The Next Chapter in Brain Stimulation Therapy

# TRANSCRANIAL MAGNETIC STIMULATION

# Outline

I. Depression and Treatment Resistant Depression
   - Barriers to Treatment
   - Treatment Options
   - Cost and Impact of Depression

II. Electroconvulsive Therapy
   - History of ECT
   - Mechanism of Administration
   - Mechanism of Action
   - Indications
   - Efficacy of ECT
   - Adverse Effects

# Outline (cont)

III. Transcranial Magnetic Stimulation(TMS)
- History of TMS
- Mechanism of Administration
- Mechanism of Action
- Indications
- Efficacy of TMS
- Proposed Role of TMS
- Cost Considerations
- Future Prospects of TMS
- Conclusion

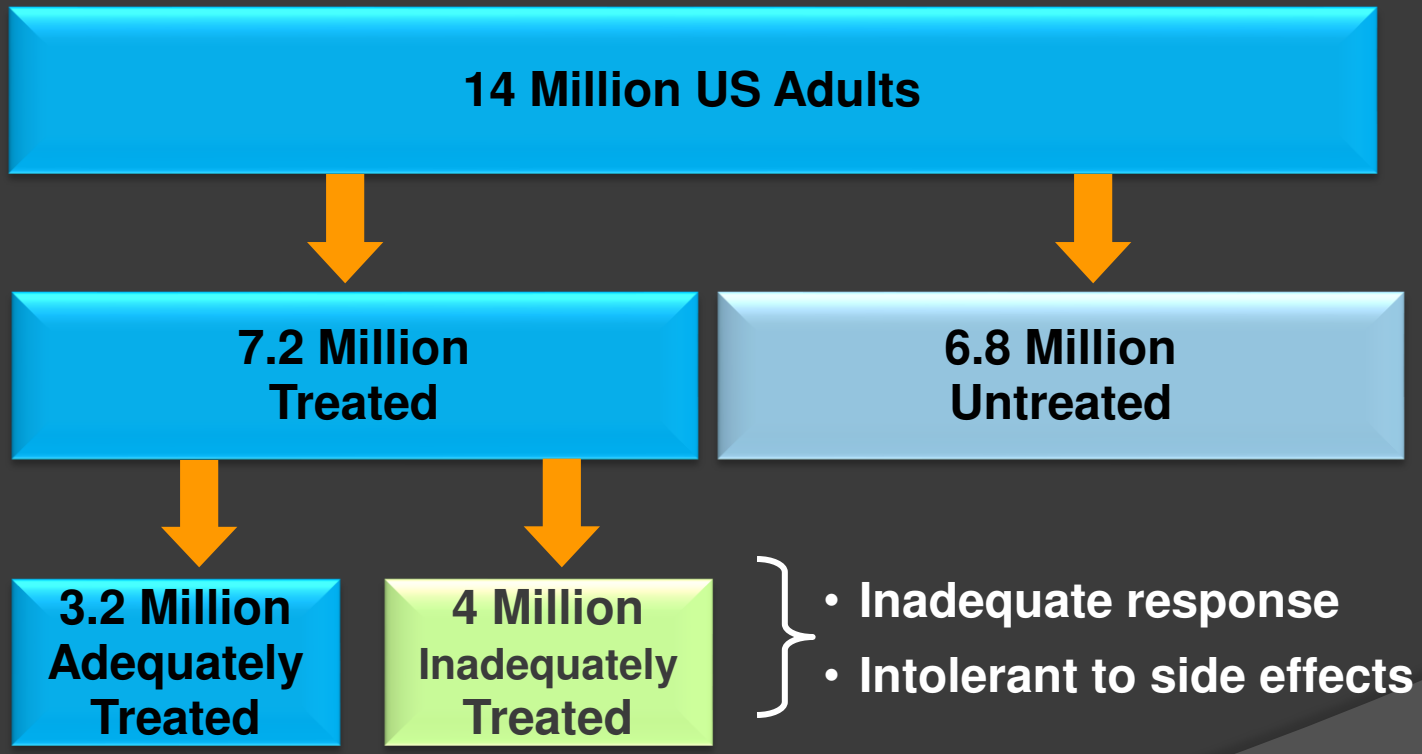
# DSM IV-TR Criteria for Major Depression

- Depressed Mood
- Decreased Interest
- Psychomotor Agitation/ Retardation
- Weight Loss/Weight Gain
- Insomnia/Hypersomnia
- Loss of Energy
- Feeling of Guilt or Worthlessness
- Decreased ability to Concentrate
- Recurrent thoughts of Death

# What is really Treatment Resistant Depression?

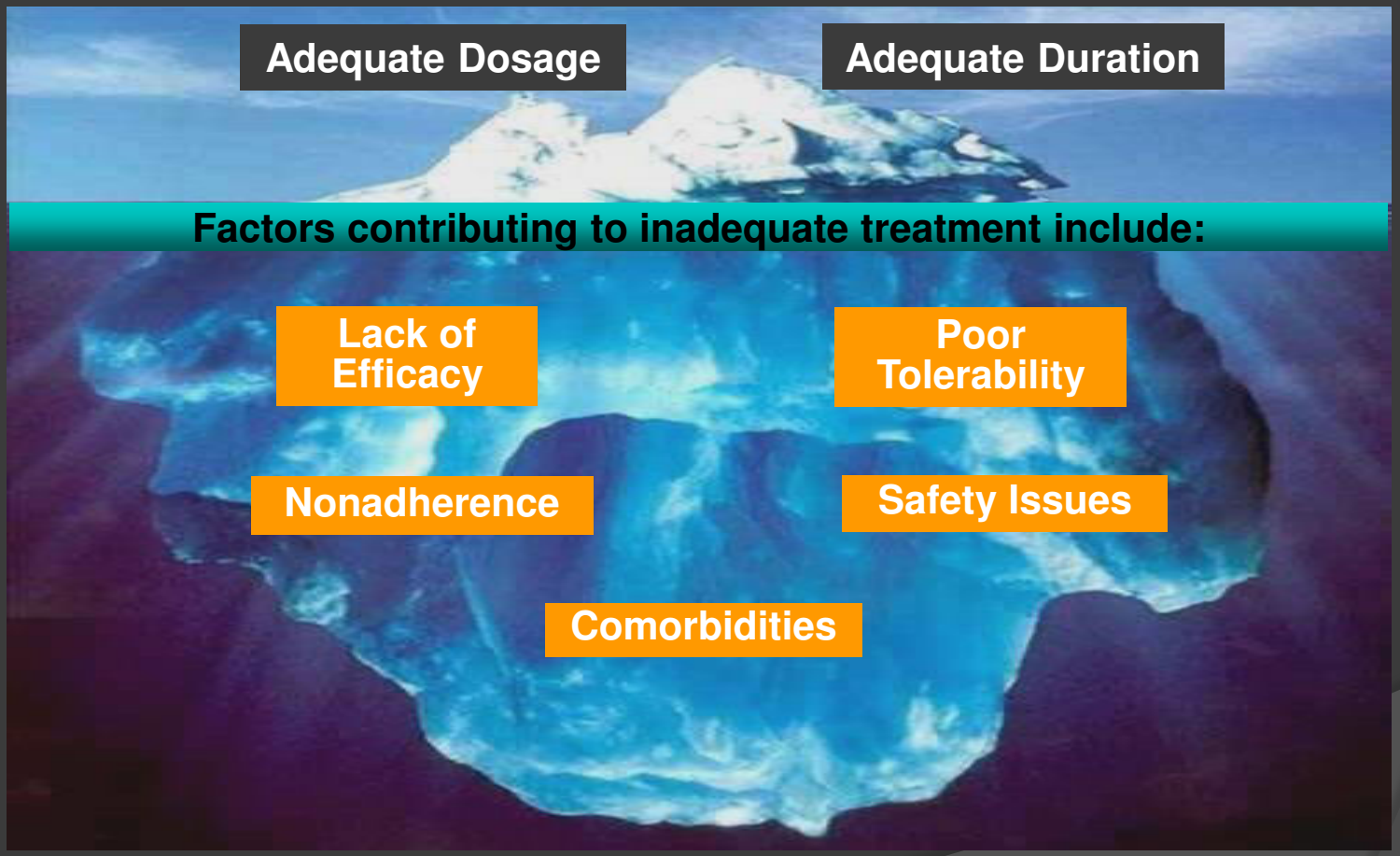
- Failure to respond to 1 adequate trial of an antidepressant
- Failure to respond to one or more adequate trials of antidepressants
- Failure to respond to 2 adequate trials of antidepressants
- Failure to respond to 2 adequate trials of antidepressants form different classes (e.g. SSRI and TCA)
- Failure to respond to 2 or more adequate antidepressant trials
- Failure to respond to 2 or more adequate antidepressants from different classes

