

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?

e-

magnet

ECT

MST

“convulsive”

“subconvulsive”

TES
(TDCS, TACS)

TMS

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

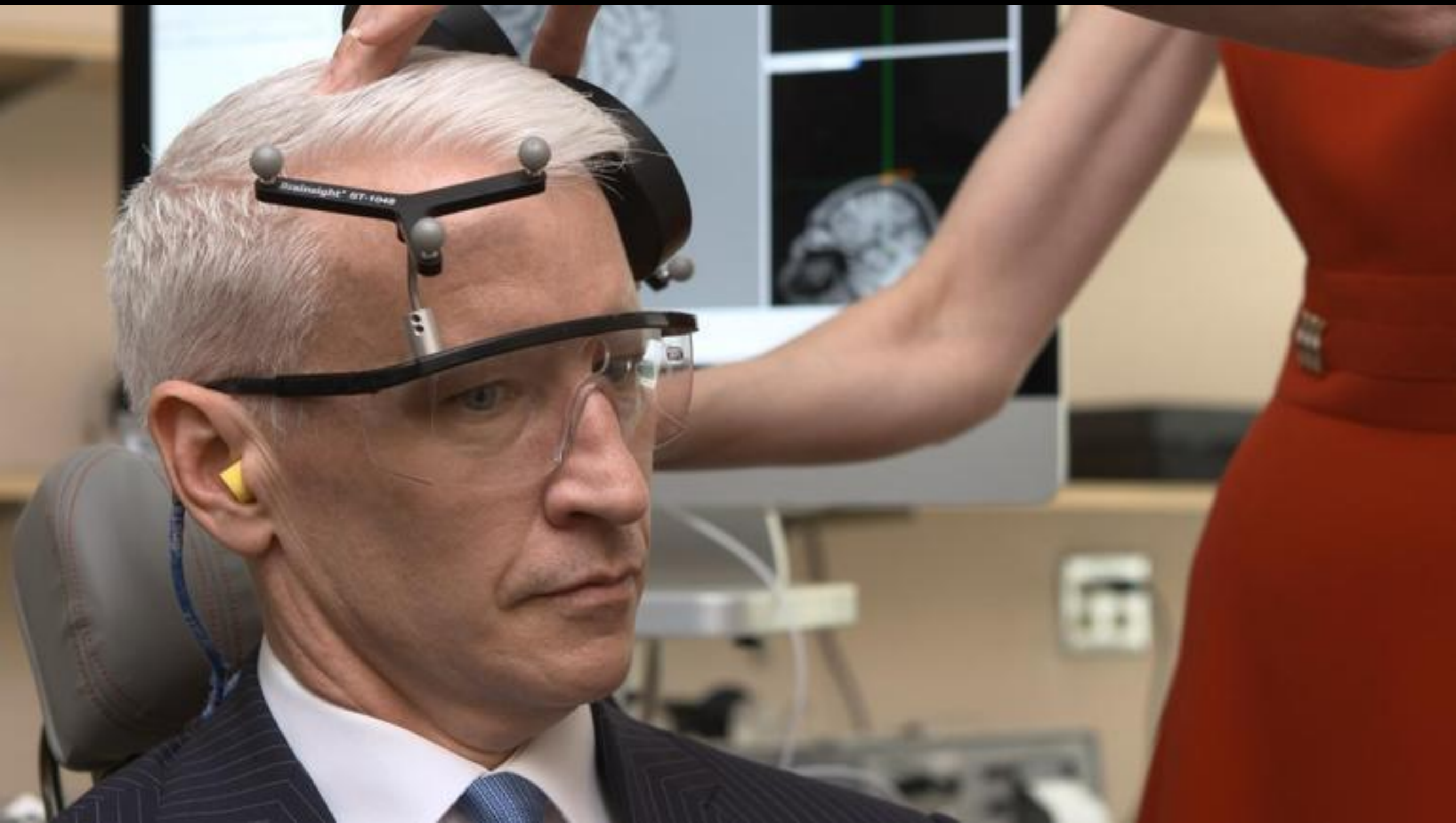




Efficacy and Safety

- 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.

