

## Interventions for Relapsing Depression: TMS, ECT, and Ketamine

MDD top cause of disability; suicide only top-10 cause of death currently increasing.

10-15% lifetime prevalence

A third of patients do not respond after multiple rounds of meds.

Remission with lithium-augmentation in third round of STAR\*D  
16%

13.7% of all level 3 patients remitted; a third of those well after 12 months.

Other approaches being investigated:

neutraceuticals, probiotics, nicotine, suboxone, psilocybin,  
hyperthermia, dopamine agonists, ketamine and derivatives

Neurostimulation:

Invasive devices: VNS,\* DBS

Non-invasive: tDCS, CES, ...

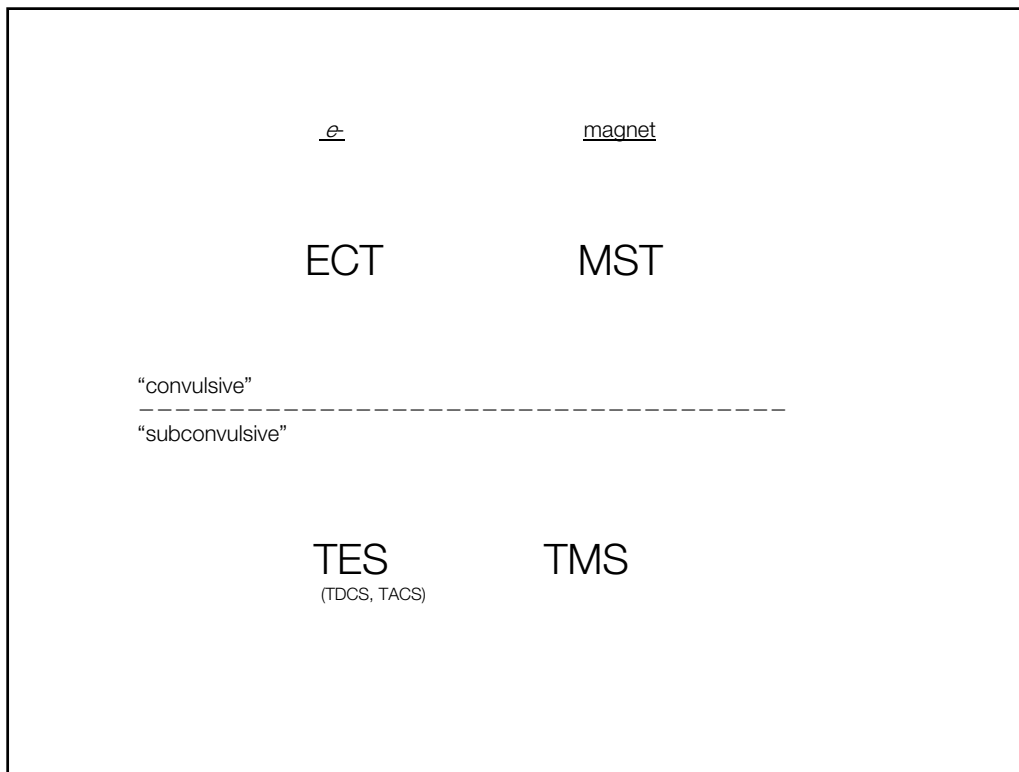
ECT\*\* and TMS: routinely covered, evidence for TRD, and  
regulatory approval