# Depression is Difficult to Treat




Kessler RC et al. *JAMA*. 2003;289(23):3095-3105.

# Difficulty in Achieving Adequate Treatment




1. Nemeroff CB. *Depress Anxiety*. 1996/1997;4(4):169-181; 2. Oquendo MA et al. *J Clin Psychiatry*. 2003;64(7):825-833; 3. Oquendo MA et al. *Am J Psychiatry*. 1999;156(2):190-194.

# What's the Real Cost of Depression?

- Estimated at $43 billion yearly
- Loss of 5.6 hours/work week
- 50% due to absenteeism and short-term disability
- 2.17 times more likely to take sick days
- Higher interactions with health care providers
- Lower productivity.

# So What are the Treatment Options?

- Psychotherapy
- Pharmacotherapy – Antidepressants are first line.
- Biological Therapies
    1. Electroconvulsive Therapy
    2. Transcranial Magnetic Simulation
    3. Deep Brain Stimulation
    4. Vagal Nerve Stimulation

# STAR*D

- Purpose of the Study
  - Compare the efficacy and tolerability of a range of diverse antidepressant therapies through four sequential levels of treatment with the goal of achieving remission
- Outcome Variable
  - HAM-D
  - QIDS-SR
- Study Design
  - 4,041 recruited from 18 primary care clinics and 23 Psychiatric care settings
  - 4 Levels of Sequential Treatment
  - 12 weeks for each level
- Acute and Long-Term Outcomes
  - 1st Level: 36.8%
  - 2nd Level : 30.6%
  - 3rd Level: 13.7%
  - 4th Level:13%

# Historical Overview of ECT

First seizure induction by Paracelsus in 16th century

1934 Ladislaw Meduna injected camphor

1938 first electrical seizure induction by Cerletti & Bini

ECT is introduced to the United States in 1940

During 1960's ECT vs Meds

1978 APA Task Force Report on ECT

1980's ECT proves superior to sham and lithium

1985 NIH and NIMH endorse ECT

Numerous RCT's over the years

# Mechanism of Action:

More than one mechanism proposed

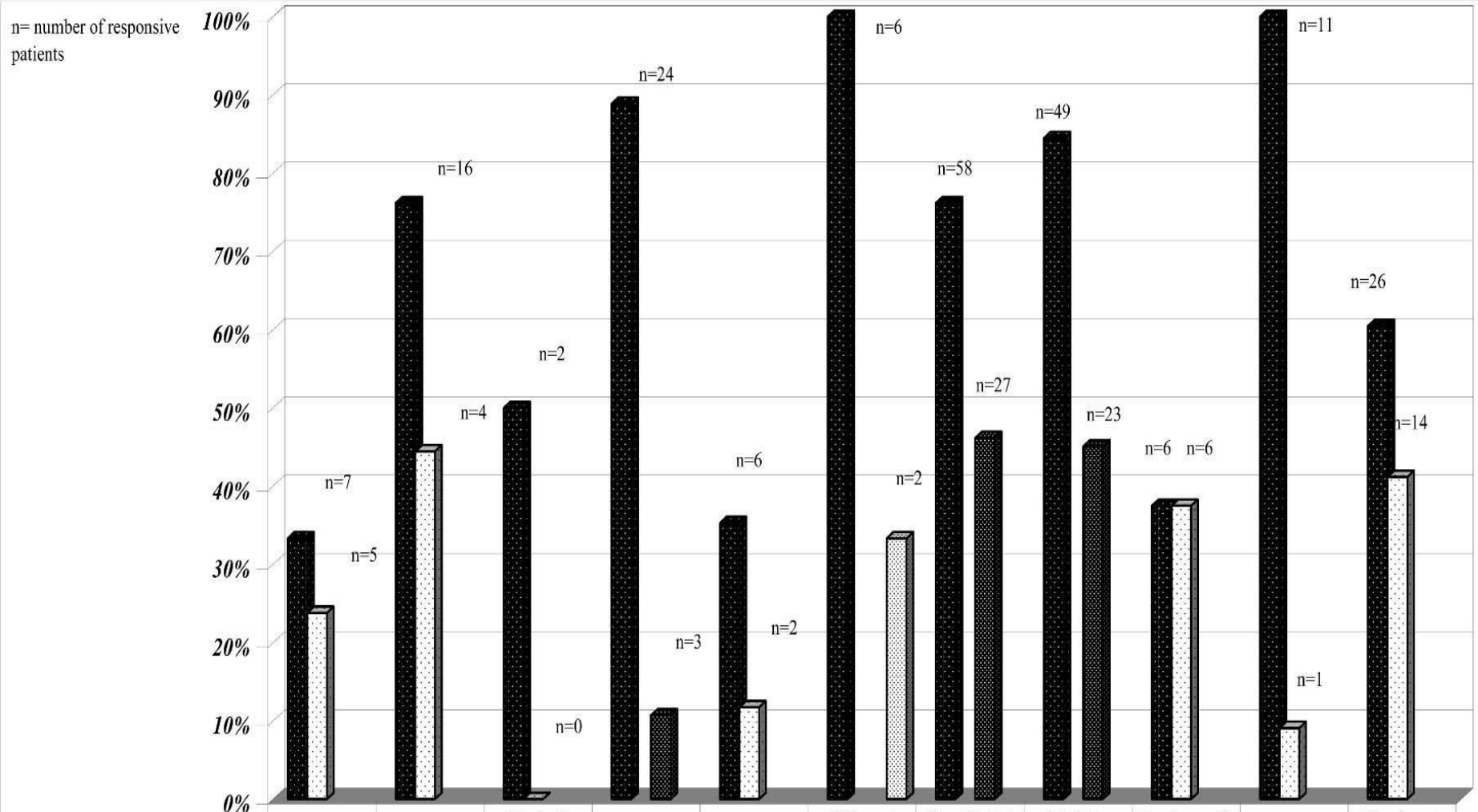
- Neurotransmitter systems
- Endocrine effects
- Synaptic plasticity and neurogenesis

# Efficacy of ECT in Depression

Meta-analytic reviews of ECT in depression have shown good response rates in patients with MDD.

