# Therapeutic Applications of Invasive Neuromodulation in Children and Adolescents

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**KEYWORDS**

• Neuromodulation • Invasive brain stimulation • Deep brain stimulation • DBS • Vagal nerve stimulation • VNS • Children • Adolescents

**KEY POINTS**

- Vagal nerve stimulation has US Food and Drug Administration approval for intractable epilepsy in patients aged 4 and older.
- Deep brain stimulation has been used on a limited basis in youth with dystonia and intractable tic disorders.
- Further measured work with invasive neuromodulation for children and adolescents with debilitating neuropsychiatric disorders could provide new treatment options and expand current knowledge base of neurocircuitry across development.

## INVASIVE NEUROMODULATION

Neuromodulation is a rapidly growing field that includes a variety of stimulation modalities. Although neuromodulation techniques have been used to treat medical conditions for thousands of years, contemporary neuromodulation began in the 1960s with the advent of deep brain stimulation (DBS). In adults, advances and growing evidence in the efficacy and safety of invasive neuromodulation techniques have already led to the study and in some cases US Food and Drug Administration (FDA) clearance for several indications. Parkinson disease, essential tremor, and

Financial Disclosures: Dr P.E. Croarkin has received research grant support from Pfizer, Inc (WS1976243), National Institute of Mental Health (K23MH10026 and R01MH113700), the Brain and Behavior Research Foundation (20883), and the Mayo Clinic Foundation. He has received equipment support from Neuronetics, Inc and receives supplies and genotyping services from Assurex Health, Inc for investigator-initiated studies. He is the primary investigator for a multicenter study of adolescent TMS funded by Neuronetics, Inc. Drs D.D. Camsari and M. Kirkovski have no financial disclosures.

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Psychiatr Clin N Am ■ (2018) ■–■

https://doi.org/10.1016/j.psc.2018.04.008 **psych.theclinics.com**

epilepsy are the most widely studied conditions in adults.[1] As of 2017, FDA clearance in children is limited to use of vagal nerve stimulation (VNS) in drug-resistant epilepsy, and DBS in dystonia.

### *Vagal Nerve Stimulation*

VNS is an invasive neuromodulatory technique that involves electrical stimulation of the 10th cranial nerve, the vagus nerve, via an implanted electrical stimulator. VNS is most commonly used to treat intractable epilepsy and treatment-resistant depression.[2] Common stimulation settings are 1 to 3 mA, 20 to 30 Hz, and 130 to 500 μs.[2] In 1997, the FDA approved the use of VNS in treatment of intractable epilepsy in adults and children aged 12 and older.[3] In 2017, another device was approved for partial-onset medication refractory epilepsy in patients as young as 4. A systematic review and meta-analysis of the efficacy of VNS in 326 children described a response rate of 38% (>50% reduction in seizure frequency). The study did note high variability and limited evidence.[4] In order to assess tolerability and side-effect profile, the investigators included additional case reports and retrospective studies, with a total of 1249 children included. Despite the high percentage of side effects (70%–80%), most of the patients tolerated these side effects well and continued treatment. Common side effects included procedure-related complications, including hoarseness (1%), dyspnea (<1%), fluid collection around the stimulator, and infection (3%). Other side effects were device-related complications, such as hardware failure (3%) and stimulus-related complications, such as aspiration (5%), due to vocal cord dysfunction during the stimulation period. Arrhythmias were noted as delayed complications. There were 5 sudden unexplained death in epilepsy patients and 4 unrelated deaths. The investigators also maintained that VNS may improve sleep quality, behavior, and mood and reduce treatment expense.[4]

### *Deep Brain Stimulation*

DBS is one of the early brain stimulation techniques that emerged in 1960s and has since been used to treat multiple different neurologic and psychiatric conditions. DBS is an invasive procedure whereby the lead is placed in the targeted areas of the brain and is connected to the implanted pulse generator, which is extracranially placed. DBS is considered favorable as compared with surgical ablation procedures with regard to reversibility of the procedure and lower risk of complications.[5] The FDA cleared DBS for Parkinson disease tremor in 2001 and essential tremor in 1997. Other indications under FDA humanitarian device exemptions include dystonia in 2007, obsessive compulsive disorder in 2009, and closed loop stimulation for epilepsy.[6] Other areas of interest include major depressive disorder, Tourette syndrome, addictions, and obesity. In children, DBS use has been primarily limited to dystonia, but epilepsy, Tourette disorder (TD), and obsessive-compulsive disorder (OCD) have also been considered as potential targets.

### *Dystonia*

When pharmacologic interventions fail to provide improvement, more invasive interventions such as pallidotomy and DBS are considered to treat symptoms and decrease disease burden in dsytonia.[7,8] The globus pallidus interna (GPi) has been the main target of DBS in treating dystonia in both adults[6] and children[9,10]; however, other regions, including the subthalamic nucleus and thalamic ventralis intermedius, have also been targeted. Bilateral stimulation of GPi with higher frequencies (100 Hz) has been reported to be the most common application of DBS in dystonia, yet lower frequencies have also been used.[8] Wider pulses were found to be poorly