### Non-Invasive Brain Stimulation

*all generate electrical current in the brain.*

1. Current vs. magnetic field at site of stimulation?

2. Seizure or not?



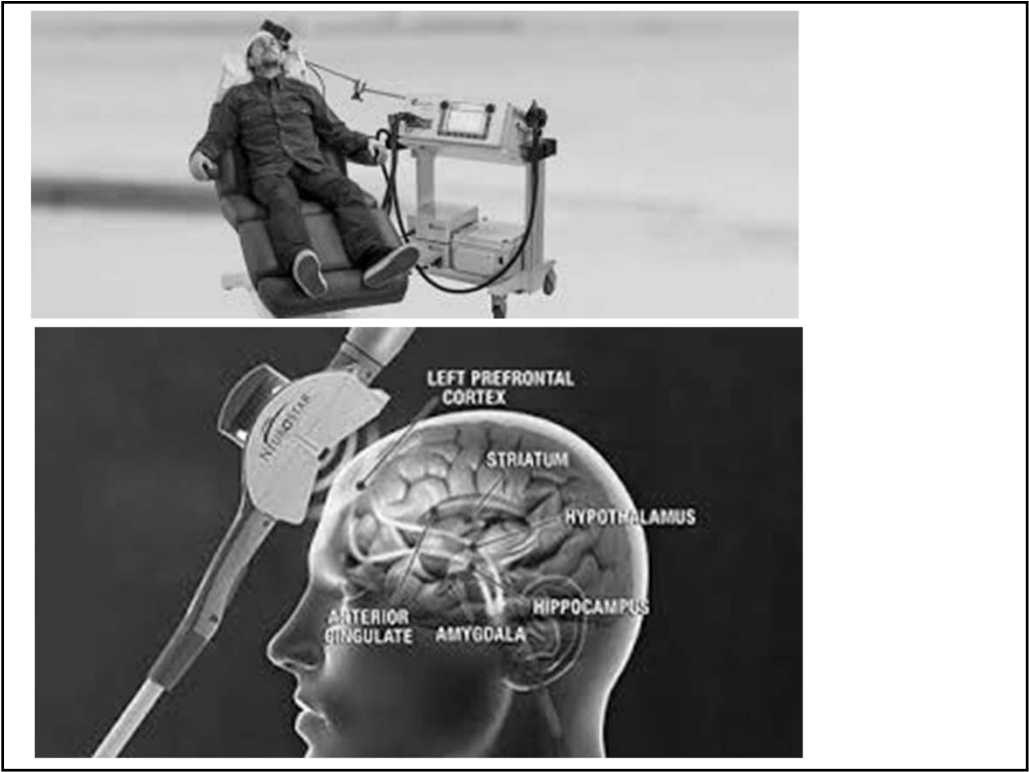
**TMS**

Why magnets:

- Faraday; cortex as conductive material
- Motor threshold for determining dose
- Activation of DLPFC and associated networks: monamine turnover, BDNF, HPA axis
- No cognitive side effects

Why subconvulsive:

- Anesthesia not used. Fewer staff, lower costs, scalable
- Less stigma, no activity restrictions



### Efficacy and Safety

- 2018 Consensus Recommendations for the Clinical Application of rTMS in the Treatment of Depression. APA and NNDC task forces
  - “Multiple randomized controlled trials and published literature have supported the safety and efficacy of rTMS antidepressant therapy.
- Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).
  - There is a sufficient body of evidence to accept with level A (definite efficacy) the antidepressant effect of HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC).

### Discussing Safety with Patients



**Patient selection**

Severe depressive episode, not responding to meds

Can attend brief sessions every weekday for 4-6 weeks.