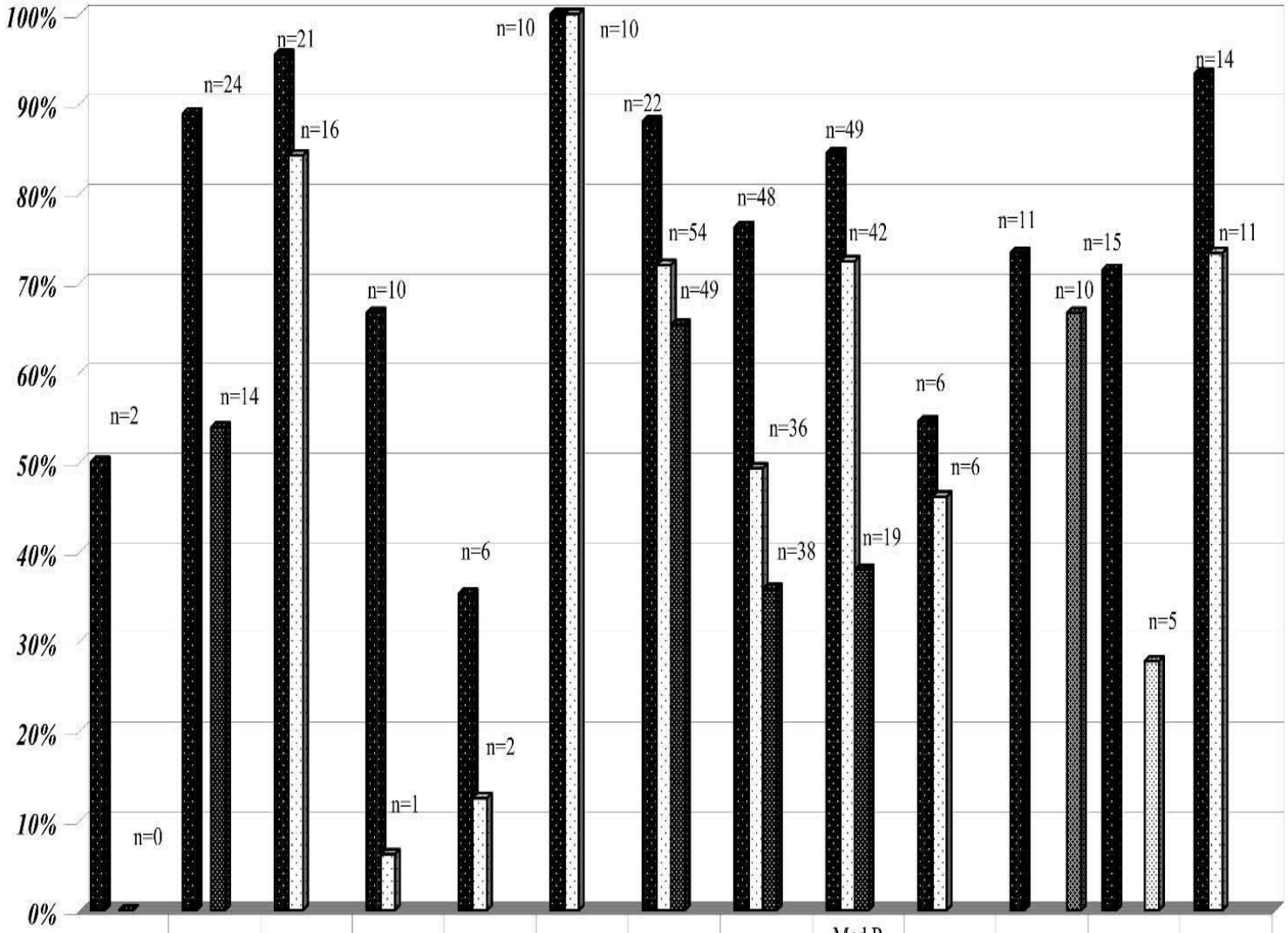
- A review of randomized controlled trials was done by Kho et al (2003) revealed ECT to be superior than simulated ECT and medications by nearly one standard deviation.
- Similar review in 2004 by Pagnin et al and revealed the significant superiority of ECT in comparison to antidepressants and simulated ECT.
- Gabor and Laszlo (2005) found ECT to more efficacious than simulation ECT or medications for severe depression and elevated suicidal risk.

# Responsive rate of ECT, ECT simulated and placebo in randomized controlled trials.




| | Ulett et al.(12) | Brill et al.(13) | Harris & Robin(14) | Kiloh et al.(15) | Fahy et al.(16) | Wilson et al.(17) | Greenblatt et al.(18) | Med Res Council(19) | Lambourn & Gill(20) | West(21) | Brandon et al.(22) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ECT | 33,33% | 76,19% | 50,00% | 88,88% | 35,29% | 100,00% | 76,19% | 84,48% | 37,50% | 100,00% | 60,46% |
| ECT simulated | 23,80% | 44,44% | 0,00% | | 11,76% | | | | 37,50% | 9,09% | 41,17% |
| Placebo | | | | 10,71% | | | 46,15% | 45,09% | | | |
| ECT simulated + Placebo | | | | | | 33,33% | | | | | |

n= number of responsive patients




| | Harris & Robin(14) | Kiloh et al.(15) | Bruce et al.(24) | Robin & Harris (25) | Fahy et al.(16) | Wilson et al.(17) | Huntchinson(23) | Green blatt et al.(18) | Med R Council (19) | Gangadahar(26) | Dinan & Barry(27) | Folkerts et al.(28) | Janakiramaiah (29) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ECT | 50,00% | 88,88% | 95,45% | 66,66% | 35,29% | 100,00% | 88,00% | 76,19% | 84,48% | 54,54% | 73,33% | 71,42% | 93,33% |
| TCA | | | 84,21% | 6,25% | 12,50% | 100,00% | 72,00% | 49,31% | 72,41% | 46,15% | | | 73,33% |
| MAOI | 0,00% | 53,86% | | | | | 65,33% | 35,84% | 38,00% | | | | |
| SSRI | | | | | | | | | | | | 27,77% | |
| Lithium + TCA | | | | | | | | | | | 66,66% | | |

# Current Indications:

Major Depressive Disorder-

- Considered as the most fastest and effective therapy available.
- Pts who have failed or intolerant to med therapy, present with severe psychotic symptoms, marked symptoms of agitation or stupor, or acutely suicidal or homicidal.
- Controlled studies show that up to seventy percent of pts who fail medication therapy have a positive response to ECT treatment.

Manic Episodes-

- Considered equal in efficacy to Lithium in controlling manic episodes. Particularly useful in pts who show dangerous levels of exhaustion. Lithium lowers seizure threshold and should not be used in these pts.

Schizophrenia-

- Indicated for acute schizophrenia with marked catatonia.

Other Indications-

- Episodic psychosis, atypical psychosis, OCD, delirium, NMS, hypopitutarism, intractable seizures, on-off phenomena of Parkinson's. Done in small studies with variable results.

# Adverse Effects:

- Amnesia, headache, confusion
- Nausea, vomiting
- Myalgias, back pain
- Damage to teeth
- At risk for brain edema or herniation
- ECT related cardiac ischemia- not recommended within 3 months of recent MI.
- Mortality is 0.002% per treatment, and 0.01% for each patient.

