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rTMS & KETAMINE: TREATMENT RESISTANT DEPRESSION

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Conflict of interest statement

- Employer: Nova Scotia Health Authority
- Stocks: None
- Research Grants: None
- Honoraria: Occasional academic talks

Depression

- Depression is a heterogeneous group of disorders involving multiple neurotransmitter systems.
- Conventional antidepressant medications primarily modulate monoaminergic neurotransmitters.
- Antidepressants have marginal benefit (10-20%) over placebo.
- 30-40% of depressed patients do not respond to conventional antidepressants.
- One-third of patients have treatment-resistant depression (failure to respond to two or more antidepressant medications).

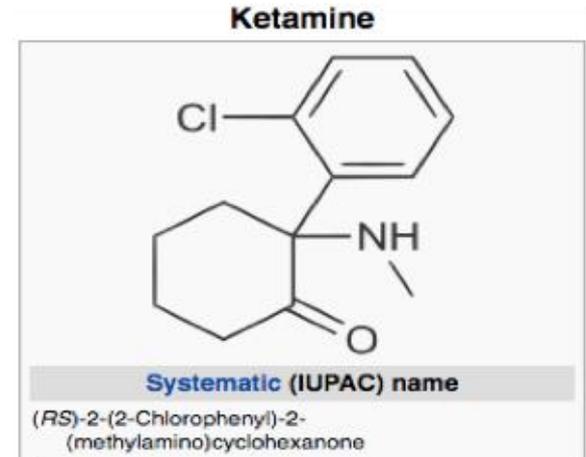
What is Treatment Resistant Depression?

- Conventional psychiatric medications for depression target monoaminergic neurotransmitters with limited benefit.
- Novel medications targeting non-monoaminergic neurotransmitters offer the hope of improved treatments.
- Ketamine and rTMS have been identified as treatment options for treatment resistant depression

INTRO TO KETAMINE

What is Ketamine?

- Ketamine is a phencyclidine (PCP) derivative
- Classified as an anesthetic and is a schedule III drug in the US
- Depending on dosage, produces a Trance-Like state, pain relief, sedation and memory loss
- Also widely used in veterinary medicine



History of Ketamine (1/2)

- First synthesized in 1962 by American Scientist Calvin Stevens
- Originally named CI-581 and was intended as an anesthesia drug
- Derived as a derivative of PCP which was first synthesized in 1926. PCP produced anesthetic effects but often left patients in unmanageable and distressing behavioral state after exposure to the drug
- Ketamine is a more suitable alternative to PCP, it causes less behavioural disturbance and fewer adverse effects



Photo of Calvin Stevens

History of Ketamine (2/2)

- First clinical use was in Belgium in 1963 as a veterinary anesthetic
- First Human testing was in 1964 where it was found to have a shorter duration and less hallucinogenic side effects than PCP
- First known recreational use of Ketamine was in 1965 by noted Professor Edward Domino who noted potent psychedelic effects and coined the term “Dissociative Anesthetic”

