal connectivity between the amygdala and other brain regions as a potential cause for symptoms. The initial hypothesis regarding the mechanism of PENFS was that it would alter the response characteristics of neurons in the amygdala and attenuate pain, regardless of whether it was visceral or somatic. This hypothesis was proven in an animal model of IBS that involved behavioral and electrophysiology experiments. In that study, PENFS effectively prevented, and in a separate group of animals, reversed the visceral and somatic hyperalgesia induced by TNBS colitis. In the electrophysiology experiments, PENFS significantly decreased the firing of neurons in the central nucleus of the amygdala by greater than 50%. Interestingly, the amygdala has also been shown to modulate spinal neurons.

The central nucleus of the amygdala has major projections to the forebrain and brainstem, through which it also influences spinal neurons. Nociceptive drives entering the spinal cord from afferent signals (somatic or visceral) are modulated by brainstem nuclei including the Rostral Ventromedial Medulla (RVM) and periaqueductal gray (PAG). These nuclei get input from the NTS, which is the first stop for the PENFS signals. Because the amygdala and NTS are modulated by PENFS, they can dampen spinal cord neurons through their effect on the brainstem. This was evident in the animal studies where PENFS caused a significant decrease (>50%) in baseline firing of lumbar spinal neurons.

The reduction in visceral pain in the pre-clinical studies was further validated in a randomized, placebo-controlled trial of PENFS in children with functional abdominal pain disorders. Children with active PENFS demonstrated improvement in pain, global symptoms and functional disability compared to those with sham devices.

Overall, abnormalities of the brain-gut axis in patients with functional abdominal pain is likely to involve limbic (amygdala) and spinal cord pathways. Neuromodulation with PENFS influences these pathways, as demonstrated in pre-clinical studies, and improves functional abdominal pain and global symptoms associated with IBS in children.

FDA DEN180057: The IB-Stim is a percutaneous electrical nerve field stimulator (PENFS) system intended to be used in patients 11-18 years of age with functional abdominal pain associated with irritable bowel syndrome (IBS). The IB-Stim is intended to be used for 120 hrs per week up to 3 consecutive weeks, through application to branches of Cranial Nerves V, VII, IX, X and the occipital nerves identified by transillumination, as an aid in the reduction of pain when combined with other therapies for IBS.