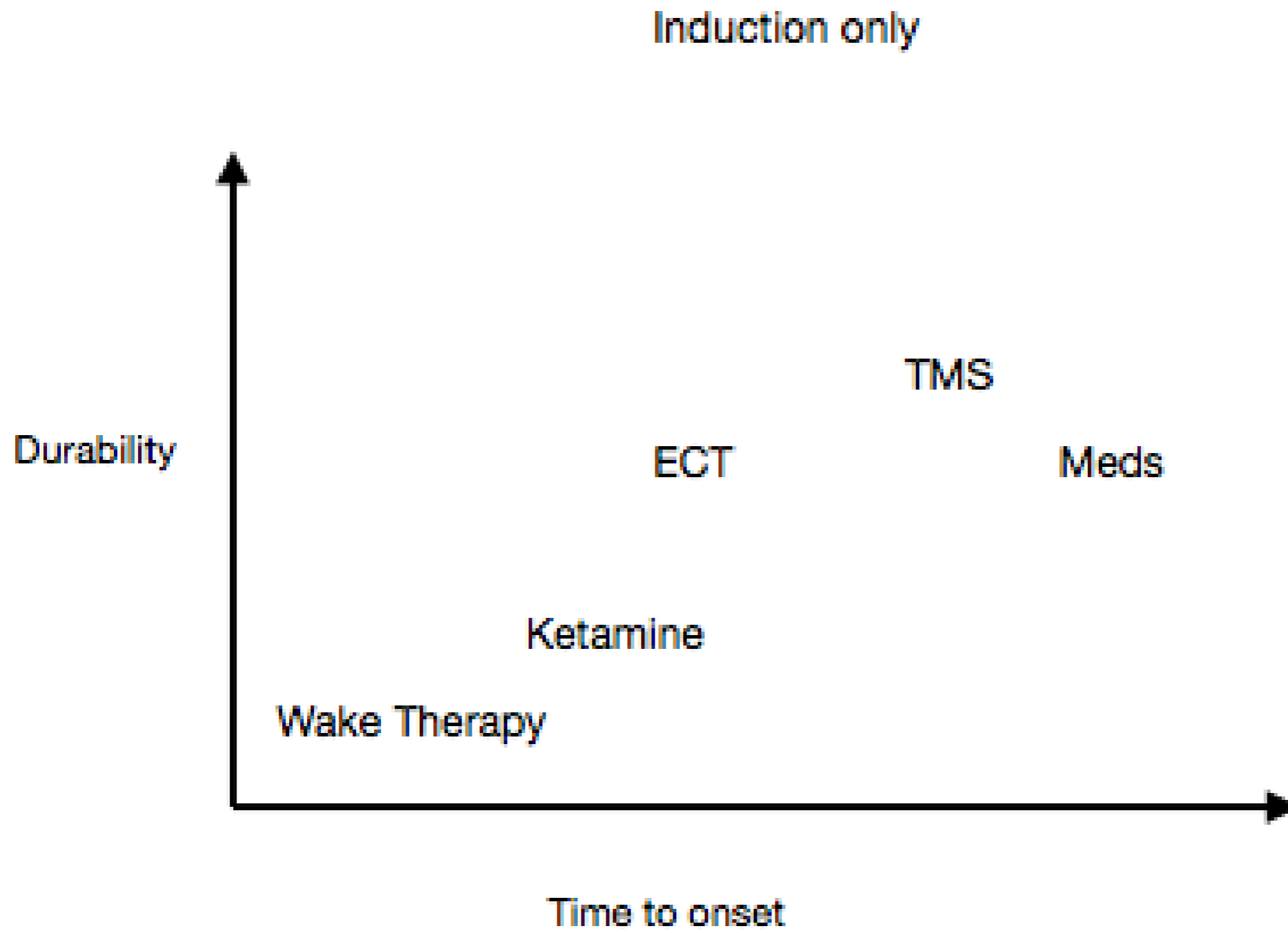
Chronic SI and anxiety disorders are common