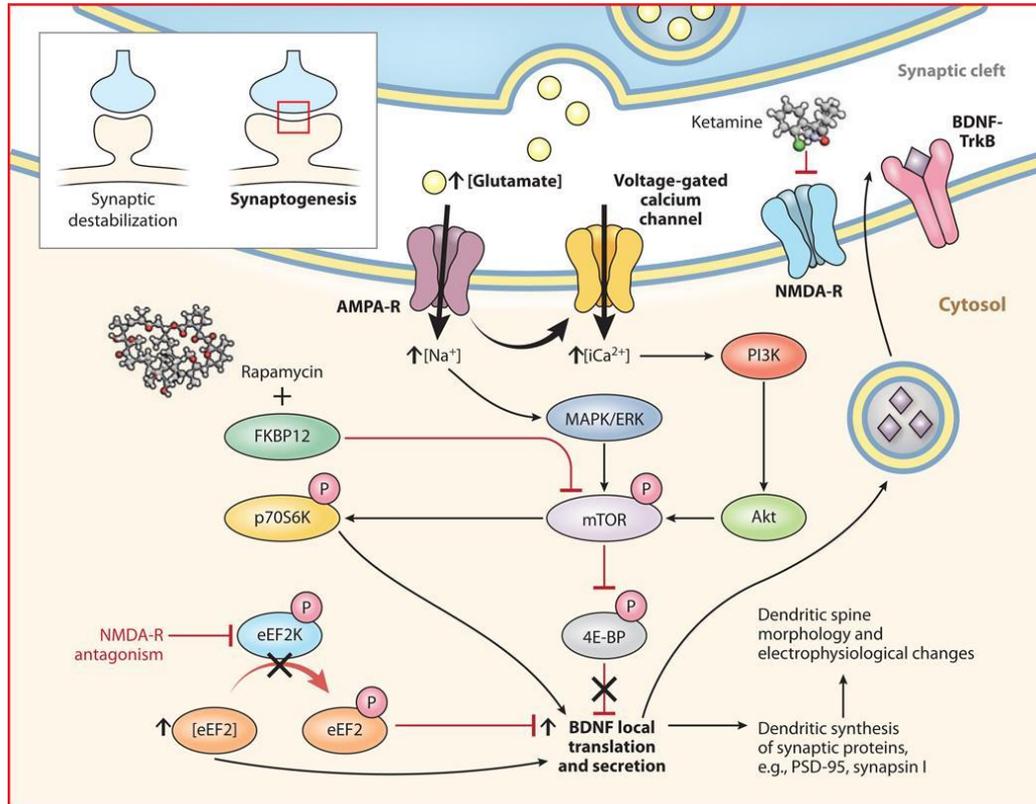
Ketamine use in psychiatric disorders

- Ketamine is a promising treatment for some people with treatment-resistant depression.
- Bipolar depression, PTSD, and OCD could potentially benefit from ketamine treatment as well.
- In the short-term, it is relatively safe; long-term safety potential needs further investigation.

Ketamine Mechanism of Action for Depression

- Postsynaptic NMDA receptor antagonism increases presynaptic glutamate release (i.e., glutamate “surge”). Glutamate is then hypothesized to increase AMPA/NMDA receptor flux. AMPA channel opening in the CNS increases sodium and, indirectly, calcium, stimulating the PI3K cascade
- *Ketamine is a known NMDA receptor antagonist. And there’s a high density of NMDA receptors in the prefrontal cortex, in pyramidal cells, in the hippocampus and that if NMDA receptors are blocked, it could translate to increased glutamate outflow in particular brain regions that are involved in mood regulation*

Ketamine Mechanism of Action for Depression



Ketamine for Treatment of Depression

- Multiple small studies have shown immediate and profound alleviation of depression symptoms in up to 75% of patients that have been refractory to conventional anti-depressants.
- Length of anti-depressant results varied but majority of patients went 2 months or greater before booster treatment needed.

Ketamine Efficacy

- Ketamine has emerged as a prototypical rapid-acting antidepressant.
- Early efficacy studies showed a high rate of response (64% to 71%) to a single dose of ketamine among individuals with treatment-resistant depression.
- Clinical reports of the effectiveness of ketamine in clinical samples is 50%.
- This discrepancy between efficacy and effectiveness is not unexpected and can frequently be seen as new treatments are taken from clinical trials to real world settings.

Ketamine Adverse Effects

- Changes in cognitive abilities and schizophrenia-like symptoms are noted among frequent ketamine recreational users.
- Compared to other groups such as ex-ketamine users and non-ketamine polydrug users, frequent ketamine users have shown impairments in spatial working memory as well as pattern recognition task.

How much ketamine is too much?

There are legitimate concerns of the long-term effects of ketamine on cognition and abuse. There have been no systematic reports of iatrogenic addiction or persistent psychosis thus far from the studies that examined the therapeutic effect of ketamine in mood disorders.

