Interventional Psychiatry: Expanding Treatment Options for Patients

Benoit H. Mulsant, MD, MS, FRCPC, FRSC
Interim Chief of Staff

Faculty/Presenter Disclosure

Faculty: Benoit H. Mulsant

Relationships with commercial interests (past 5 years):

Grants/Research Support: Capital Solution Design LLC and HAPPYneuron: software used in studies founded by CAMH Foundation and Brain Canada

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Other: None

Potential for, and Mitigation of, Potential Bias

Potential for conflicts of interest:

Approved, off-label, and investigational interventions for mental disorders will be discussed, including specific devices and drugs.

Mitigation:

Generic names will be used.

The regulatory status of each intervention (approved, off-label, or research-only) will be identified explicitly.

Key Learning Objectives

At the conclusion of this session, the participants should be able to:

1. Describe the interventional treatments that are available in clinical practice (ECT, rTMS, ketamine, esketamine) and those available only in research settings (MST, tDCS, psilocybin and other psychedelics).

2. Compare the acute efficacy, long-term outcomes, and adverse effects of these interventions.

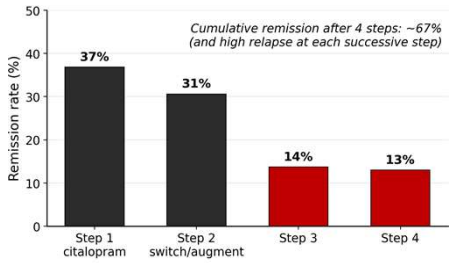
3. Identify which patients are most likely to benefit from each intervention and when to refer them.

Outline

- Why interventional psychiatry?
- Electroconvulsive therapy (ECT)
- Repetitive transcranial magnetic stimulation (rTMS)
- In research settings: MST and tDCS
- IV ketamine and intranasal esketamine
- Psilocybin and other psychedelics
- Questions

One Third of Patients Do Not Remit Despite Multiple Medication Trials

*STAR*D (N = 3,671): remission by sequential treatment step (QIDS-SR)*



Rush et al (2006) Am J Psychiatry; 163:1905-17

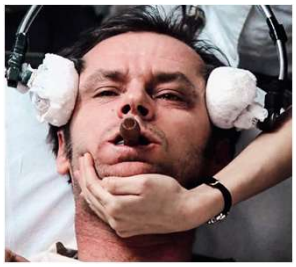
Patients (and Clinicians) Need More Options

- Antidepressants take 4–8 weeks to work: too slow when symptoms are severe (e.g., suicidality, catatonia, extreme dysfunction)
- Some patients do not tolerate antidepressants (e.g., sexual dysfunction, weight gain, emotional blunting; falls and hyponatremia in older adults)
- After 2 failed antidepressant trials, odds of remitting with a 3rd medication fall to below 1 in 4; with a 4th, below 1 in 5
- **Interventional psychiatry:** procedure-based treatments delivered under monitoring; not “last resorts” but structured treatments with specific indications

The Interventional Landscape in 2026

Intervention	How it is delivered	Status
ECT	Seizure under anesthesia, 2–3×/week	Approved; “gold standard”
rTMS	Magnetic pulses, awake, daily	Approved; expanding access
Esketamine	Intranasal, in-clinic monitoring	Approved for depression that is treatment-resistant or requires “urgent psychiatric care”
IV ketamine	Sub-anesthetic infusion, monitored	Off-label in specialized clinics
tDCS	Weak scalp current, portable	Not approved for mental disorders in Canada
Psychedelics	Drug + structured psychotherapy	Not approved
VNS, MST, DBS	*Other brain stimulation modalities*	*Not approved for mental disorders in Canada*

Electroconvulsive Therapy (ECT)



The oldest and still most effective treatment for severe depression

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1938-2026: From “Shock Therapy” to Modern ECT

