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CANMAT 2023 UPDATE:
CLINICAL GUIDELINES FOR THE MANAGEMENT OF MDD IN ADULTS

QUESTION 8

When Should Neuromodulation Treatments Be Used?

What are neuromodulation treatments?

Treatments that alter CNS activity through application of electrical or magnetic stimulation of the brain

Usually used when initial therapies are unsuccessful

Can be non-invasive or surgical

CNS, central nervous system.

Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Types of neuromodulation treatments

Noninvasive treatments

- Electroconvulsive therapy (ECT)
- Repetitive transcranial magnetic stimulation (rTMS)
- Transcranial direct current stimulation (tDCS)
- Magnetic seizure therapy (MST)

Surgical treatments

- Vagus nerve stimulation (VNS)
- Deep brain stimulation (DBS)

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Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Recommendations for neuromodulation treatments

Line of treatment	Neuromodulation treatment	Level of evidence	
		Acute efficacy	Maintenance efficacy
1st Line	ECT for severe MDE*		
	rTMS for TRD		
2nd Line	ECT for DTD		
3rd Line	Adjunctive use of tDCS for mild-moderate MDE		
	VNS for DTD		
Investigational	DBS for DTD		Not known
	MST for DTD		Not known

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

*With severe psychotic or catatonic features, severe suicidal ideation, or deteriorating physical condition.

DBS, deep brain stimulation; DTD, difficult-to-treat depression; ECT, electroconvulsive therapy; MDE, major depressive episode; MST, magnetic seizure therapy; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; TRD, treatment-resistant depression; VNS, vagus nerve stimulation.

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Noninvasive Neuromodulation Treatments

Electroconvulsive therapy (ECT)

- Electrical stimulus adjusted to individualized parameters transmitted to the brain via electrodes placed on scalp to induce a brief seizure (~30 seconds)
- Delivered under general anesthesia
- Acute course is 6 to 12 sessions
- Limitations:
  - Stigma
  - Concerns about cognitive adverse effects
  - High relapse rates after cessation

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Recommendations for ECT protocols

Line of treatment	ECT protocol	Level of evidence
1st Line	Brief pulse, bifrontal (at 1.5x seizure threshold)	●
	Brief pulse, right unilateral (at 1.5x seizure threshold)	●
	Ultrabrief pulse, right unilateral (at 6x seizure threshold)	●
2nd Line	Brief pulse, bitemporal (at 1.5x seizure threshold)	●
	Ultrabrief pulse, bifrontal (at 1.5x seizure threshold)	●

LoE, Level of Evidence ● Level 1 ◔ Level 2 ◑ Level 3 ◕ Level 4

ECT, electroconvulsive therapy.

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Efficacy and safety of ECT in acute treatment

- Response rates of 65% to 75% in TRD 
- Superiority to pharmacological intervention particularly for patients with:
  - Treatment resistant depression
  - Severe depression
  - Psychotic or catatonic features
  - Older patients
- Generally safe and well tolerated
  - Short-term cognitive effects usually resolve in days to weeks following cessation of ECT
  - Low potential for long-term cognitive effects or cardiac events
- Antidepressants can usually be continued 
- Benzodiazepines and anticonvulsants should generally be discontinued or held

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

ECT, electroconvulsive therapy; TRD, treatment-resistant depression.

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Efficacy and safety of ECT in maintenance treatment

- Recurrence rates of 60% to 80% after 6 months
- Maintenance strategy is recommended for prevention of recurrence:
  - Continued ECT more effective than maintenance pharmacotherapy
  - Combination of lithium and ADT more effective than ADT alone
  - No differences in cognitive outcomes
- Choice of strategy should be guided by:
  - Previous ECT responses
  - Previous trials of pharmacotherapy (i.e., after multiple failures)
  - Episode severity and degree of treatment resistance
  - Consequences of recurrence
  - Adverse effects
  - Patient preference

LoE, Level of Evidence  Level 1 Level 2 Level 3 Level 4

ADT, antidepressant; ECT, electroconvulsive therapy.

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Transcranial magnetic stimulation (rTMS)

- Stimulation or inhibition of cortical neurons using focused magnetic field pulses
- Externally applied over the scalp using a magnetic coil
- Does not require anesthesia
- No cognitive side effects
- 20 to 40 minutes per session, 5 days per week for 4 to 6 weeks (depending on type of rTMS and protocol)

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rTMS, repetitive transcranial magnetic stimulation.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

Recommendations for rTMS protocols

Line of treatment	rTMS protocol	Level of evidence
1st Line	iTBS to left DLPFC	
	High-frequency rTMS to left DLPFC	
	Low-frequency rTMS to right DLPFC	
2nd Line	Sequential bilateral rTMS to DLPFC (right low frequency then left high frequency)	
	Accelerated iTBS to left DLPFC	
	Sequential bilateral TBS to DLPFC (right continuous TBS then left intermittent TBS)	

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

DLPFC, dorsolateral prefrontal cortex; iTBS, intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation; TBS, theta burst stimulation.