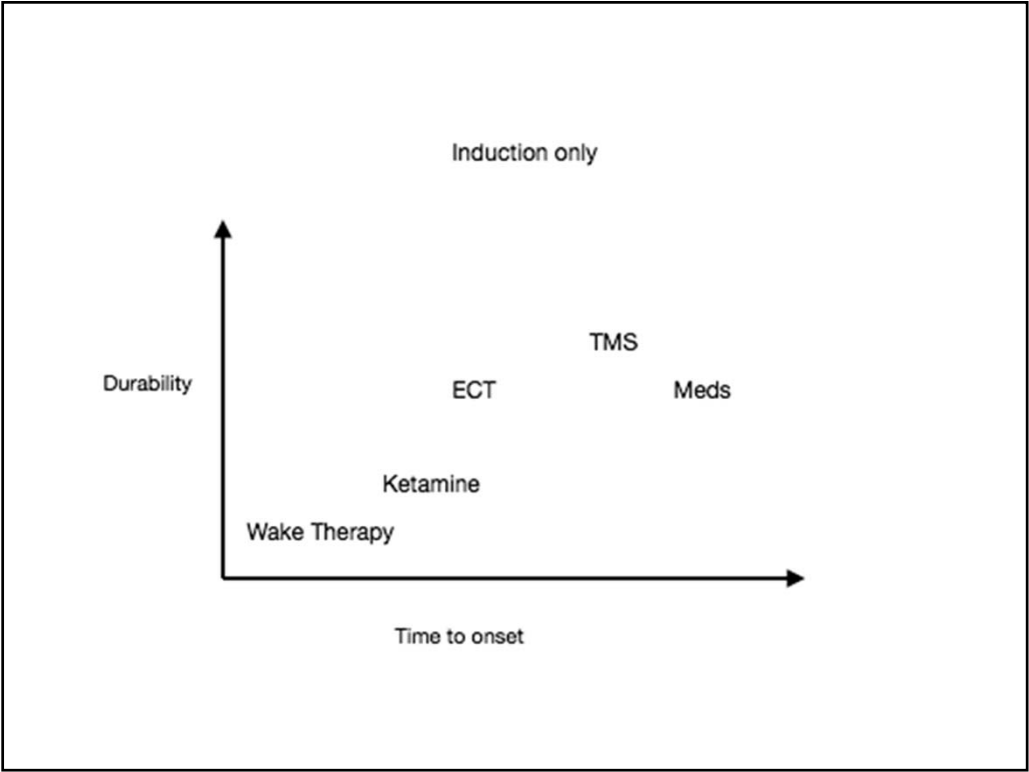
Chronic SI and anxiety disorders are common

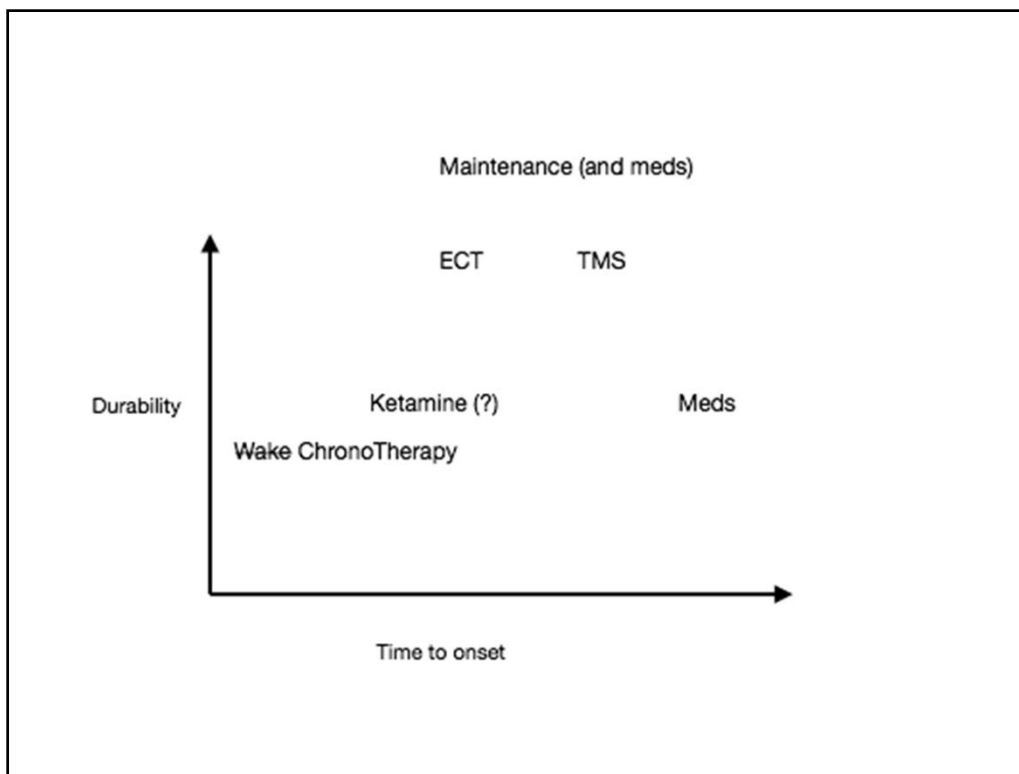
Compatible with ongoing psychotherapy, group therapy, IOP, etc.