- **1934:** Meduna treats psychosis with chemically induced generalized seizures (camphor, then pentylenetetrazol)
- **1938:** Cerletti & Bini deliver the first electrically induced seizure
- **1940s-50s:** Widely used but “unmodified” (no anesthesia; fractures, fear, lasting stigma)
- **1950s-60s:** Modified ECT with general anesthesia, muscle relaxation, oxygenation
- **1970s-80s:** Brief-pulse devices, EEG monitoring, individualized dosing
- **2000s:** Ultrabrief right unilateral ECT, preserving efficacy while sparing memory

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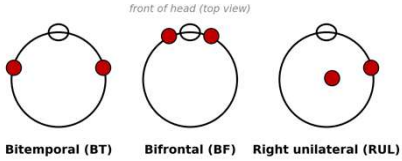
Modern ECT in Practice

- General anesthesia (methohexital, propofol, etomidate) + muscle relaxant (succinylcholine) + oxygenation
- A generalized seizure of ~20–60 seconds, monitored by EEG; patients wake within minutes
- 2–3 sessions/week; typical course 6–12 treatments, inpatient or outpatient
- Electrode placement, energy (pulse width, duration) are chosen to balance efficacy against memory effects



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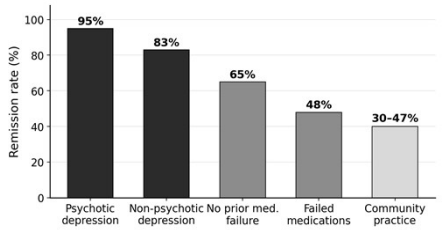
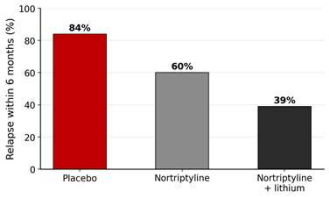
ECT: Still the Most Effective Acute Treatment for Major Depressive Disorder

Real vs. sham ECT: ~10-point advantage on depression scale; 2-3 times larger than antidepressant–placebo difference



UK ECT Review Group (2003) Lancet • Petrides et al (2001) J ECT • Heijnen et al (2010) J Clin Psychopharm • Prudic et al (2004) Biol Psychiatry

The Achilles' Heel of ECT: Relapse After Remission



- Without continuation treatment, most remitters relapse within 6 months
- Continuation pharmacotherapy (e.g., antidepressant + lithium) or continuation ECT cuts relapse in half
- Plan the continuation strategy *before* initiating ECT

Sackeim, Haskett, Mulsant et al (2001) JAMA • Kellner et al (2006) Arch Gen Psych (CORE) • Kellner et al (2016) Am J Psychiatry (PRIDE)

ECT: Safety amd Adverse Effects

- Mortality ≈ 2 per 100,000 treatments: among the safest procedures under general anesthesia
- Common and transient headache, muscle aches, nausea, post-ictal confusion
- Cognition: temporary anterograde learning difficulties (recover within ~2 weeks); retrograde amnesia (mostly autobiographical, around the treatment period) can persist for some patients
- Memory effects depend on technique: bitemporal > right unilateral; standard pulse > ultrabrief pulse
- No evidence of structural brain damage; yet stigma and media portrayals remain the main barrier

Tørring et al (2017) Acta Psychiatr Scand • Semkovska & McLoughlin (2010) Biol Psychiatry • Sackeim et al (2007) Neuropsychopharm

Which Patients Should Be Referred for ECT?

- When speed matters:

- Psychotic depression, catatonia, pregnancy
- Severe depression with acute suicide risk, refusal to eat
- Older and medically frail adults with physical deterioration

- **Prior good response to ECT; patient preference**
- **When a different approach is needed (12-18 months)**

Issues to discuss: anesthesia and cardia risks, consent, (no) driving or working during the course

Repetitive Transcranial Magnetic Stimulation (rTMS)