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Efficacy and safety of rTMS

- Response rates of 40% to 50% in DTD
- Clinical features associated with lower remission rates:
  - Higher baseline symptom severity
  - Greater number of previous ADT trial failures
- Similar efficacy between accelerated iTBS and conventional rTMS protocols
- Concurrent ADT therapy may augment response rates
- Benzodiazepines may impair response rates

LoE, Level of Evidence Level 1 Level 2 Level 3 Level 4

ADT, antidepressant; DTD, difficult-to-treat depression; iTBS, intermittent theta burst stimulation; rTMS, repetitive transcranial magnetic stimulation.

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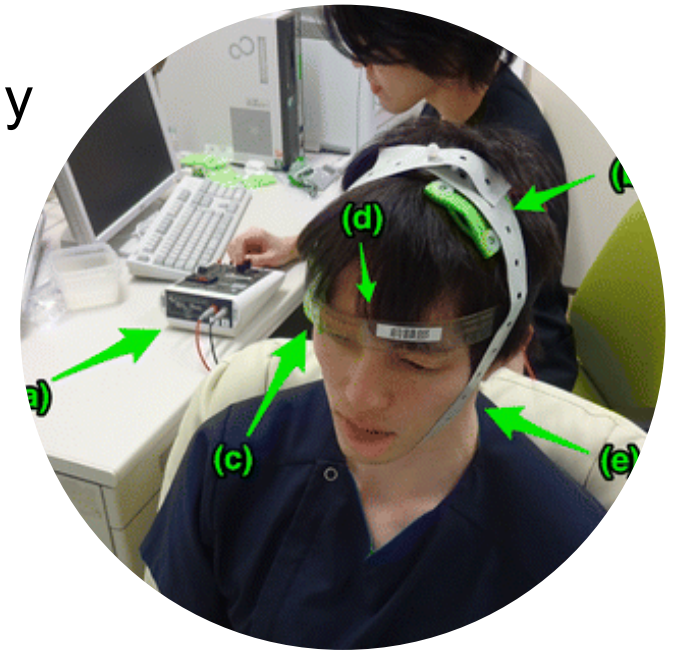
Transcranial direct current stimulation (tDCS)

- Modulates cortical excitability
- Scalp electrodes deliver constant, weak electrical current
- Effective for treatment of mild to moderate MDD especially when combined with an ADT
- Advantages:
  - Inexpensive equipment
  - Relative ease of use (e.g., can be delivered at home)
  - Few side effects or safety concerns



LoE, Level of Evidence Level 1 Level 2 Level 3 Level 4

ADT, antidepressant; MDD, major depressive disorder; tDCS, transcranial direct current stimulation.
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Magnetic seizure therapy (MST)

- Vertex or frontal placement of single or paired coils
- Elicits a generalized seizure
- Similar efficacy as right unilateral ultrabrief ECT with fewer cognitive side effects
- Investigational treatment due to lack of definitive studies 

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

ECT, electroconvulsive therapy; MST, magnetic seizure therapy.