# Contraindications

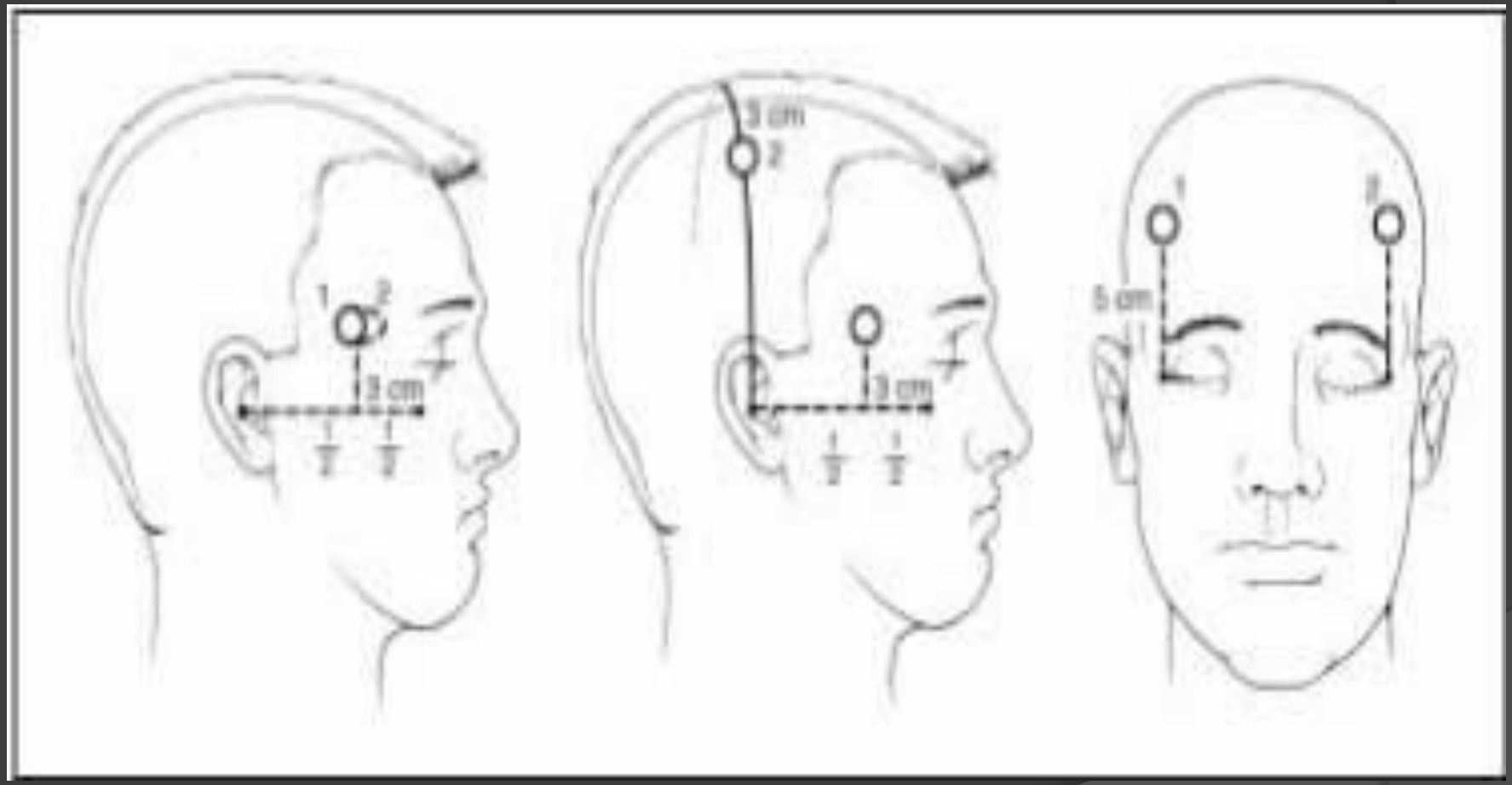
- Increased ICP (mass)
- Unstable Angina
- Recent Stroke
- Recent MI
- Pheochromocytoma
- Retinal Detachment

# Administration of ECT

# ECT Administration:

- Pretreatment Evaluation
- Pretreatment Preparation
- Administer Anesthetics
- Treatment Schedule
- Electrode Placement.
  - Sine and pulse?

# Bilateral RUL Bifrontal



Rasmussen KG et al. Mayo Clin Proc. 2002:77:552-556

# Electrical Pathway

ECT output device

Stimulus electrodes

Scalp

Cerebrospinal fluid

Brain tissue

# Stimulus Dosing

1. Empirical Titration Method
2. Preselected Dosage Method

Motor seizure consists of two phases:

→Tonic Phase: lasts 10 to 20 seconds and involves contraction of the jaw and facial muscles, plantar extension, and high-frequency sharp EEG activity.

→Clonic Phase: involves rhythmic contractions and bursts of polyspike EEG activity which lasts a few seconds.

- Seizure is considered effective if it lasts 20-25 seconds.
- Prolonged seizures can be terminated by Intravenous benzodiazepines.
- In US treatment is usually administered 3 times a week, although experimentally twice weekly administration with bilateral ECT has been shown to have optimal results.
- Number of treatment depends on the pts but generally 8-12 sessions are given.