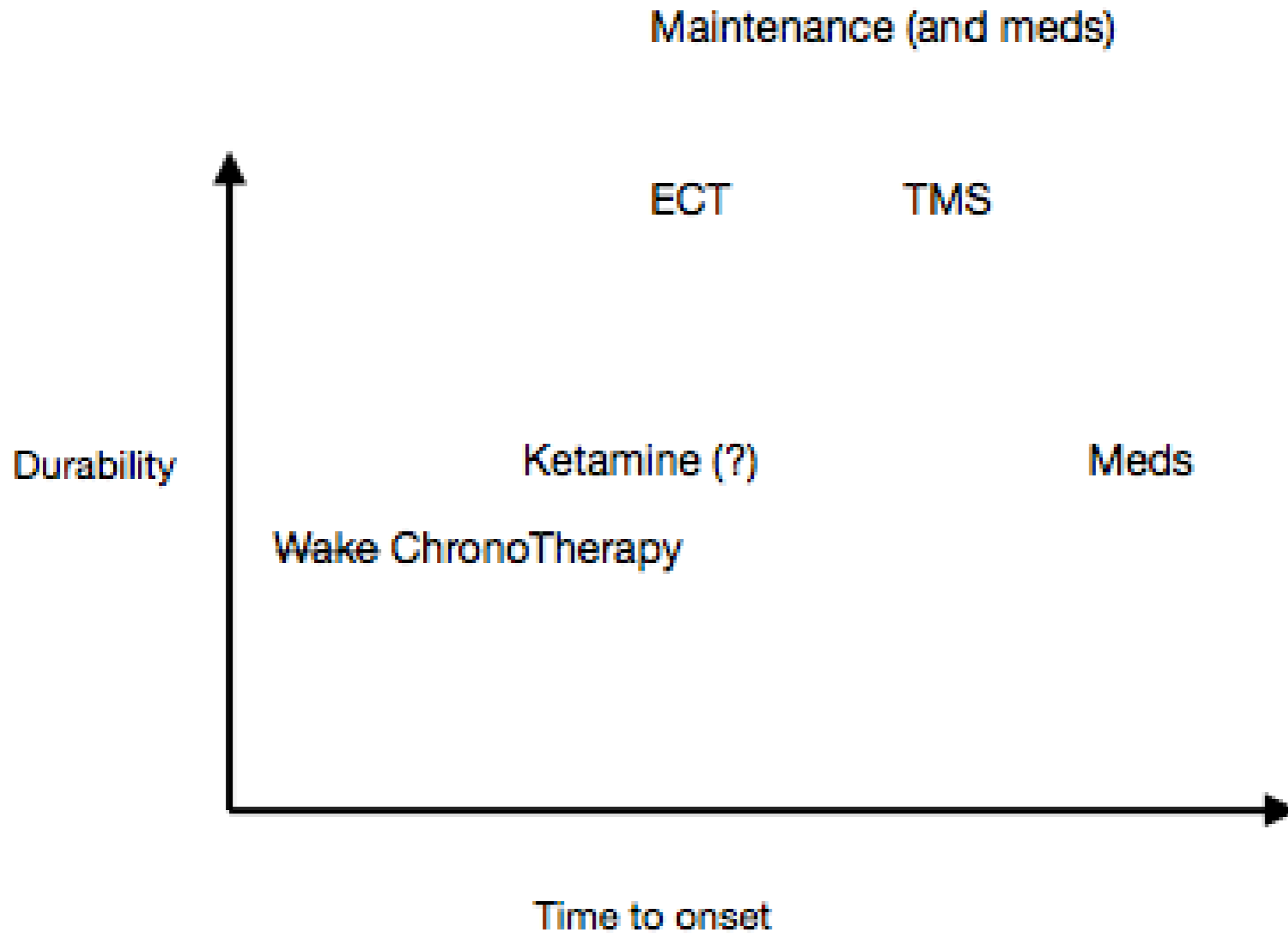
Compatible with ongoing psychotherapy, group therapy, IOP, etc.

