

Background and Final Key Questions

Vagal nerve stimulation for epilepsy and depression

Background

Technology of Interest

Vagal, or vagus, nerve stimulation (VNS) is a neuromodulatory therapy that sends electric signals to the brain.¹ A small device, called a pulse generator, is implanted into the left side of the chest to produce repeating, low-level pulses of electrical current along the vagus nerve to the brain.¹ Transcutaneous VNS (tVNS) targets the cutaneous receptive field of the auricular branch of the vagus nerve (ABVN) at the outer ear, and can be a noninvasive alternative to the implanted or invasive VNS for some conditions.² The mechanism of action of VNS is not fully understood, but is assumed to involve the immunomodulatory action of the vagus nerve resulting in anticonvulsant effects and changes in mood, behavior, and cognition.³

Clinical Need and Target Population

An estimated 1.2% of the U.S. population had active epilepsy in 2015.⁴ This is about 3.4 million people nationwide, representing 3 million adults and 470,000 children.⁴ There are many different types of epilepsy, and VNS is not always an appropriate treatment. In 1997, the U.S. Food and Drug Administration (FDA) approved the use of VNS as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents older than 12 years of age with partial onset seizures refractory to antiepileptic medications.⁵ In 2017, the FDA lowered the age of use in children from 12 to 4 years.⁵ tVNS is not currently FDA approved for use in epilepsy. Because of the expanded indication for the use of VNS, there is interest in the clinical and cost-effectiveness evidence for the use of VNS for epilepsy.

Major depression is one of the most common mental disorders in the United States.⁶ In 2017, an estimated 17.3 million adults (7.1%) in the U.S. had at least one major depressive episode.⁶ Many people with major depression respond to treatment with medication or psychological therapies, either alone or in combination.⁷ However, up to 33% of people with major depressive disorder (MDD) will not respond to an adequate trial of antidepressant medication, and the chances of response tend to decline with each new trial of medication.⁷ Treatment-resistant depression (TRD) is commonly defined as a failure of treatment to produce response or remission for patients after 2 or more treatment attempts of adequate dose and duration, but no clear consensus exists about this definition.⁸ VNS is indicated for the adjunctive long-term treatment of chronic or recurrent depression for adults who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments.⁹ tVNS is not currently FDA approved for use in depression.

In 1999, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage decision (NCD) to cover VNS for patients with medically refractory partial onset seizures, for whom surgery is not

recommended or for whom surgery has failed.¹⁰ In 2006, CMS received a request to expand the NCD to include coverage of VNS for TRD for patients who had either been previously treated with or refused electroconvulsive therapy (ECT) for the treatment of depression, or who had been previously hospitalized for depression.¹⁰ The specific indication requested for VNS coverage was for the adjunctive long-term treatment of chronic or recurrent depression in adults who were experiencing a major depressive episode and had not had an adequate response to 4 or more adequate depression treatments. In 2007, CMS concluded there was sufficient evidence that VNS was not reasonable and necessary for TRD and it has remained noncovered.¹⁰ In 2019, CMS issued a decision memo on the use of VNS for depression in the context of research only:¹⁰

- CMS will cover FDA-approved VNS devices for TRD through Coverage with Evidence Development (CED) when offered in a CMS-approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least 1 year with the possibility of extending the study to a prospective longitudinal study when the CMS-approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim findings.

CMS's decision was based on an evidentiary review of the literature, which concluded VNS for TRD seemed promising, but not convincing.¹⁰ Coverage in the context of ongoing clinical research helps ensure the technology is provided to appropriate patients in controlled settings while developing evidence that the treatment improves health outcomes and is safe.¹⁰ CMS also approved coverage for a VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction in patients currently implanted with a VNS device for TRD.¹⁰ Questions therefore remain on the clinical and cost-effectiveness of VNS for TRD.