**Not manic or mixed, psychotic, acutely suicidal.**

If ECT is an antipsychotic, mood stabilizer, antidepressant...

...then TMS is just an antidepressant.





### Cost Trends

#### ECT:

performance continues improving with "modern ECT"  
anesthesia, staff requirements limit potential for cost reduction  
facility bound (payer rules against even ASC)

#### TMS:

v1: high variable costs, 37 min. session  
v2: "generic" systems, 17 min. session  
v3: ultra rapid (theta burst) 3-4 min. session, FDA cleared protocol in 2018

### Ketamine

#### Brain Stimulation-Like:

High percentage of drug-resistant patients respond

Rates between TMS and ECT

Dosed intermittently and facility-bound

TMS in clinics, ECT in hospitals, Ketamine in clinics with IV, RN

#### Drug-like:

“Bottom-up” MOA: NMDA, AMPA?, opioid systems

Durability of benefit in drug-resistant population being studied

For severe depression, suicidal ideation, chronic pain; NOT psychotic

Sessions twice per week for several weeks.

Mildly dissociative or drowsy for up to an 1 hour post infusion.

When chronically abused at high doses cognitive or systemic (cystitis) side effects reported

#### Dependency/MOA controversy:

Naltrexone blocks antidepressant but not dissociative effects

Short term opioid effect + NMDA antagonism for longer term benefit

### Summary

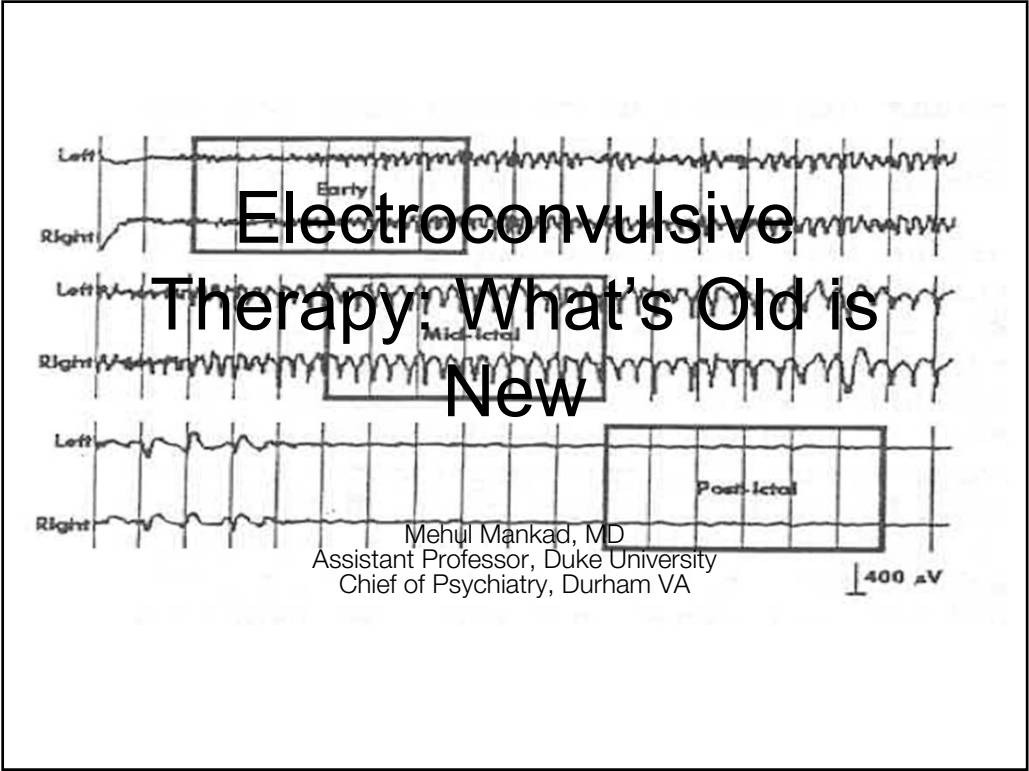
Drug-resistant depression a growing problem

The safety and efficacy of TMS and ECT for TRD are well established.