Focal, non-invasive stimulation
No anesthesia, no seizure, no drug exposure

Rapid magnetic pulses (~1.5–2 T) pass unimpeded through the skull

Induce a focal electrical current ~2–3 cm deep in the cortex

Repeated sessions re-tune activity in prefrontal–limbic mood circuits

From Curiosity to First-Line Option

- 1985: Barker builds the first modern TMS device (Sheffield, UK)
- 2002: Health Canada approves rTMS for major depressive disorder; 2008: FDA follows after the first industry pivotal trial
- 2016-2024 CANMAT guidelines: rTMS is a first-line recommendation for patients whose depression has failed at least one adequate antidepressant trial
- 2026 Ontario: provincial funding for hospital-based programs across the province including The Royal in Ottawa

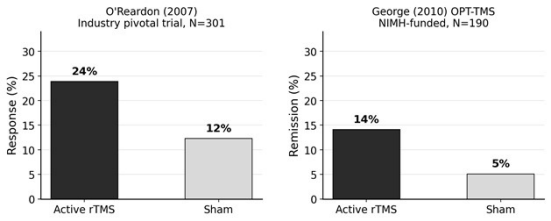
Barker et al (1985) Lancet • Milev et al (2016) Can J Psychiatry (CANMAT) • Lam et al (2024) Can J Psychiatry (CANMAT update)

What a Patient Experiences

- Awake and seated; no anesthesia or sedation; patients can drive to and from sessions
- The figure-8 coil rests on the scalp over the left dorsolateral prefrontal cortex (DLPFC); the energy is personalized, based on the motor threshold
- Loud clicking and a tapping sensation on the scalp
- Sessions lasts 3–37 minutes depending on the protocol:
  - High-frequency (10 Hz) — 37-mins, standard protocol
  - Intermittent theta burst (iTBS) — 3 mins, same efficacy
- 5 days/week for 4–6 weeks (20–30 sessions), often followed by a taper

rTMS Works — the Pivotal Trials

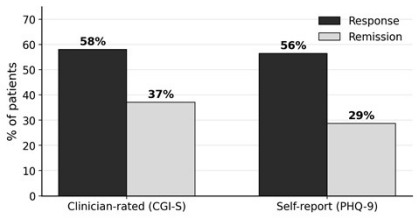
- In rigorously hard-to-treat patients, active rTMS roughly doubles response and remission vs. sham



O'Reardon et al (2007) Biol Psychiatry • George et al (2010) Arch Gen Psychiatry

In Real-World Practice, Outcomes Are Better

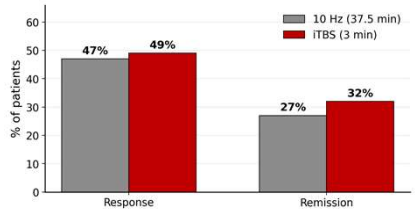
- Naturalistic outcomes across 42 US clinics (N = 307), on concurrent medications



Carpenter et al (2012) Depress Anxiety

THREE-D (CAMH): Three Minutes As Good As Thirty-Seven

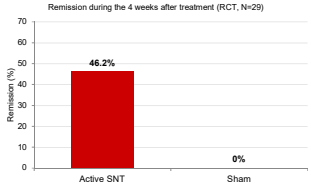
Largest rTMS trial to date (N = 414, three Canadian sites)
3-minute iTBS non-inferior to standard 37.5-minute 10 Hz protocol



Blumberger et al (2018) Lancet

Accelerated rTMS: The Stanford (SNT) Protocol

10 iTBS sessions per day for 5 days (~90,000 pulses)
Left DLFC individually targeted with functional MRI
Sham-controlled RCT in treatment-resistant depression
FDA-approved 2022
Caveats: small samples, limited availability, cost, still under study



Cole et al (2022) Am J Psychiatry

rTMS Beyond Major Depressive Disorder

- **OCD:** deep TMS (H-coil) approved by US FDA (2018) – Response: 38% vs. 11% sham when added to SRIs/ERP
- **Smoking cessation:** deep TMS approved by FDA (2020)
- **Anxious depression:** responds as well as non-anxious depression; anxiety symptoms improve too
- **Adolescents (15–21):** approved by FDA as an adjunct for MDD (2024)
- **Bipolar depression, PTSD, negative symptoms:** promising but still investigational

Carmi et al (2019) Am J Psychiatry • Zangen et al (2021) World Psychiatry

How Long Does the Benefit Last?

