Washington State Health Care Authority, HTA Program
Vagus Nerve Stimulators
Final Key Questions and Background

Introduction

HTA has selected vagus nerve stimulators to undergo a health technology assessment where an independent vendor will systematically review the evidence available on the safety, efficacy, and cost-effectiveness. HTA posted the topic and gathered public input about available evidence. HTA published the draft key questions, and considered all public comment input and any additional evidence submitted prior to finalizing the key questions. Key questions guide the development of the draft evidence report.

VNS uses a stimulator that sends electric impulses to the left vagus nerve in the neck via a lead implanted under the skin. VNS affects blood flow to different parts of the brain and affect neurotransmitters. VNS implantation is usually done as an out-patient procedure. An incision is made in the upper left chest and the generator is implanted into a little "pouch" on the left chest under the clavicle. A second incision is made in the neck and the surgeon wraps the leads around the left branch of the vagus nerve, and connects the electrodes to the generator. Once successfully implanted, the generator sends electric impulses to the vagus nerve at regular intervals. The left vagus nerve is stimulated rather than the right because the right plays a role in cardiac function such that stimulating it could have negative cardiac effect.

Epilepsy --

Patients:	Adults ($\geq$ 18 y.o.) and children with epilepsy
Intervention:	Vagus nerve stimulators plus anti-epileptics medication
Comparator:	Anti-epileptic medications alone
Outcomes:	Frequency of seizures, quality of life, harms/safety (infection, hoarseness, cough, pain, paraesthesias).
Timing / Setting:	Not applicable.
Policy Context:	Given the unclear benefit of VNS and the significant costs to implant and maintain the device, it would be useful to know whether evidence exists regarding the effectiveness of VNS. In addition, there are concerns about harms and safety issues (e.g. infection) that may outweigh the benefits.

Epilepsy Key Questions:

For VNS (either used alone or in combination with anti-epileptic medication) used in patients with epilepsy, compared to either placebo or treatment with medications:

1. What's the evidence of efficacy and effectiveness in improving clinical outcomes, including reducing the frequency of clinical seizures (vs. on EEG) and improving quality of life?
2. What is the evidence about the safety profile?
3. Is there evidence of differential efficacy or safety issues among specific patient subgroups, including (e.g. patients with epilepsy refractory to anti-epileptic medications, adults, under 13, and under 21)?
4. What is the evidence of cost implications and cost effectiveness?

Depression --

Patients:	Adults (≥ 18 y.o.) and children with depression.
Intervention:	Vagus nerve stimulators with or without antidepressant medications.
Comparator:	Antidepressants (plus psychotherapy) or electroconvulsive therapy (ECT).
Outcomes:	Depression symptom improvement, harms / safety (infection, hoarseness, cough, pain, paraesthesias).
Timing:	Short-term or acute treatment phase (e.g. 12 weeks) and long term (6 month and 12 month).
Setting:	Not applicable.
Policy Context:	Given the unclear benefit of VNS and the significant costs to implant and maintain the device, it would be useful to know whether evidence exists regarding the effectiveness of VNS. In addition, there are concerns about harms and safety issues (e.g. infection) that may outweigh the benefits.

Depression Key Questions:

For VNS (either used alone or in combination with antidepressant medication) used in patients with depression, compared to either placebo or treatment with antidepressant medications:

5. What's the evidence of efficacy and effectiveness in improving clinical outcomes, including reduction of severity of depression symptoms and improvement in quality of life?
6. What is the evidence about the safety profile?
7. Is there evidence of differential efficacy or safety issues among specific patient subgroups, including treatment resistant depression and age categories (especially, adults, under 13 and under 21)?
8. What is the evidence of cost implications and cost effectiveness?

Technology Background

Bone growth stimulation is a technique of promoting bone growth in difficult to heal fractures or in areas trying to be fused by applying a low electrical current or ultrasound to the fracture. Fully implantable direct current stimulators are installed in a hospital under general or regional anesthesia. Both the stimulator and the power source are implanted. The surgeon makes an incision and places a spiral shaped cathode inside the bone. A wire leads to the power source and a small anode. The power source is a battery pack that is implanted in the nearby muscle. Partially implanted stimulators are cathode pins that are implanted at the edge of each bone that is fractured. Wires lead to the surface of the skin where a power source and the anode are located. Wires complete the circuit. The external portion of the device is held in place by a cast. This source of stimulation also runs continuously. Ultrasound stimulation is a device that generates low intensity pulses of sound and is applied to the skin over the fracture. Each method (electrical and ultrasound) must be used for at least three to six months to be effective. Questions about the effectiveness and durability of the treatment remain, as well as safety questions related especially to implanted techniques that carry attendant surgical risks.