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

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

Electroconvulsive Therapy: What's Old is New

Mehul Mankad, MD
Assistant Professor, Duke University
Chief of Psychiatry, Durham VA

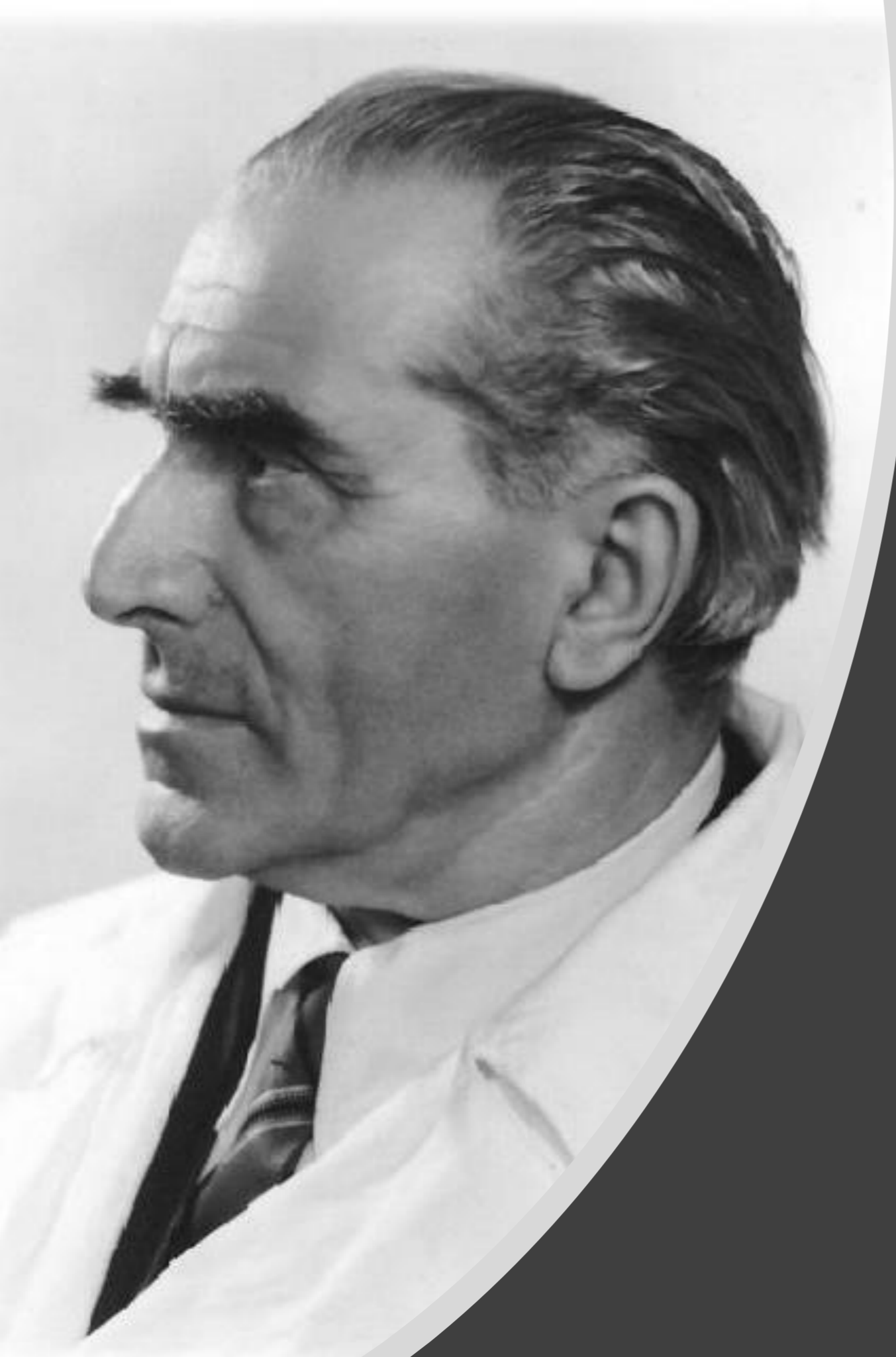






In the beginning...