Policy Context

VNS can be a treatment option for adults and children with epilepsy, and adults with TRD. There is some uncertainty about the appropriateness of VNS for different types of epilepsy and the use of VNS for depression. This topic was selected for a health technology assessment because of high concerns for the safety of VNS and medium concerns around efficacy and costs.

This evidence review will help inform Washington's independent Health Technology Clinical Committee as the committee determines coverage regarding VNS for epilepsy and depression.

Key Questions

Epilepsy

1. What is the evidence on the efficacy and effectiveness of VNS in adults and children with epilepsy?
2. What direct harms are associated with VNS in adults and children with epilepsy?
3. Do important efficacy/effectiveness outcomes or direct harms of VNS in adults and children with epilepsy vary by:
 - a. Patient characteristics (e.g., age, time since diagnosis)
 - b. Type of seizure
 - c. Duration of treatment

- d. Intensity of treatment
- 4. What are the cost-effectiveness and other economic outcomes of VNS in adults and children with epilepsy?

Depression

1. What is the evidence on the efficacy and effectiveness of VNS in adults with TRD?
2. What direct harms are associated with VNS in adults with TRD?
3. Do important efficacy/effectiveness outcomes or direct harms of VNS in adults with TRD vary by:
 - a. Patient characteristics (e.g., age)
 - b. Duration or type of depression (e.g., unipolar vs. bipolar)
 - c. Duration of treatment
 - d. Intensity of treatment
4. What are the cost-effectiveness and other economic outcomes of VNS in adults with TRD?

Scope

Epilepsy

Study Component	Inclusion	Exclusion
Populations	Adults and children (aged 4 and older) with epilepsy	<ul style="list-style-type: none"> • Studies including individuals with suspected epilepsy • Studies including individuals with seizures related to conditions other than epilepsy • Studies in individuals with pseudoseizures • Studies focused on the treatment of status epilepticus alone
Interventions	VNS alone, or in combination with treatment as usual (e.g., antiepileptic medications) tVNS alone, or in combination with treatment as usual (e.g., antiepileptic medications)	<ul style="list-style-type: none"> • Other CNS or vagal nerve stimulation techniques
Comparators	<ul style="list-style-type: none"> • Antiepileptic medication • Surgery • Other types of brain stimulation (invasive or noninvasive) • Sham VNS • VNS at a subtherapeutic level • No treatment 	<ul style="list-style-type: none"> • Studies without a comparator intervention • Studies with indirect comparisons • Studies with an outdated comparator or a comparator intervention not available in the U.S.
Outcomes	<ul style="list-style-type: none"> • Primary outcomes: seizure frequency • Secondary outcomes: seizure cessation; seizure severity (measured with a validated tool); seizure duration; treatment withdrawal; mood or cognitive changes (e.g., 	<ul style="list-style-type: none"> • Other outcomes • Cost of VNS from studies performed in non-U.S. countries • Cost of VNS from studies performed in the U.S. that are older than 5 years