- About two thirds of acute responders maintain their benefit over 12 months, provided re-treatment is available when symptoms return (~1 in 3 need it)
- Re-induction works: most patients who responded once respond again
- Continuation schedules (e.g., tapering to weekly–monthly sessions) are used in practice; the evidence base is thin
- Relapse clusters in the first 3–6 months: almost all patients need continuation (and maintenance) pharmacotherapy

Dunner et al (2014) J Clin Psychiatry

rTMS: Adverse Effects and Contraindications

- Scalp discomfort at the stimulation site (~40%) and headache (~30%); both fade over the first week; acetaminophen works
- Seizure is very rare: with Figure-8 coil, ≈1 per 30,000–60,000 sessions with modern screening or less than ≈1 per 1000 patients (higher with deep-TMS H-coil ≈5 per 1000 patients)
- Rare hypomanic switch: monitor patients with possible bipolar
- No memory impairment, no systemic effects; hearing protection is mandatory
- **Contraindications:** seizure disorder; ferromagnetic metal or implanted stimulators in/near the head (cochlear implants, aneurysm clips or coils)

Perera et al (2016) Brain Stimulation • Rossi et al (2021) Clin Neurophysiol

Which Patients Should Be Referred for rTMS?

- MDD after 1–2 adequate antidepressant trials (each additional failed trial lowers the odds of response)
- MDD in patients who cannot tolerate 3-4 antidepressants, or who do not want to take antidepressants
- Must be able and willing to attend daily visits
- Comorbid anxiety is not a barrier

Screen for: seizure disorder, implanted devices or metal in head

rTMS is not the right approach for: psychotic depression, catatonia, imminent safety concerns

rTMS or ECT?

	rTMS	ECT
Effectiveness	Remission ~30%	Remission 50–80%
Procedure	No anesthesia, no seizure	General anesthesia + modified seizure
Burden	Daily × 4-6 weeks Can drive self	2-3/week × 3-4 weeks No driving
Cognitive effects	None	Typically transient memory effects
Best-suited patients	Moderate non-psychotic depression	Severe, psychotic, catatonic, urgent

Head-to-head meta-analyses favor ECT on efficacy; rTMS on tolerability and acceptability - Berlim et al (2013); Ren et al (2014)

Magnetic Seizure Therapy (MST): ECT's Efficacy Without the Amnesia?

- Like ECT, requires general anesthesia and a treatment series
- Like ECT, a seizure is still occurring, but it is induced with high-power magnetic pulses instead of an electrical current
- The induced field stays superficial and focal, sparing deep memory structures with a goal of ECT-like efficacy and minimal cognitive effects
- First human treatment in 2001; comparative trials vs. ECT (including the Canadian CREST-MST program) suggest comparable antidepressant effects with faster reorientation and less amnesia

Status: research only; no Health Canada or US FDA approval

Lisanby et al (2001) Arch Gen Psychiatry • Kayser et al (2011) J Psychiatric Res

Transcranial Direct Current Stimulation (tDCS): Promising, Portable, Investigational

- A weak (1–3 mA) direct current between scalp electrodes modulate cortical excitability
- No seizure; tingling, itching, skin redness; inexpensive; portable, home use is feasible
- Mixed evidence: better than sham but inferior to antidepressant in head-to-head trials
- Adverse effects: under electrodes

Status: investigational for depression in North America - Caution about personal (non-medical) devices bought online

Brunoni et al (2017) NEJM • Woodham et al (2024) Nature Medicine

IV Ketamine: A Different Kind of Antidepressant

- Anesthetic in use since 1970; blocks the NMDA glutamate receptor and triggers rapid synaptic plasticity (different from other antidepressant treatments)
- Acts as an antidepressant at a sub-anesthetic dose (0.5 mg/kg IV over 40 minutes); effect within hours of IV infusion, not weeks