INTRO TO rTMS

What is rTMS?

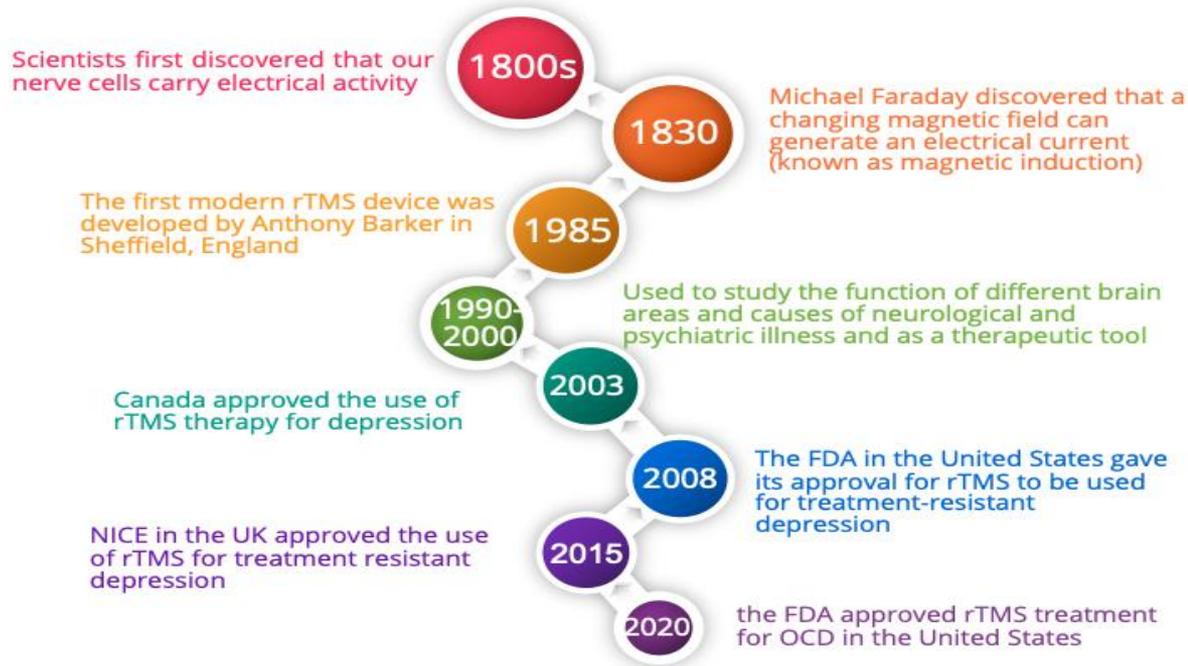
- rTMS is a brain stimulation technique
- High intensity current (through a magnetic coil placed on the head) can produce a magnetic field that stimulates the brain tissue.
- rTMS uses an electromagnetic field to stimulate areas of the brain that are underactive or overactive, gradually returning them to healthy patterns of activity.
- Uses an electromagnetic field to non-invasively stimulate cortical neurons.
- rTMS uses powerful, focused magnetic field pulses that are applied using a magnetic coil placed against the scalp, over the target brain region.
- Produced at either Low Frequency or High Frequency
- When applied repeatedly, these pulses can strengthen or weaken the connections between neurons, known as synapses.
- The long-lasting changes in neural connections can achieve lasting changes in brain activity, reversing the abnormal patterns associated with depression or other conditions

TYPES OF rTMS TREATMENT

- TMS encompasses a wide spectrum of treatments.
- Aside from a single TMS stimulation, repetitive TMS, and deep TMS, strategies for using rTMS vary based on:
 - types of coils,
 - region of the brain stimulated (i.e., left or right dorsolateral prefrontal cortex, or bilateral),
 - “dose” (e.g., intensity, percent of resting motor threshold (% RMT)),
 - speed of pulses (i.e., Hz, pulses per second),
 - pulse train duration,
 - inter-train interval,
 - trains per session,
 - total number of pulses
 - number of weekly sessions, duration (i.e., 2 to 6 weeks), and total number of sessions.