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



Pushing electrons

Ugo Cerletti (late 1930s)

Alternating, sinusoidal current

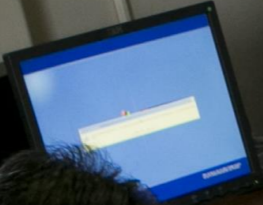
Reliably produced GTC sz

Bilateral electrode placement

Scientific embargo until after WWII



Get a step ahead of certain conditions such as asthma/COPD, coronary artery disease, diabetes, heart failure and hypertension with DukeWELL on your side.



The ECT Procedure Now

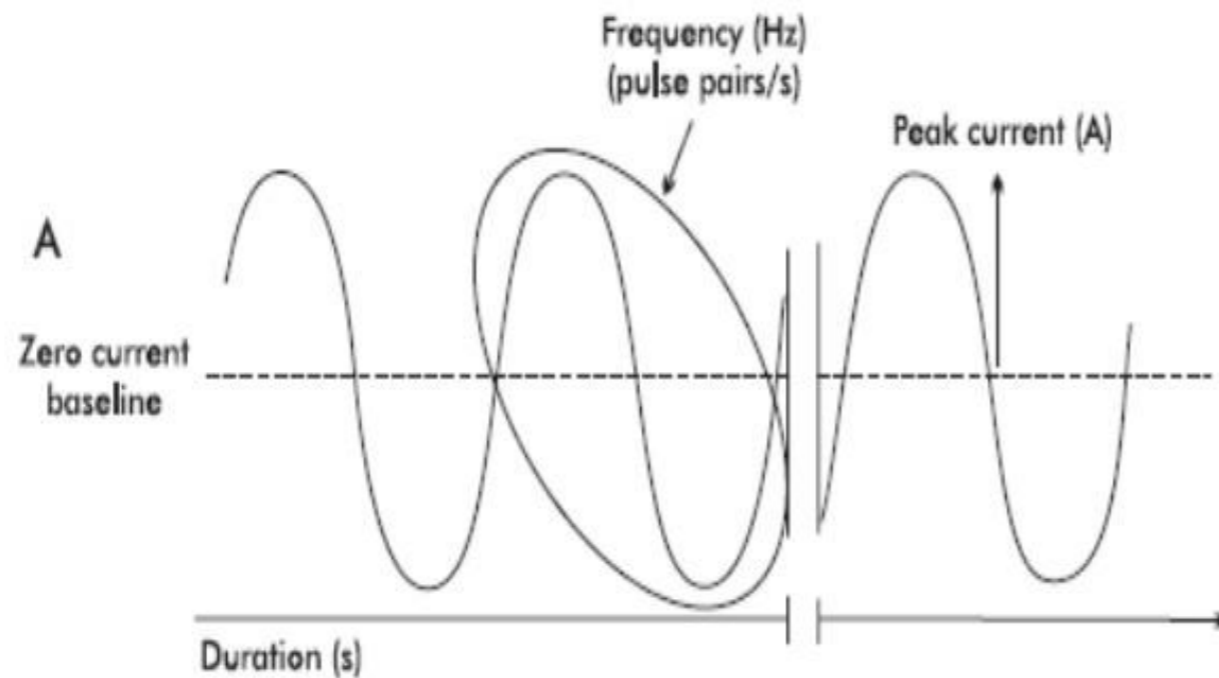
Index Treatment: 6-12
individual sessions, typically
MWF