Study Component	Inclusion	Exclusion
	<ul style="list-style-type: none"> depression, memory); quality of life (measured with a validated tool) • Safety: harms directly related to VNS (e.g., infection or hoarseness); reimplantation; failure rate • Economic: cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per QALY, ICER) 	
Setting	<ul style="list-style-type: none"> • Any outpatient or inpatient clinical setting in countries categorized as <i>very high</i> on the UN Human Development Index¹¹ 	<ul style="list-style-type: none"> • Nonclinical settings (e.g., studies in healthy volunteers) • Countries categorized other than <i>very high</i> on the UN Human Development Index¹¹
Study design	<ul style="list-style-type: none"> • Key Questions 1–4 <ul style="list-style-type: none"> ○ Randomized controlled trials ○ Nonrandomized, comparative studies with 10 or more participants in each group • Additional studies/data for Key Questions 2 and 3 (harms) <ul style="list-style-type: none"> ○ Governmental or other large, multisite registries with 100 or more participants and databases containing reports of procedure-related harms or device recalls (e.g., FDA MAUDE database, FDA Medical Device Recall database) • Additional studies/data for Key Question 4 <ul style="list-style-type: none"> ○ Cost-effectiveness studies and other formal comparative economic evaluations 	<ul style="list-style-type: none"> • Abstracts, conference proceedings, posters, editorials, letters • Nonrandomized, comparative studies with fewer than 10 participants in each group • Studies without a comparator • Proof-of-principle studies (e.g., technology development or technique modification) • Studies with harms outcomes for an intervention not included in Key Question 1 • Registries with fewer than 100 participants
Publication	<ul style="list-style-type: none"> • Studies in peer-reviewed journals, technology assessments, or publicly available FDA or other U.S. government reports • Published in English • Published since June 2009 (search date in the original HTA report) 	<ul style="list-style-type: none"> • Studies with abstracts that do not allow study characteristics to be determined • Studies that cannot be located • Duplicate publications of the same study that do not report different outcomes or follow-up times, or single site reports from published multicenter studies • Studies in languages other than English

Abbreviations. CNS: central nervous system; FDA: U.S. Food and Drug Administration; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; tVNS: transcutaneous VNS; UN: United Nations; VNS: vagal nerve stimulation.

Depression

Study Component	Inclusion	Exclusion
Populations	Adults (aged 18 and older) with TRD	<ul style="list-style-type: none"> • Studies including individuals with depression responsive to treatment • Studies including individuals with postpartum depression
Interventions	VNS alone, or in combination with treatment as usual (antidepressant medications or non-pharmacological therapies) tVNS alone, or in combination with treatment as usual (antidepressant medications or non-pharmacological therapies)	<ul style="list-style-type: none"> • Other CNS or vagal nerve stimulation techniques
Comparators	<ul style="list-style-type: none"> • Antidepressant medication • Non-pharmacological treatments (e.g., CBT) • Other types of invasive or non-invasive brain stimulation (e.g., ECT) • Sham VNS • VNS at a subtherapeutic level • No treatment 	<ul style="list-style-type: none"> • Studies without a comparator intervention • Studies with indirect comparisons • Studies with an outdated comparator or a comparator intervention not available in the U.S.
Outcomes	<ul style="list-style-type: none"> • Primary outcomes: depression severity (measured using a validated tool) • Secondary outcomes: mortality; suicidal ideation and severity; response and duration of response; remission and duration of remission; treatment withdrawal; compliance with other depression treatments; anxiety (measured using a validated tool); cognitive changes (e.g., memory); quality of life (measured using a validated tool), including sleep • Safety: harms directly related to VNS (e.g., infection or hoarseness); reimplantation; failure rate • Economic: cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per QALY, ICER) 	<ul style="list-style-type: none"> • Other outcomes • Cost of VNS from studies performed in non-U.S. countries • Cost of VNS from studies performed in the U.S. that are older than 5 years
Setting	<ul style="list-style-type: none"> • Any outpatient or inpatient clinical setting in countries categorized as <i>very high</i> on the UN Human Development Index¹¹ 	<ul style="list-style-type: none"> • Nonclinical settings (e.g., studies in healthy volunteers) • Countries categorized other than <i>very high</i> on the UN Human Development Index¹¹
Study design	<ul style="list-style-type: none"> • Key Questions 1–4 <ul style="list-style-type: none"> ◦ Randomized controlled trials ◦ Nonrandomized, comparative studies with 10 or more participants in each group 	<ul style="list-style-type: none"> • Abstracts, conference proceedings, posters, editorials, letters • Nonrandomized, comparative studies with fewer than 10 participants in each group