Status: used off-label for depression in Canada and the US in specialized clinics with medical monitoring

Berman et al (2000) Biol Psychiatry • Krystal et al (2019) Neuron

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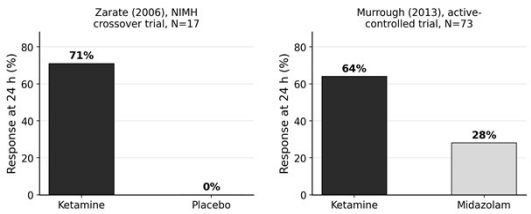
IV Ketamine: Antidepressant Effects Within 24 Hours

In treatment-resistant depression, a single infusion beats placebo or midazolam within one day



Zarate et al (2006) Arch Gen Psychiatry • Murrough et al (2013) Am J Psychiatry

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Beyond a Single Ketamine Infusion: Durability and Suicidality

- The benefit of a single infusion typically fades within 3–7 days
- Standard induction of 6 infusions over 2–3 weeks: response ~70%; median time to relapse ~18 days after the last infusion
- Maintenance infusions (weekly, then spaced out) preserve response in some patients; long-term RCT evidence is thin
- Suicidal ideation falls within 24 hours of an infusion making ketamine a potential intervention for acute risk

A bridge, not a substitute: needs to be paired with continuation pharmacotherapy, psychotherapy, from day one

Murrough et al (2013) Biol Psychiatry • Phillips et al (2019) Am J Psychiatry • Wilkinson et al (2018) Am J Psychiatry

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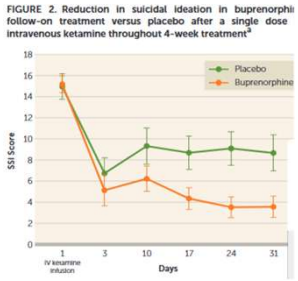
New Research: Continuation Treatment with Oral Buprenorphine Following IV Ketamine



- Randomized placebo-controlled trial (N=45 with Major Depressive Disorder)
- Low-dose oral buprenorphine, sustained and enhanced antisuicidal effects of a single dose of IV ketamine.

Tucciarone et al (2026) Am J Psychiatry

IV Ketamine: Logistics, Which Patients to Refer

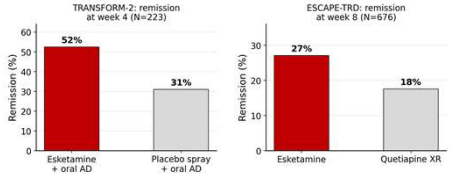
- Not publicly funded in Ontario; typically $300–800 / infusion
- During the infusion: dissociation; increased blood pressure & heart rate; nausea - transient, resolve within ~2 hours
- With long-term repeated (recreational) use: bladder toxicity, liver enzyme elevation
- Caution: uncontrolled hypertension, unstable cardiac disease, psychosis, active substance use disorder

Candidates: (future) alternative to ECT for treatment-resistant depression that needs rapid improvement (special role for suicidality?)

Swainson et al (2021) Can J Psychiatry (CANMAT)

Intranasal Esketamine: An Approved Alternative

- S-enantiomer of ketamine as a self-administered nasal spray, in clinic with 2-hour monitoring
- 56–84 mg twice weekly, then weekly every 2 weeks; approved with an oral antidepressant in Canada (2020); as monotherapy in US (2025)



Popova et al (2019) Am J Psychiatry • Reif et al (2023) NEJM

Intranasal Esketamine: Logistics, Which Patients to Refer

- Continuing esketamine cut relapse in ~half over ~6 months (27% vs. 45%) - Plan for ongoing dosing, not a short course
- Adverse effects during the 2-hour monitoring window: dissociation (~25%), dizziness, sedation, nausea, BP rise
- No take-home use; no driving until the next day.
  In real world: limited by capacity, cost, visit burden