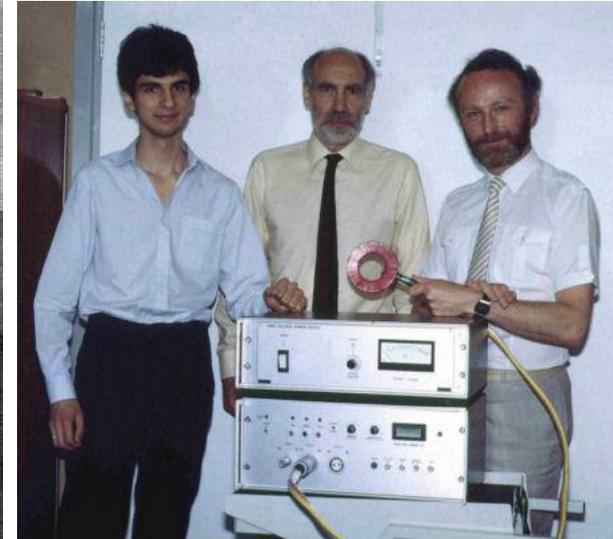
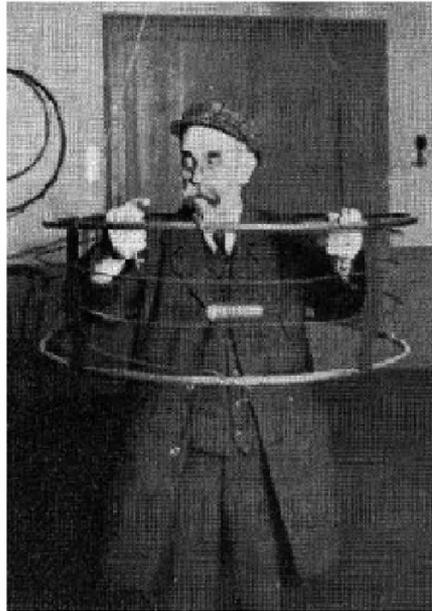
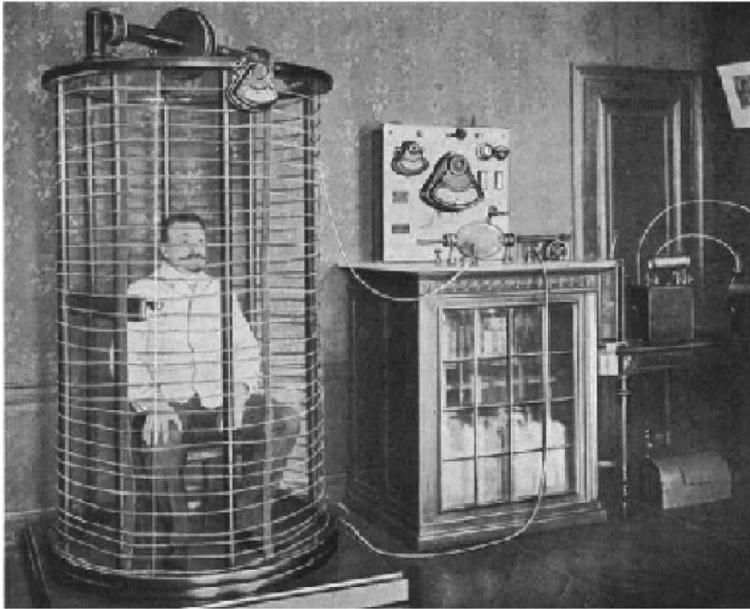
History of rTMS