# ECT Induced Seizure

1. Tonic Phase
2. Clonic Phase
3. Post – Ictal Suppression

# Transcranial Magnetic Stimulation

# History and Background of TMS

1931 Michael Faraday discovers principle of magnetic induction.

1896 D'arsonval first uses power magnetic coil in humans

1902 Pollacsek and Beer file a patent.

1985 Anthony Barker builds the first modern TMS device.

1987 Bickford conducts research into neuropsychiatry

1993 Hoflich et al begin the first open trials

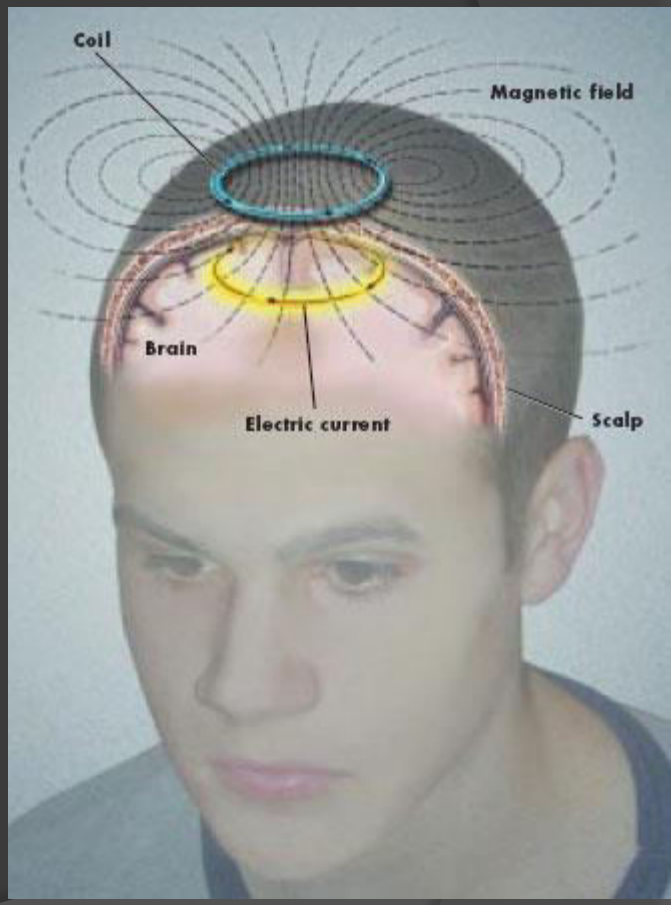
2002 TMS is approved by Canada

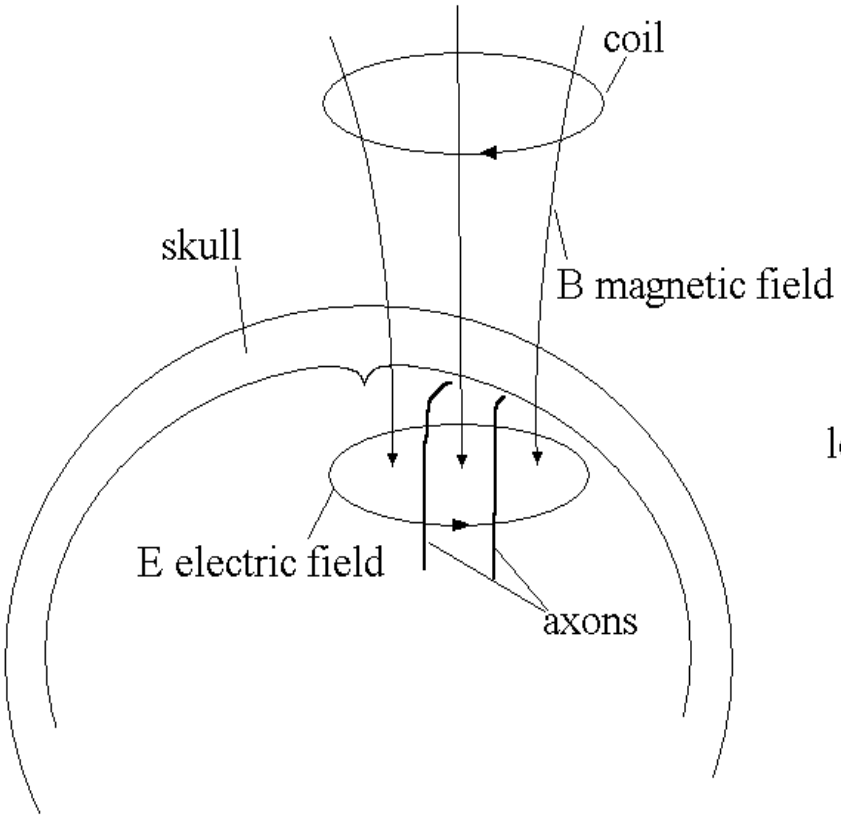
2008 FDA approves TMS

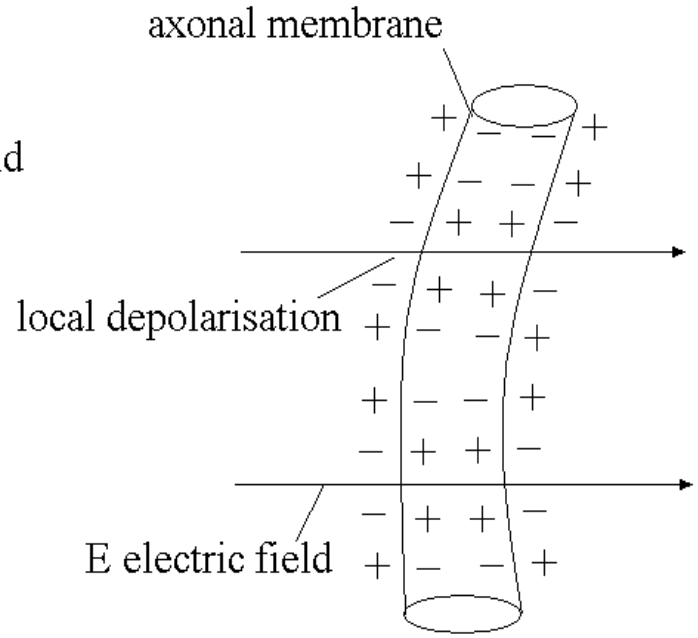
Currently in use by growing number of centers

# Laws of Electromagnetism

- TMS is based on two primary laws of electromagnetism
- → Ampere's Law: relates the integrated magnetic field around a closed loop to the electrical current passing through the loop.
- → Faraday's Law: states that the induced electromotive force in any closed circuit is equal to the rate of change of the magnetic flux through the circuit.