For many cases of severe depression, TMS fills a gap between drug resistance and ECT

Longer term safety and efficacy of Ketamine being studied and debated

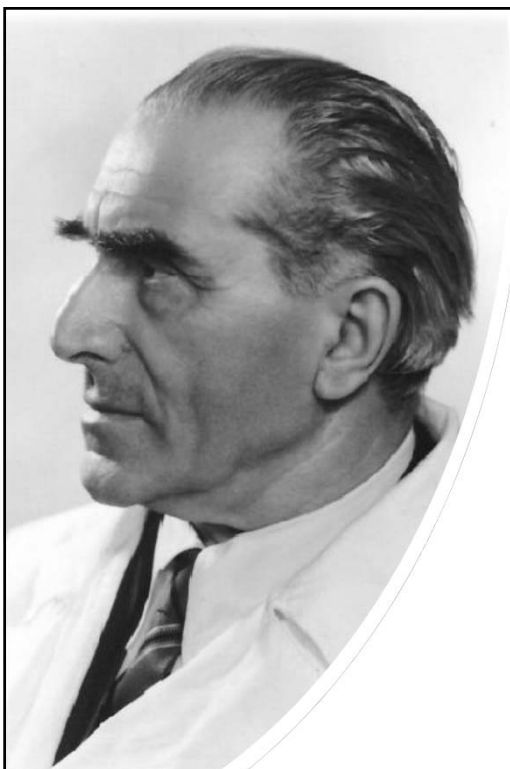






## In the beginning...

- Ladislav Von Meduna (1930s)
- Gliosis, Seizures, and Psychiatry
- Chemical Convulsive Therapy
  - Camphor and pentylenetetrazol



## Pushing electrons

Ugo Cerletti (late 1930s)  
Alternating, sinusoidal current  
Reliably produced GTC sz  
Bilateral electrode placement  
Scientific embargo until after  
WWII

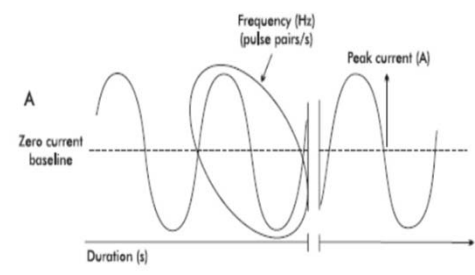


Index Treatment: 6-12 individual sessions, typically MWF

Can be delivered inpt or outpt

Requires full general anesthesia (sedation and relaxation)

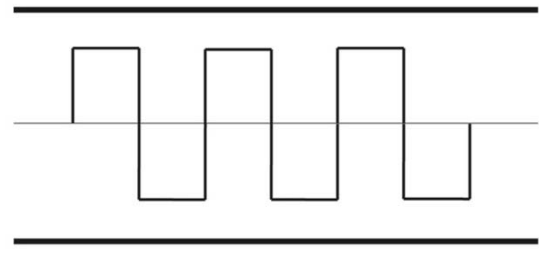
Variation in anesthesia, waveform, and electrode placement