1800
1830s
1985
1990s
2000s
2003
2008
2015
2020



History of rTMS

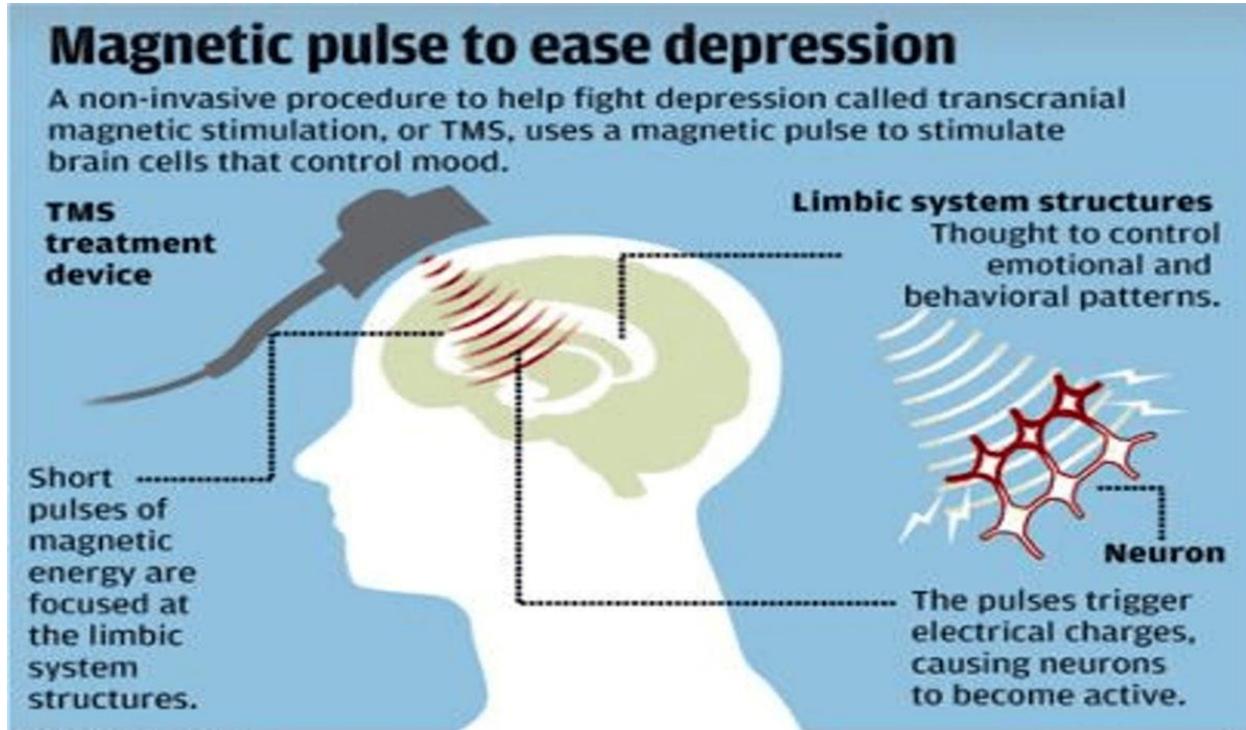
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EXAMPLES OF rTMS DEVICES



rTMS Technology



J Clin Psychiatry. 2018 ; 79(1): . doi:10.4088/JCP.16cs10905.

Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression

- HF rTMS DLPFC: 29 RCTs, 1371 patients
 - Response: OR 3.3 NNT 6
 - Remission: OR 3.3 NNT 7

REVIEW

Clinically Meaningful Efficacy and Acceptability of Low-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) for Treating Primary Major Depression: A Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials

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- 38% vs 15% responders OR 3.35
- 35% vs 10% remitters OR 4.76

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments

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- rTMS is now a first-line recommendation for patients with MDD who have failed at least 1 antidepressant
- ECT remains a second-line treatment for patients with treatment-resistant depression, although in some situations, it may be considered first line
- Third-line recommendations include tDCS and VNS