BRAIN STIMULATION – AN ALTERNATIVE TO DRUG THERAPY IN MATERNAL DEPRESSION?

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CA Maternal Mental Health Initiative - 2013

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MAJOR DEPRESSIVE DISORDER: WHAT WE ARE UP AGAINST

- 17% Lifetime risk of depression
- 1 in 4 diagnosed with depression get adequate care
- 15% risk of suicide
- 15% treatment resistant

Hasin, DS, et al. *Arch Gen Psychiatry*. 2005;62:1097–1106.
Kessler, RC, et al.. *JAMA*. 2003;289:3095–3105.

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RISKS MDD *DURING* PREGNANCY:

Up to 23% of expectant women either enter pregnancy already suffering from a MDE or become clinically depressed during pregnancy

- Ongoing depression during pregnancy is associated with negative maternal and fetal outcomes
  - ✓ **Maternal Factors:**
    - ✧ Poor Maternal self-care: Diet, exercise, sleep hygiene, prenatal care
    - ✧ Symptoms of maternal: irritability, overwhelmed, anxiety, insomnia
    - ✧ Increased risk of substance abuse
    - ✧ Increased risk of postpartum depression
  - ✓ **Pregnancy Factors:**
    - ✧ Low birth weight
    - ✧ Preterm Labor
    - ✧ Developmental delay
    - ✧ Neurobehavioral difficulties

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RISKS OF DEPRESSION *DURING* THE POSTPARTUM

- Antenatal depression increases the risk of postpartum depression and hospitalization
- Children of depressed mothers are more likely to have:
  - Conduct problems
  - Emotional instability
  - Increased risk of requiring psychiatric care

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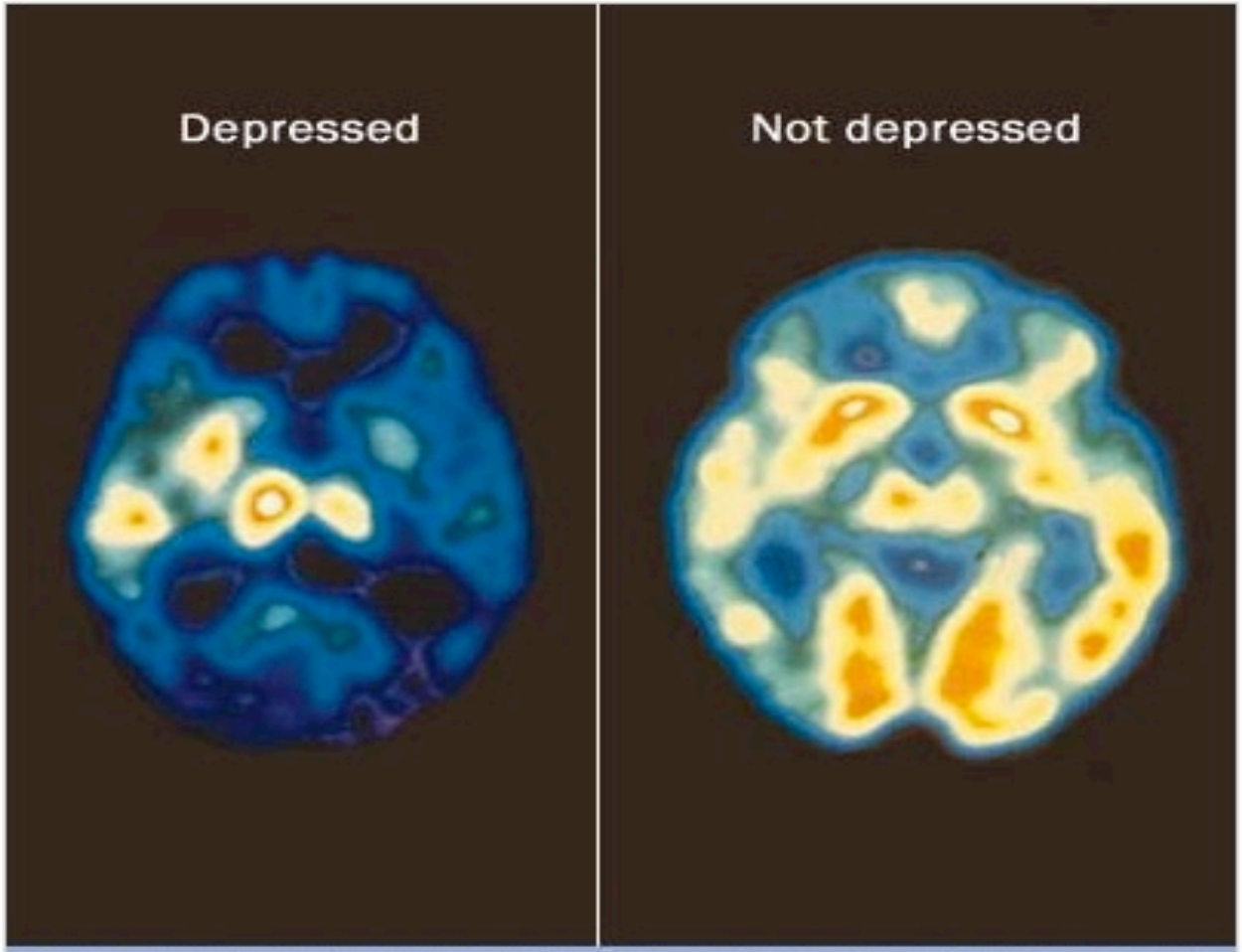
Image