Candidates: treatment-resistant depression; preferring an approved option, able to pay for it ($800 per session!) and to commit to frequent monitored visits

Daly et al (2019) JAMA Psychiatry (SUSTAIN-1) • Reif et al (2023) NEJM

Psilocybin-Assisted Therapy: A Drug Inside a Psychotherapy

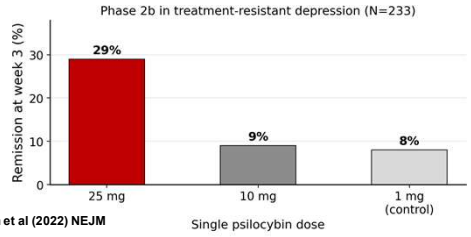
- A classic psychedelic (serotonin 5-HT2A agonist) from Psilocybe ("magic") mushrooms; synthetic formulations
- Not a standalone pill: one-hour preparatory session → 5-6 hour dosing session → one-hour integration session
- One or two doses — Not a daily medication

Status: research only — In Canada, access is through clinical trials or Health Canada's Special Access Program, assessed on a case by case basis (cost: $2,500-$6,000)

Goodwin et al (2022) NEJM • Health Canada Special Access Program (SAP)

Psilocybin: Current Evidence

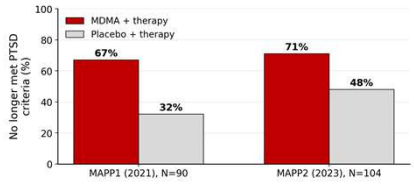
- Phase 2b: rapid benefit after a single 25 mg dose; wanes in many patients by week 12; acute anxiety and confusion; rare psychosis, suicidality
- Phase 3 (2025–26): both pivotal trials met their primary endpoints, with oa modest advantage (≈ 4 MADRS points); FDA submission in late 2026
- No evidence supports the effect of "micro-dosing"



Goodwin et al (2022) NEJM

MDMA ("Ectasy, Molly") for PTSD: Large Effects, Regulatory Setback

- After three MDMA-assisted therapy sessions, 67–71% no longer met PTSD criteria (among the largest effects ever reported in PTSD)
- FDA declined approval (2024) over unblinding, trial-conduct, and safety-data gaps; a new phase 3 is required



Mitchell et al (2021, 2023) Nature Medicine

The Broader Psychedelic Pipeline

LSD (MM120) for generalized anxiety: single 100 µg dose with no psychotherapy component: 65% response; 48% remission at week 12 (phase 2b, N=198); FDA breakthrough designation; first phase 3 read out positive (2026)

Short-acting tryptamines: DMT and 5-MeO-DMT compress the psychedelic session to under an hour. Early-phase trials in depression

Next generation: non-hallucinogenic "psychoplastogens" to keep the plasticity without the trip

None are approved: all remain research-only

JAMA (2025) MM120 phase 2b • MindMed (2026) phase 3 topline

Conclusion: Which Patient, Which Intervention?

Clinical picture	Consider
Psychotic depression, catatonia, imminent risk	ECT
Outpatient who did not respond to 1–2 trials	rTMS
Needs rapid improvement; prominent suicidality	ECT; IV ketamine or IN esketamine
Wants an approved medication after oral failures	IN esketamine
Cannot tolerate oral antidepressants	rTMS; IV ketamine; ECT
Interested in psychedelic approaches	Referral to a clinical trial

Conclusion: Some Take-Home Points

- Interventional psychiatry is now mainstream care, not the “last resort”
- ECT remains the most effective treatment for severe depression; modern technique has transformed its safety and tolerability
- rTMS is a first-line. Refer early, when the odds are best
- Ketamine and esketamine work quickly speed
- Psychedelics are promising. Cannel interested patients toward trials
- Plan continuation (long-term) treatment from day one

Thank you — questions & discussion