## ECT Waveform

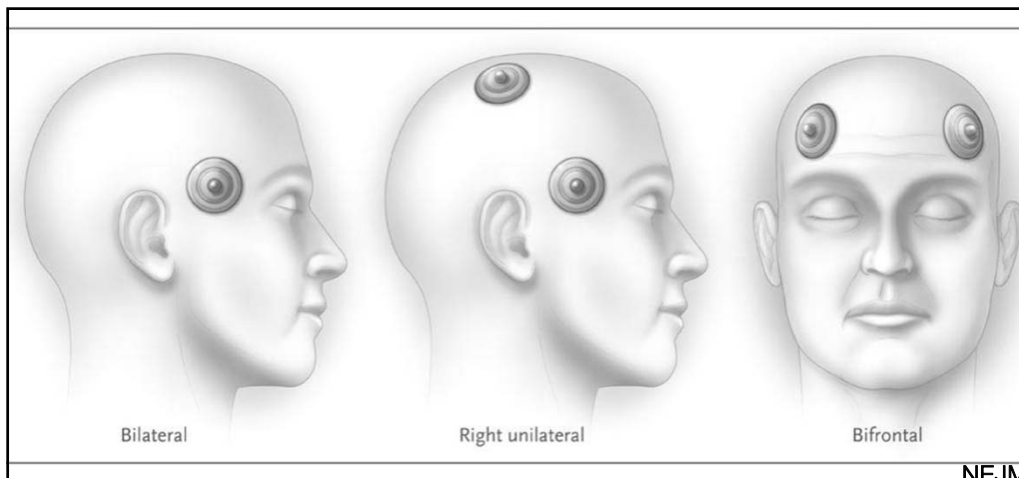
- 1. Pulse width
- 2. Frequency
- 3. Peak current
- 4. Duration

SQUARE WAVE



## ECT Waveform

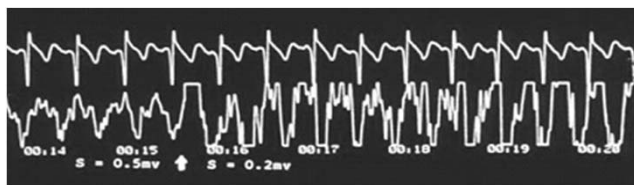
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## Electrode Placement

## ECT Efficacy

- Higher acute remission rates than with ANY OTHER treatment (48% for TRD pts)
- Relapse rates are high if ECT monotherapy is stopped, but can be mitigated with continuation pharmacotherapy (34%)
- M-ECT is surprisingly equally effective to rx



Jelovac et al., 2013

## ECT Adverse Effects

- Cognitive
- Cardiovascular
- Neurologic



Mankad et al., 2010

## ECT Experience

- Driving = No!
  - Cannot drive to/from ECT
  - Recommended not to drive during index course
- Working and big decisions are not recommended
- If outpatient, need a reliable support system
- Early mornings and possible long wait times



## DIY Brain Stimulation

CES, TDCS, etc.

## Cranial Electrotherapy Stimulation (CES)

- FDA Class III through pre-amendment pathway, requires rx
- Alternating current, may increase monoamines, may have similar effects in EEG as meditation
- Fisher Wallace:
  - Scalp electrodes, 2 AA batteries
- Alpha Stim
  - Ear clips, 2 AAA batteries



# CES

- 26 trial meta-analysis of RCTs. No conclusive evidence for efficacy in fibromyalgia, headache, DJD, depression, or insomnia
- Cochrane review was negative.
- Really difficult to do blinded studies
- Data suggests that CES is very safe
- ...but is there an opportunity cost?

Shekelle et al., 2018

## Transcranial Direct Current Stimulation (TDCS)

- Polarity matters:
  - Anode = depolarization
  - Cathode = hyperpolarization
  - Hypoactive L DLPFC and hyperactive R DLPFC can be addressed simultaneously
- Mixed results in treatment of depression or improving cognition
- 9V battery, available on Amazon





## ...and more

- Vagus Nerve Stimulation
- Deep Brain Stimulation
- Low intensity cranial ultrasound
- Magnetic seizure therapy

## Déjà vu all over again

- *"The employment of electricity in medicine has passed through many vicissitudes, being at one time recognized and employed at the hospitals, and again being neglected, and left for the most part in the hands of ignorant persons, who continue to perpetrate the grossest impositions in the name of electricity. As each fresh important discovery in electric science has been reached, men's minds have been turned anew to the subject, and interest in its therapeutic properties has been stimulated. Then after extravagant hopes and promises of cure, there have followed failures, which have thrown the employment of this agent into disrepute, to be again after time revived and brought into popular favor."*

*H. Lewis Jones, MD, J Mental Science, 1901*