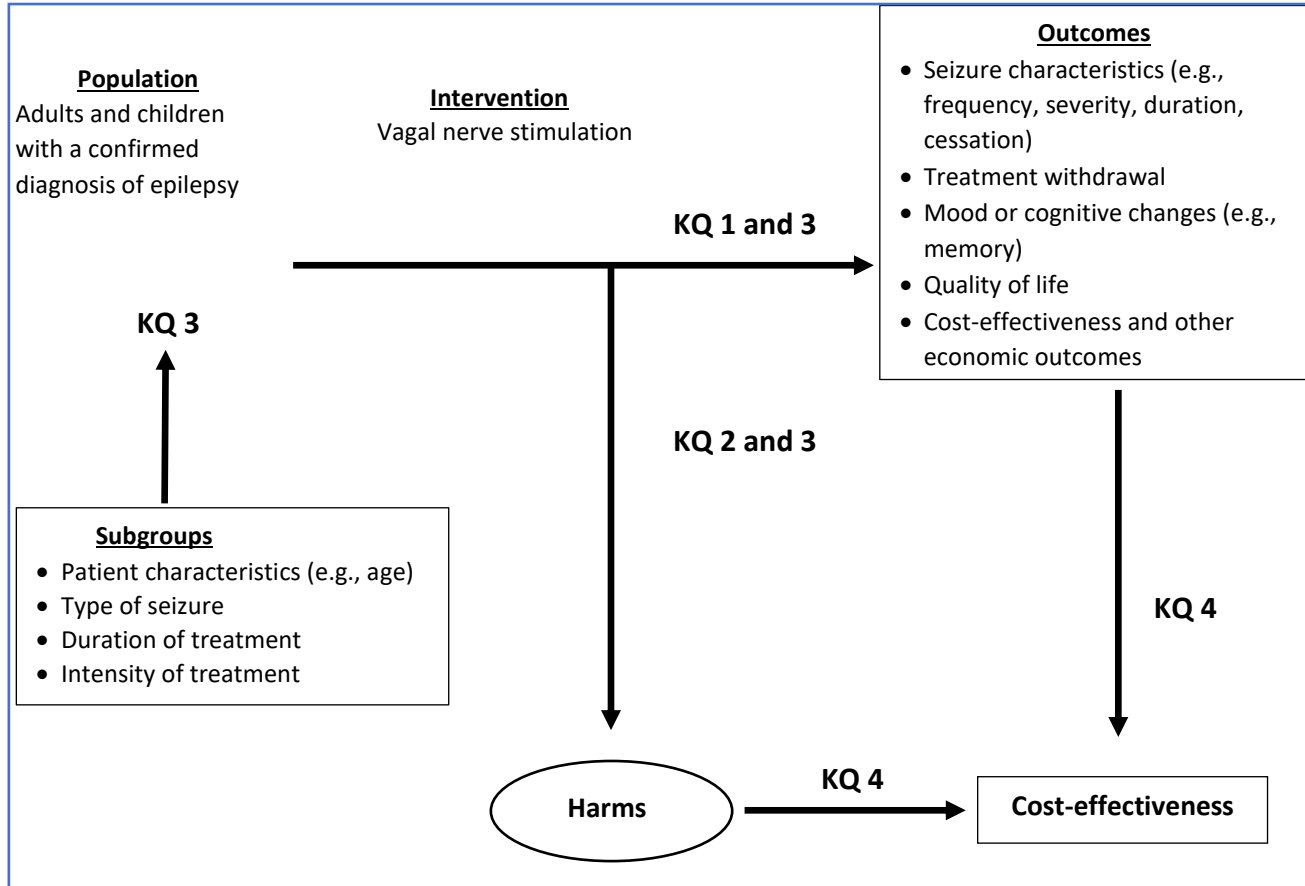
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Abbreviations. CBT: cognitive behavioral therapy; CNS: central nervous system; FDA: U.S. Food and Drug Administration; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; TRD: treatment-resistant depression; tVNS: transcutaneous VNS; UN: United Nations; VNS: vagal nerve stimulation.