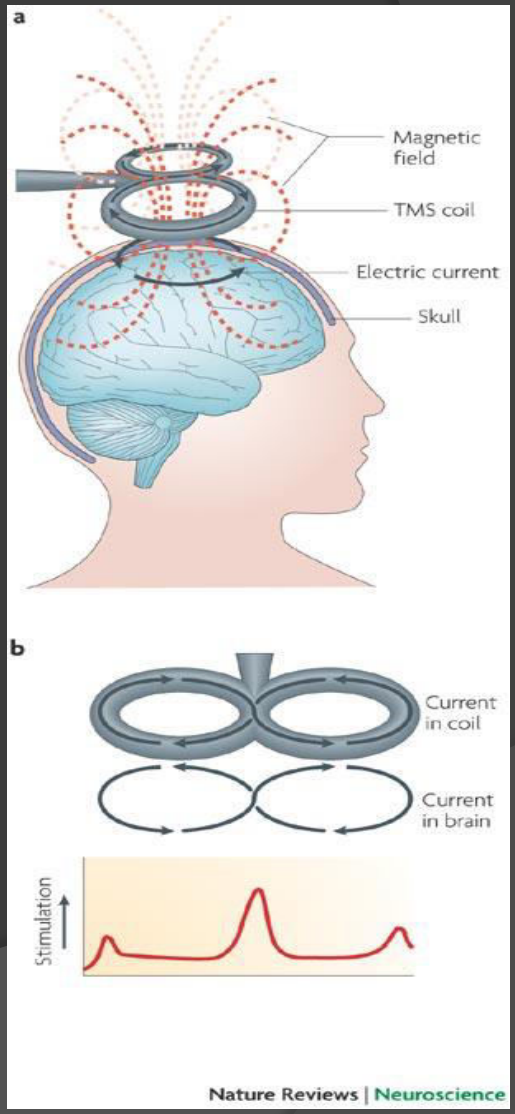


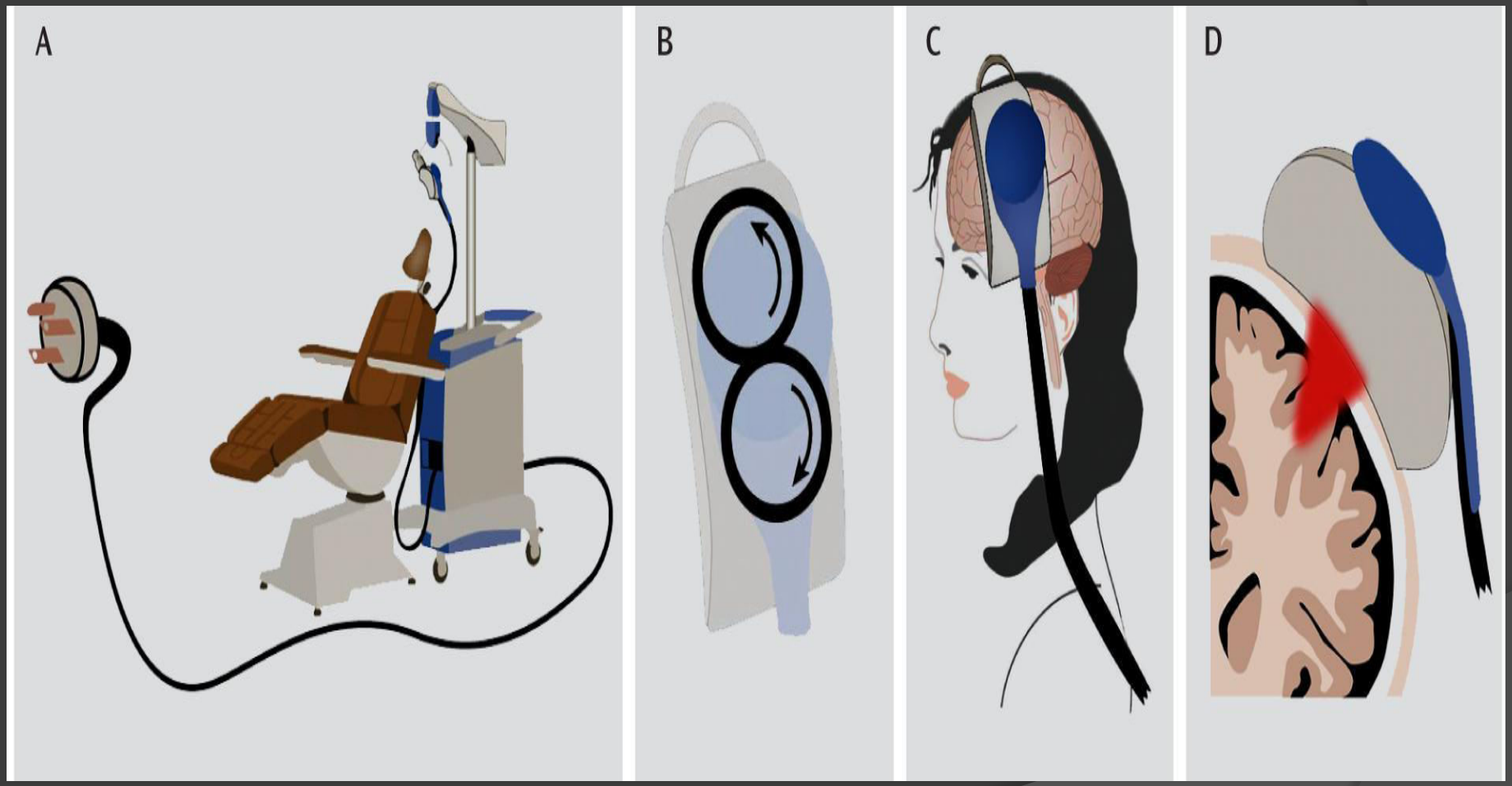

coil
skull
B magnetic field
E electric field
axons


axonal membrane
local depolarisation
E electric field

# Application of TMS

1. Stimulus Administered
2. Metal Coil
3. Determining Position of Coil
4. Determining Motor Threshold




A
B
C
D

# Mechanism of Action

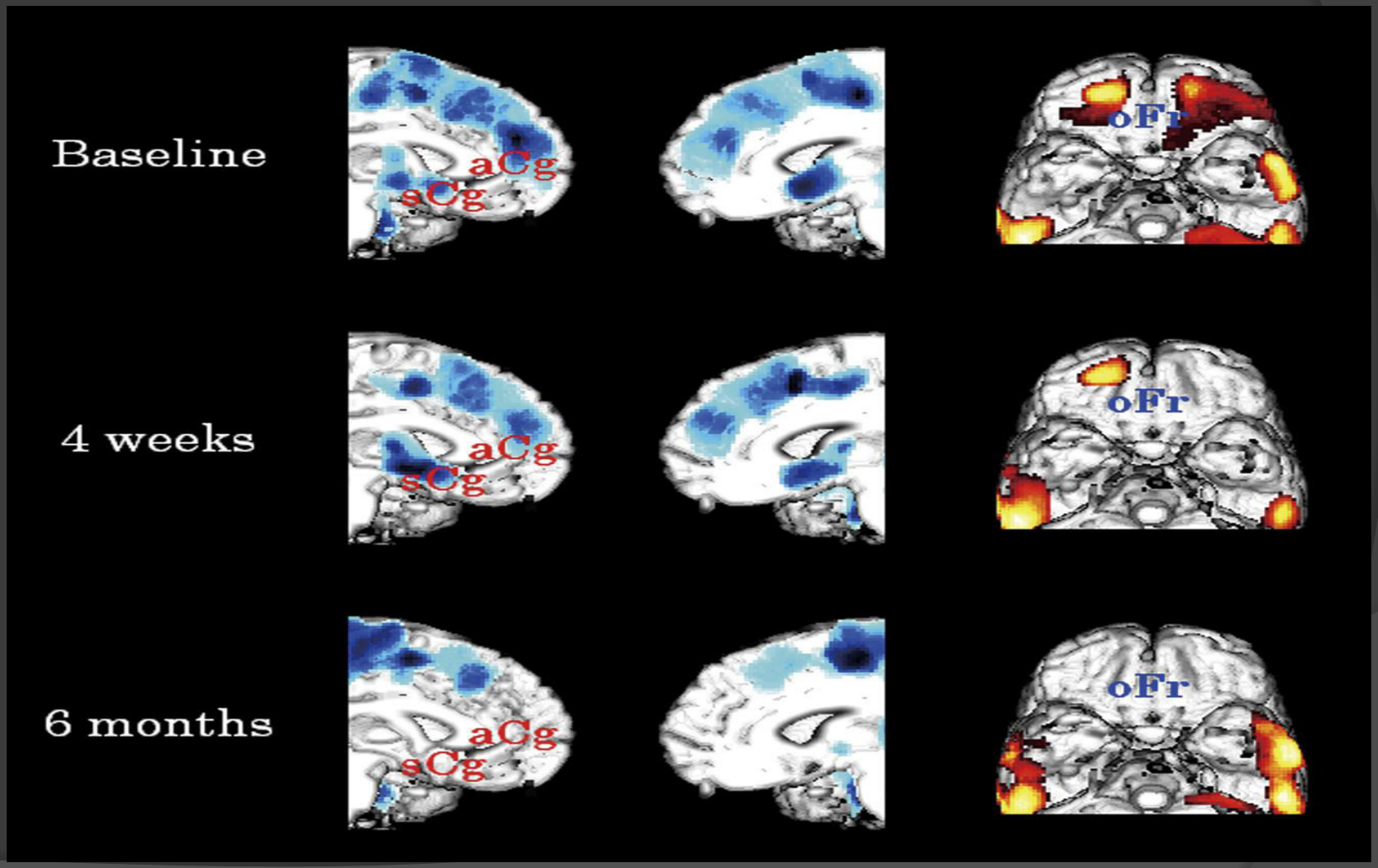
# High and Low Frequency rTMS

- Low activity levels in Left Dorsolateral Prefrontal Cortex (DLPFC)

- Antidepressant effect dependent on
  1. Side of Stimulation
  2. Frequency of Stimulation

- SPECT and PET Imaging

# Change in Cerebral Blood Flow



# Neuroplasticity

- Up-Regulation of Genes
- Synaptic connections, neurogenesis, neuronal viability
- c-fos, c-jun, glial fibrillary acidic protein.