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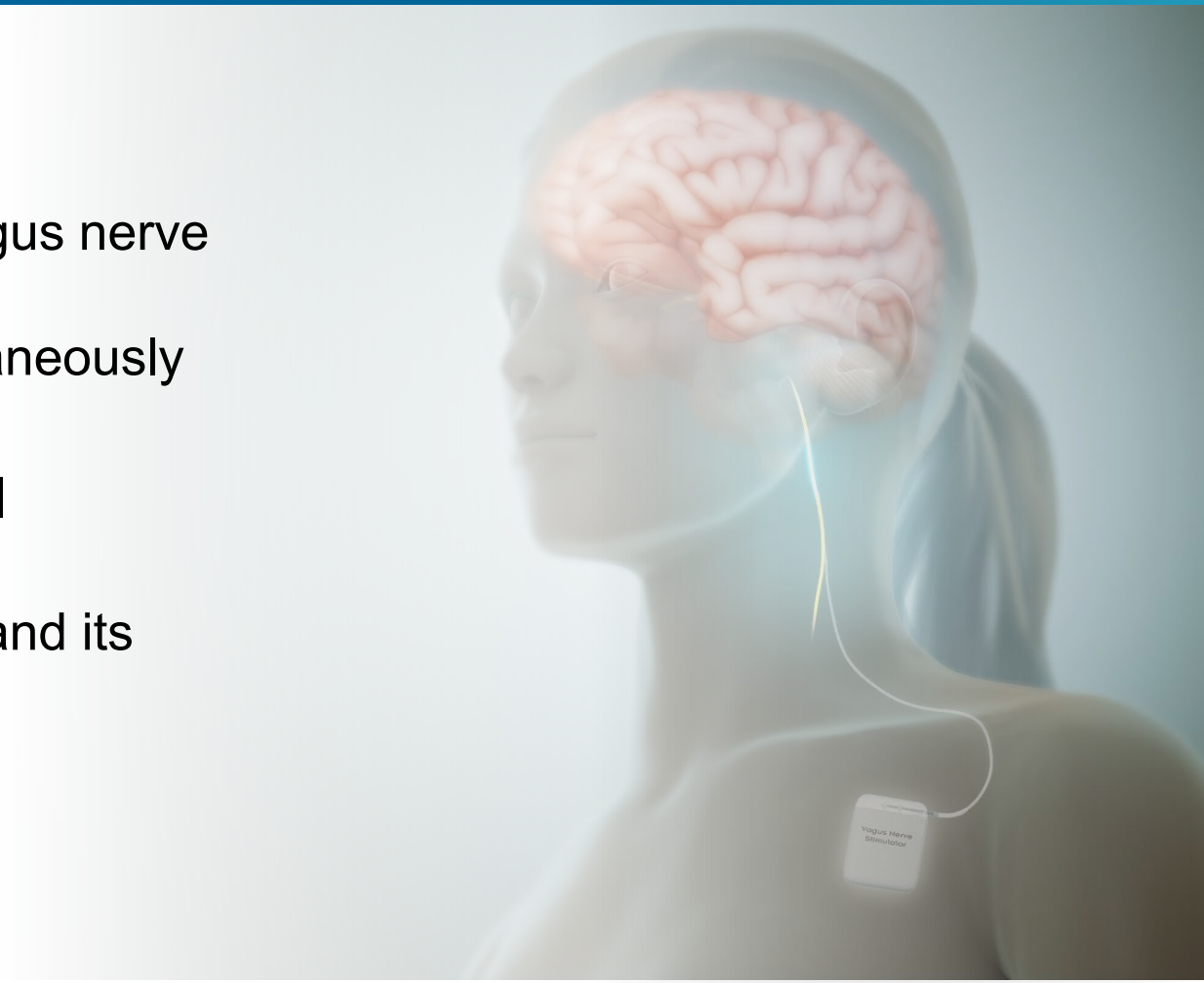
Surgical Neuromodulation Treatments

Vagus nerve stimulation (VNS)

- Implantable neurostimulation technology
  - Electrode coiled or wound around left vagus nerve (mid-cervical neck region)
  - Nerve pulse generator implanted subcutaneously in the chest area
- Generates low-level intermittent electrical stimulation to vagus nerve
  - Stimulates the nucleus tractus solitarius and its cortical/subcortical connections



VNS, vagus nerve stimulation.

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Efficacy and safety of VNS

- Approved for treatment of TRD in Canada in 2001
- RCTs failed to demonstrate superior efficacy to sham control conditions in short-term treatment
- Systematic reviews of open-label studies suggest superior response and remission rates vs. treatment as usual with longer-term treatment (2 to 5 years) in DTD 
- Generally safe and well tolerated

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

DTD, difficult-to-treat depression; RCT, randomized controlled trial; TRD, treatment-resistant depression; VNS, vagal nerve stimulation.

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Deep brain stimulation (DBS)

- Neurosurgical implantation of electrodes to specific brain regions
  - Connected to implantable pulse generator in the chest
  - Most frequent target is the subcallosal cingulate cortex
- Generates constant or intermittent electrical stimulation

DBS, deep brain stimulation.
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Efficacy and safety of DBS

- Inconsistent evidence in small, short-term clinical studies of patients with highly refractory illness
- Therapeutic effects increase over longer term treatment 
- Safety and tolerability profile:
  - Transient side effects associated with stimulation
  - Serious adverse events related to neurosurgery implantation

LoE, Level of Evidence  Level 1  Level 2  Level 3  Level 4

DBS, deep brain stimulation.

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Summary: Neuromodulation Treatments

When should neuromodulation treatments be selected?

- Noninvasive treatments are generally safe and well tolerated
  - Choice depends on side effect burden, feasibility, and patient burden
  - Can be considered 1st choice treatments in some clinical situations:
    - ECT 1st-line for severe illness (e.g., psychotic features, suicidal risk)
    - rTMS for patients with tolerability concerns with pharmacotherapy
  - rTMS should generally be considered before ECT

- Surgical treatments should generally be considered after noninvasive treatments
  - Lower level of evidence for efficacy
  - Greater associated risks

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