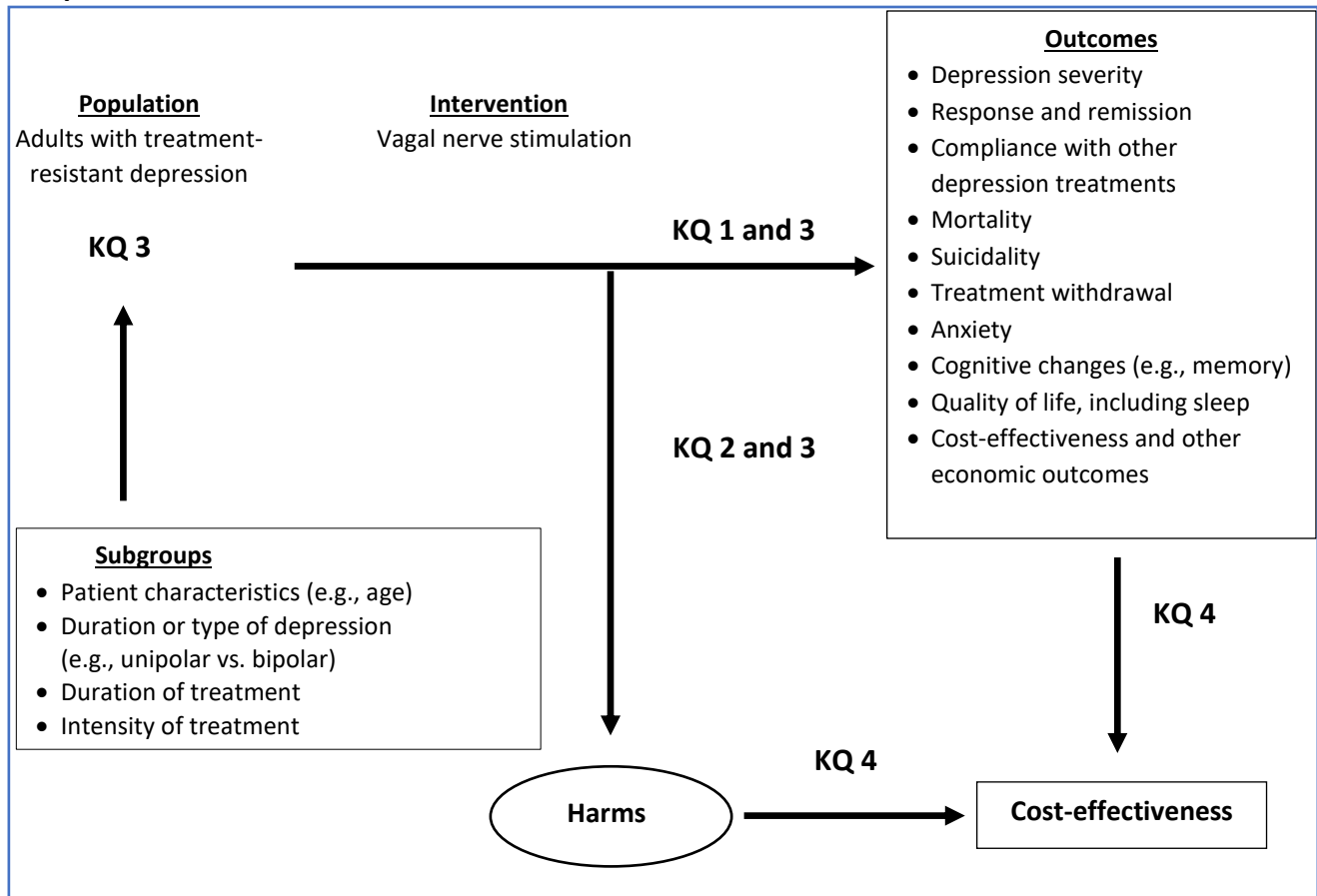
Analytic Framework

The analytic frameworks below will guide the selection, synthesis, and interpretation of available evidence.

Epilepsy



Depression



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