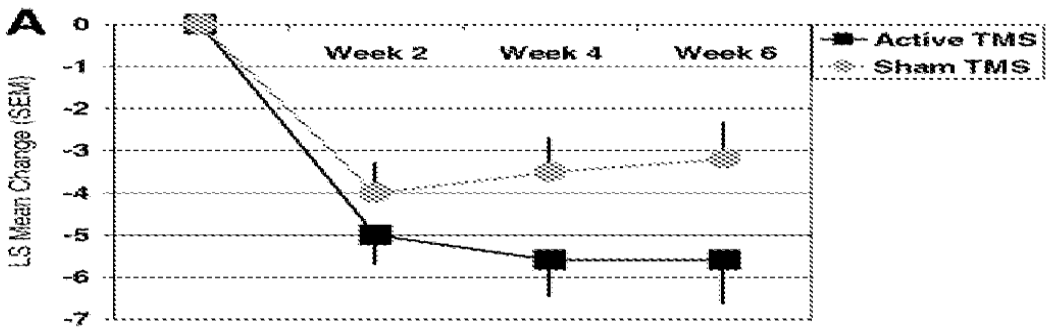
# 2008 FDA Approval
# TMS vs Sham
## O'Reardon et al

# Inclusion Criterion

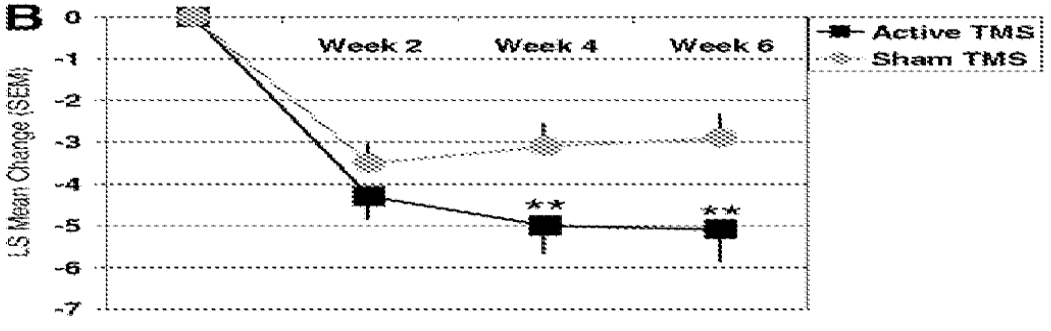
- Diagnosis, Disease Severity & Illness Course
  - DSM-IV Diagnosis: Major Depressive Disorder, unipolar, non-psychotic
  - Average age 50 yrs
  - 95% recurrent illness course
  - Approximately 50% unemployed due to illness
  - Moderate to severe symptom burden
    - Avg. HAMD24 = 30, MADRS = 32
- Antidepressant Treatment History
  - Moderate to severe treatment resistance in current episode
    - Patients failed an average of 4 medication trials

# Summary of Study

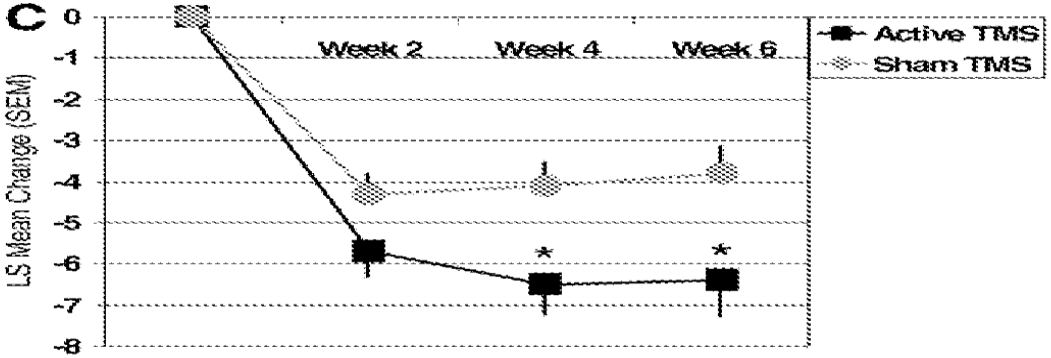
- Efficacy established in large multi-site, randomized, sham-controlled clinical trial.
  - Primary outcome (MADRS): 22.1% reduction in MADRS total score with active NeuroStar TMS vs 9.1% on sham
  - Clinically meaningful effect size = 0.52
- In open label extension study:
  - 1 in 2 patients reached response
  - 1 in 3 patients achieved remission
- In a 6 month, follow up study <10% of patients experienced relapse of illness




(p=0.057 for week 4 contrast, p=0.058 for week 6 contrast)




** P < 0.01
(p=0.006 for week 4 contrast, p=0.005 for week 6 contrast)




* P < 0.05
( p=0.012 for week 4 contrast, p=0.015 for week 6 contrast)

**Figure 2.** (A) Montgomery–Asberg Depression Rating Scale total score change from baseline during the acute treatment phase. (B) Hamilton Depression Rating Scale (HAMD; 17 item) total score change from baseline during the acute treatment phase. (C) HAMD (24-item) total score change from baseline during the acute treatment phase.

# Efficacy of TMS: How Does it Stack Up to ECT?

**Table 1. Summary of rTMS vs. ECT Studies**

| Author (Year) | Patients/Design | Parameters | Comments |
|---|---|---|---|
| Grunhaus et al. (2000)[3] | 40 MDD<br>Random assignment<br>UL-ECT or rTMS<br>(8 patients switched to bilateral-ECT)<br>HDRS | L-DLPFC<br>10 Hz<br>90% MT<br>2-sec trains (n = 8)<br>6-sec trains (n = 12)<br>ITIs not reported<br>20 trains per session<br>Up to 20 sessions | rTMS = ECT in nonpsychotic MDD<br>ECT plus meds > rTMS in psychotic MDD* |
| Pridmore et al. (2000)[4] | 32 MDD<br>Random assignment<br>UL-ECT or rTMS<br>HDRS, BDI, VAS | L-DLPFC<br>20 Hz<br>100% MT<br>2-sec trains<br>28-sec ITIs<br>30–35 trains per session<br>Mean no. 12 (± 3.4) sessions | rTMS = ECT<br>Based on:<br>– HDRS % change<br>– remission rates |
| Janicak et al. (2002)[7] | 31 MDD<br>Random assignment, with crossover option for nonresponders<br>rTMS or BT-ECT<br>HDRS | L-DLPFC<br>10 Hz<br>110% MT<br>5-sec trains<br>30-sec ITIs<br>20 trains per session<br>Mean no. 14 (± 3.4) sessions | rTMS = ECT<br>Based on:<br>– HDRS % change<br>– a priori definition of response |
| Grunhaus et al. (2003)[5] | 40 nonpsychotic MDD<br>rTMS or UL-ECT<br>(7 patients switched to BL-ECT)<br>HDRS; GAF | L-DLPFC<br>10 Hz<br>90% MT<br>6-sec trains<br>30-sec ITIs<br>20 trains per session<br>Up to 20 sessions | rTMS = ECT<br>Based on:<br>– HDRS % change<br>– GAF ≥ 60 |
| O'Connor et al. (2003)[6] | 28 MDD<br>Non-random assignment<br>UL-ECT plus meds or rTMS alone<br>HDRS; cognitive battery | L-DLPFC<br>10 Hz<br>90% MT<br>8-sec trains<br>24-sec ITIs<br>20 trains per session<br>10 sessions | ECT plus meds > rTMS alone<br>Based on:<br>– HDRS change scores<br>rTMS > ECT for cognitive AEs<br>At baseline: ECT group had significantly higher HDRS scores vs. rTMS group |