Can be delivered inpt or outpt

Requires full general
anesthesia (sedation and
relaxation)

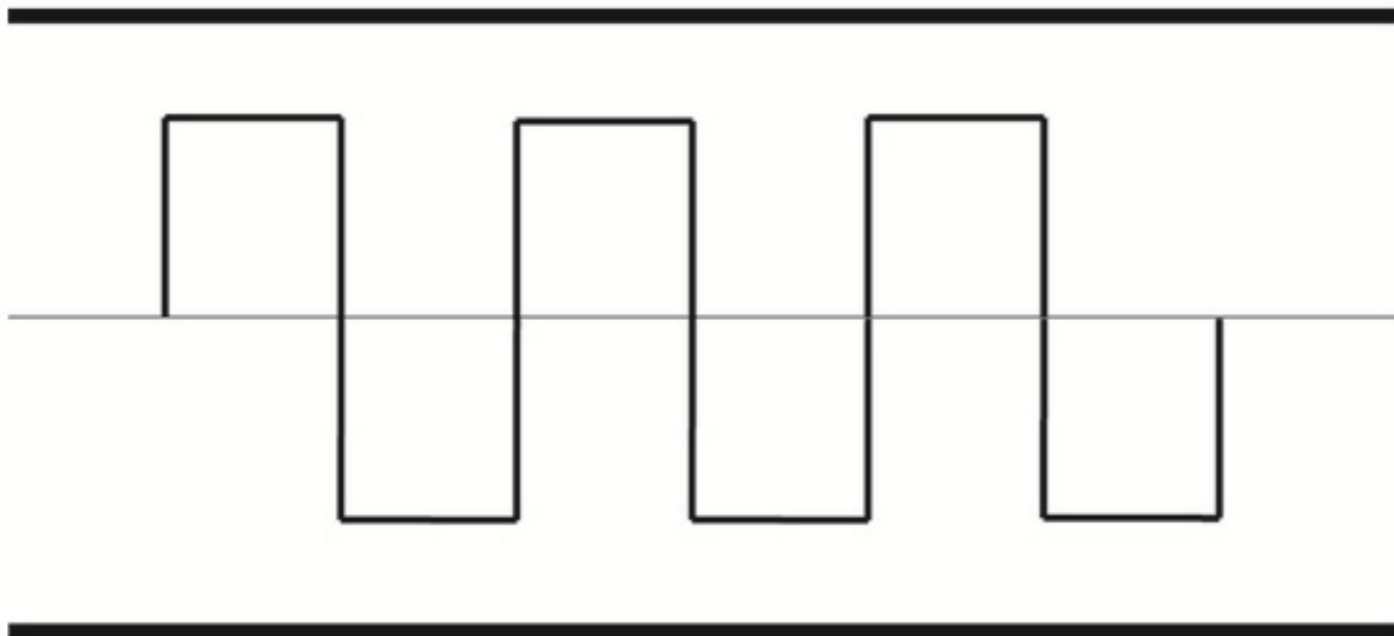
Variation in anesthesia,
waveform, and electrode
placement