**Table 1. Summary of rTMS vs. ECT Studies (cont.)**

| | | | |
|---|---|---|---|
| McLoughlin et al. (2005)[8] | 46 MDD<br>Random assignment<br>HDRS (17-item)<br>rTMS or BT-ECT<br>HDRS, BDI-II<br>(Raters blind) | L-DLPFC<br>10 Hz<br>110% MT<br>5-sec trains<br>55-sec ITIs<br>20 trains per session<br>Up to 15 sessions | BT-ECT > rTMS<br>Based on:<br>- HDRS change score<br>Patients continued on medications<br>Both groups demonstrated significant improvement from baseline HDRS scores |
| Schulze-Rauschenbach et al. (2005)[9] | 30 MDD<br>Non-random assignment<br>UL-ECT plus meds or rTMS plus meds<br>HDRS | L-DLPFC<br>10 Hz<br>100% MT<br>2-sec trains<br>5-sec ITIs<br>20–30 trains per session<br>Mean number = 10.8 (± 1.4) | rTMS = ECT<br>Based on:<br>- HDRS % change<br>rTMS > ECT for cognitive AEs |
| Rosa et al. (2006)[6] | 42 nonpsychotic MDD<br>Random assignment<br>UL-ECT (2 patients switched to BL-ECT) alone or rTMS alone<br>HDRS, VAS, CGI, cognitive battery | L-DLPFC<br>10 Hz<br>100% MT<br>10-sec trains<br>20-sec ITIs<br>20 trains per session<br>Up to 20 sessions | rTMS = ECT<br>Based on:<br>- HDRS % change<br>- VAS and CGI<br>No cognitive differences |

AEs, adverse effects; BDI, Beck Depression Inventory; BDI-II, BDI Version II; BL-ECT, bilateral ECT; BT-ECT, bitemporal ECT; CGI, Clinical Global Impression; ECT, electroconvulsive therapy; GAF, Global Assessment of Functioning; HDRS, Hamilton Depression Rating Scale; ITI, intertrain interval; L-DLPFC, left dorsolateral prefrontal cortex; MDD, major depressive disorder; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; UL-ECT, unilateral nondominant electroconvulsive therapy; VAS, visual analog scale.

*Psychotic patients in ECT group also were on antipsychotics.

Adapted from Janicak et al.[10]

# Cost Considerations

# Cost Comparison

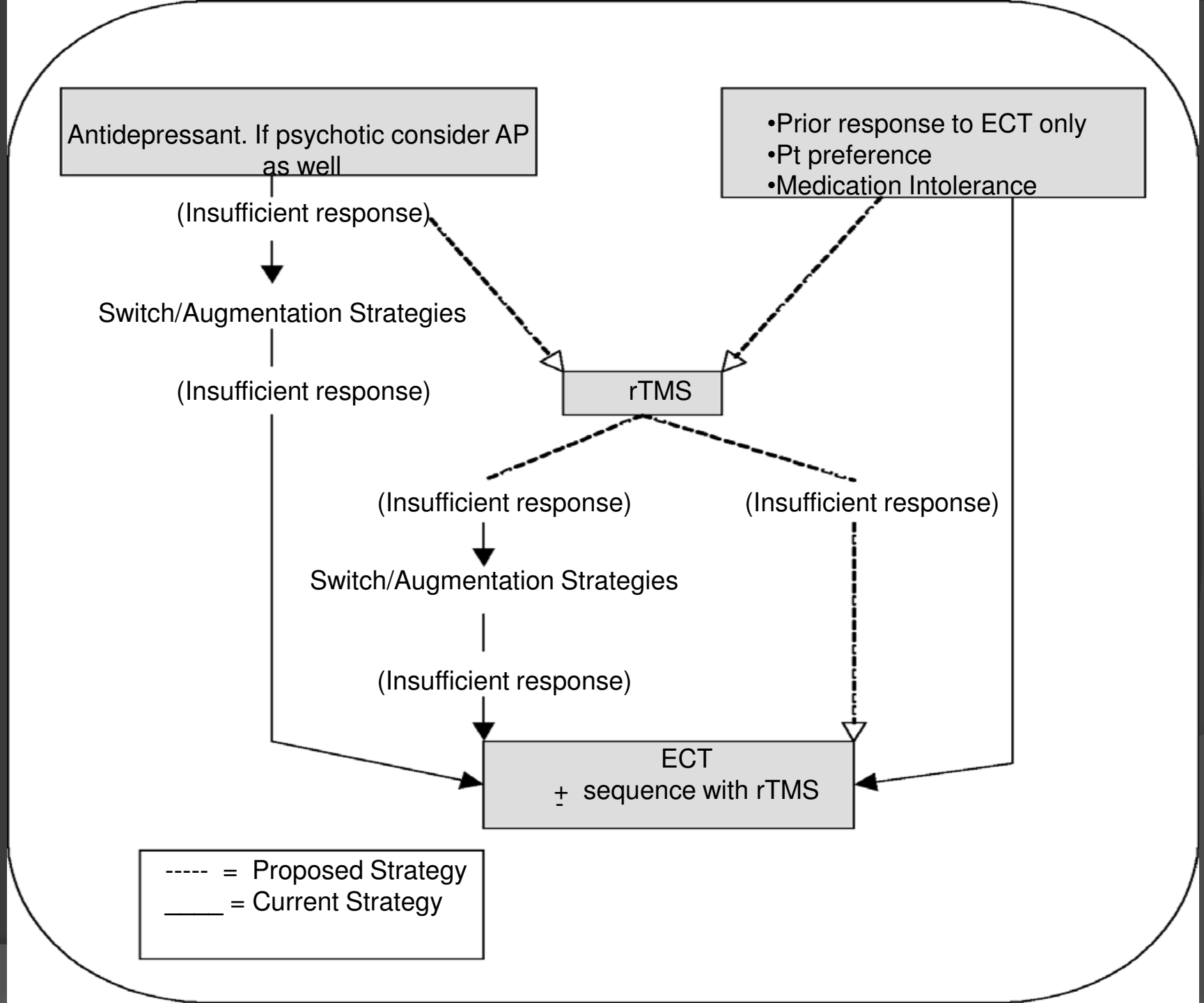
| | ECT | TMS |
|---|---|---|
| **Session per Week** | 2 – 3 | 5 - 6 |
| **Total Duration of Treatment** | 8 – 12 sessions<br>2 – 6 Weeks | 20 – 30 sessions<br>3 – 6 Weeks |
| **Cost of session** | $600 -1000 | $300 |
| **Estimated Cost per Course** | $7000 - 12000 | $6000 - 10000 |

# Convenience or Inconvenience?

- Hospitalization
- Travel Time/Waiting Time
- Number of Sessions per Week
- Total number of Sessions
- Duration of Treatment
- Recovery Period
- Time off from Work and Driving Restrictions

# Proposed Role of TMS

(Adapted from: Dowd SM, Janicak PG.The attraction of magnetism: how effective—and safe—is rTMS? Current Psychiatry.2003;2:59.66.)


Antidepressant. If psychotic consider AP as well
(Insufficient response)
Switch/Augmentation Strategies
(Insufficient response)
•Prior response to ECT only
•Pt preference
•Medication Intolerance
rTMS
(Insufficient response)
(Insufficient response)
Switch/Augmentation Strategies
(Insufficient response)
ECT
± sequence with rTMS
----- = Proposed Strategy
_____ = Current Strategy

# Past, Current, and Future Uses of TMS

- *Major Depressive Disorder :*

  FDA Approved in 2008

- *Diagnostic, Prognostic, and Therapeutic Role in Neurology:*

  Brain mapping, Excitability studies, Aphasia, Spastic Muscle, Post-Stroke, Pain Management

- *Potential Applications in the Future:*

  PTSD, Anxiety, Fibromyalgia, ADHD, Migraines, Addictions, Obesity, Autism, Epilepsy

# Adverse Effects and Contraindications

- Risk of Seizure:

  h/o seizures, stroke, head injury, TCA's or any neuroleptics which lower seizure threshold.

- Minor Side Effects:

  Headache, site pain, facial pain, eye pain, ear pain, tinnitus, toothache, muscle twitching, MSK stiffness, neck pain, hypoasthesia, paraesthesia, anxiety.

- Contraindications:

  metallic objects, implants, wearable or removable devices.

# References: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