ECT Waveform



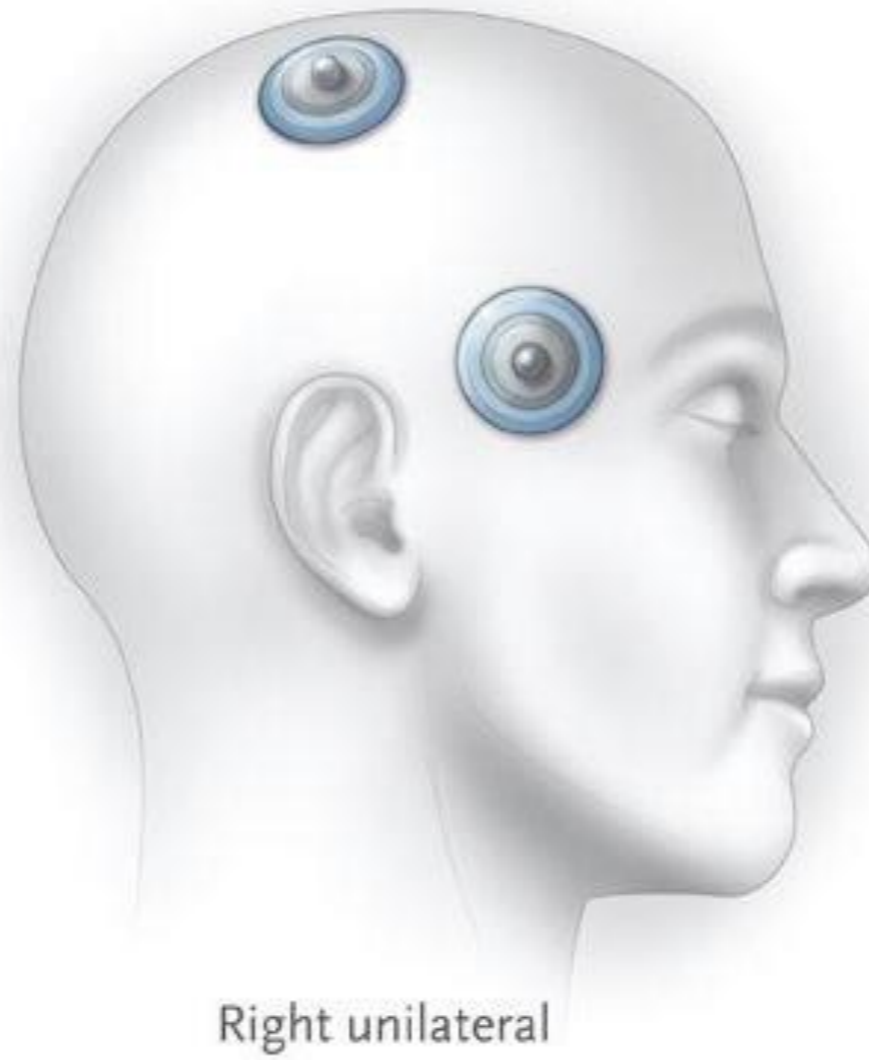
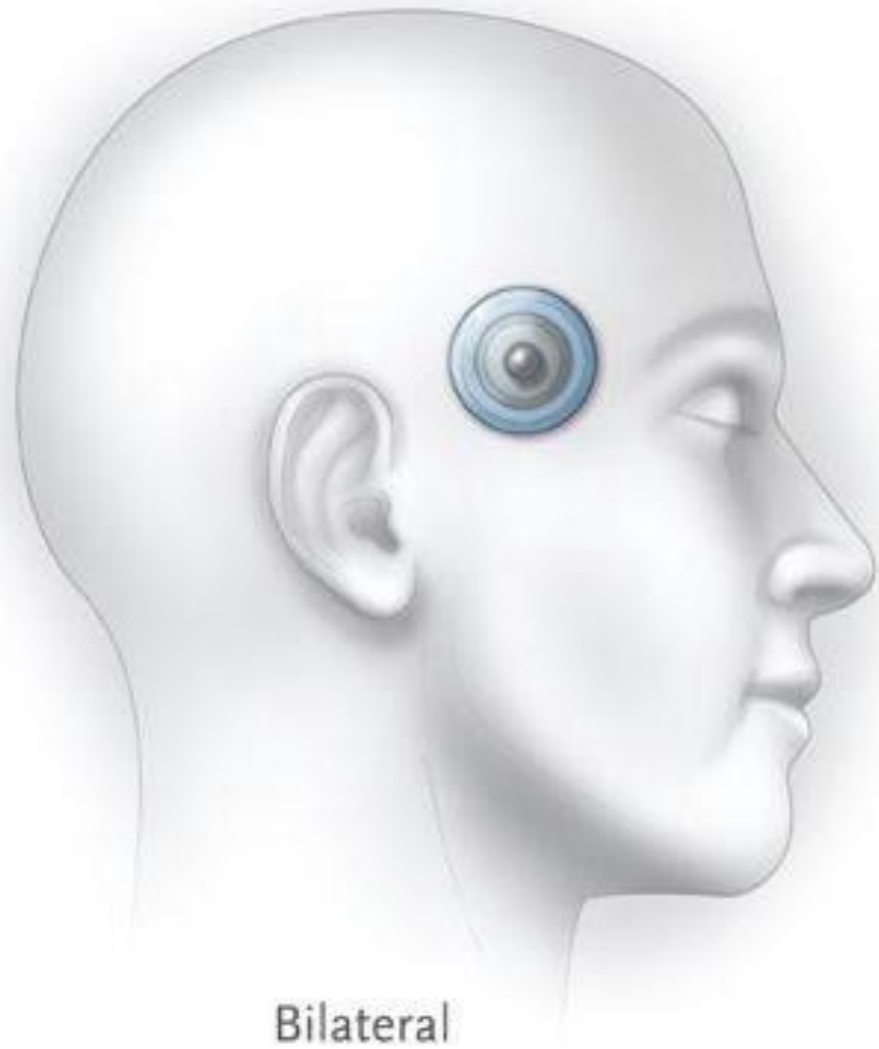
- 1. Pulse width
- 2. Frequency
- 3. Peak current
- 4. Duration

SQUARE WAVE



ECT Waveform

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

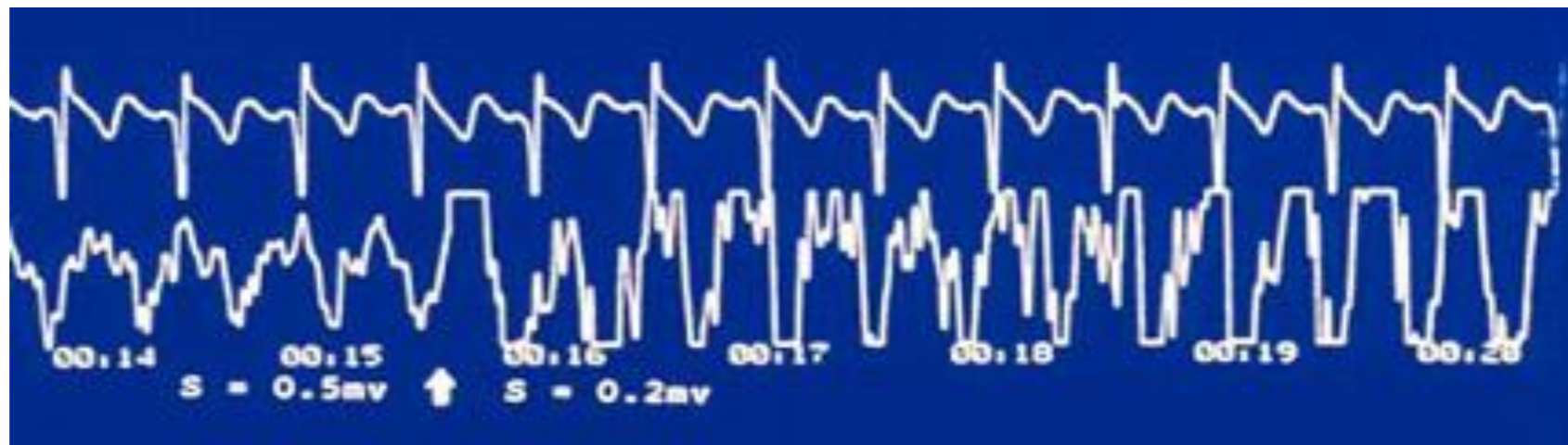


NEJM

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



ECT Adverse Effects

- Cognitive
- Cardiovascular
- Neurologic



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?

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