PET scan of the brain for depression



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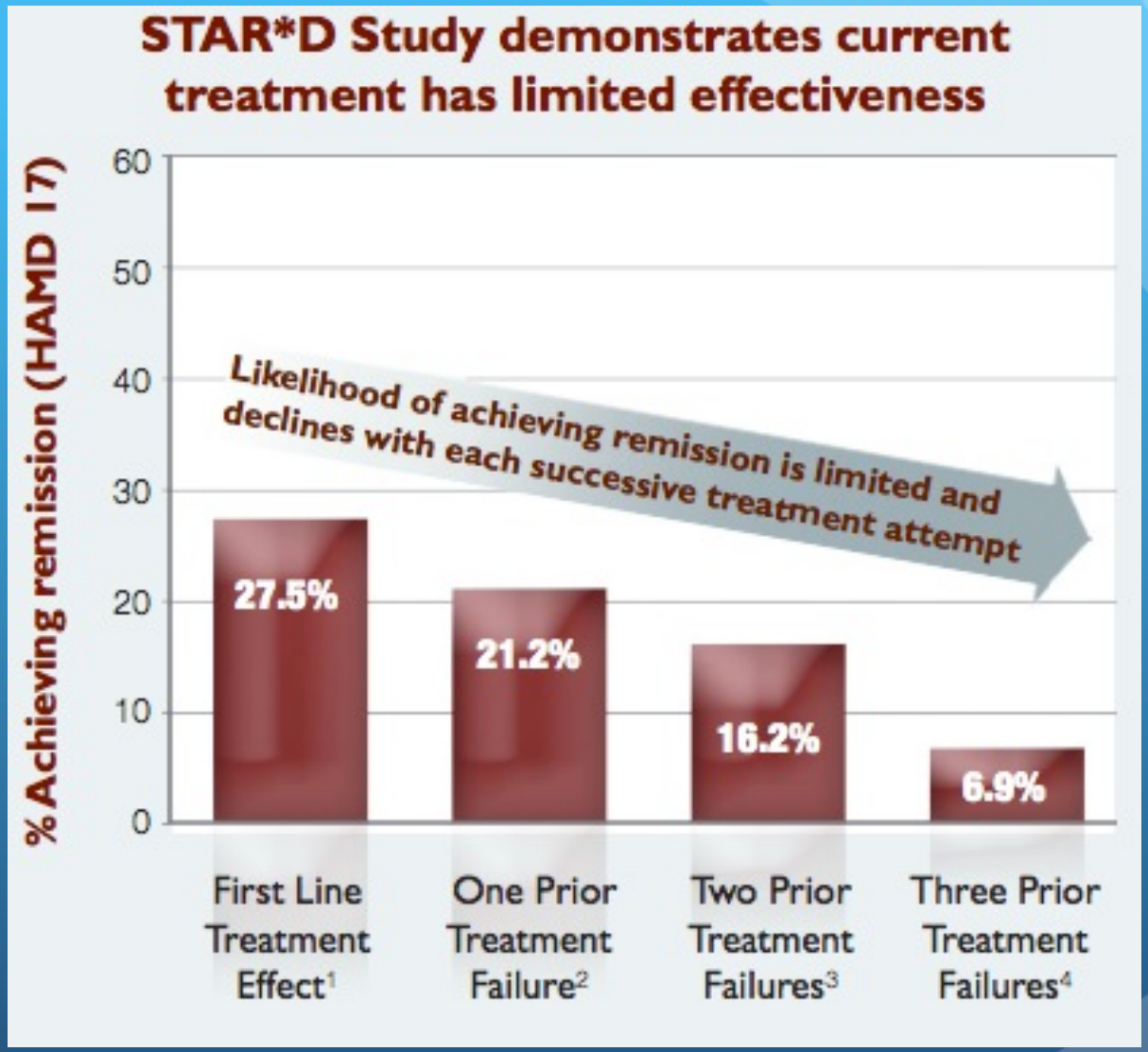
A PET scan can compare brain activity during periods of depression (left) with normal brain activity (right). An increase of blue and green colors, along with decreased white and yellow areas, shows decreased brain activity due to depression.

EFFICACY OF ANTIDEPRESSANT DRUGS



Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*

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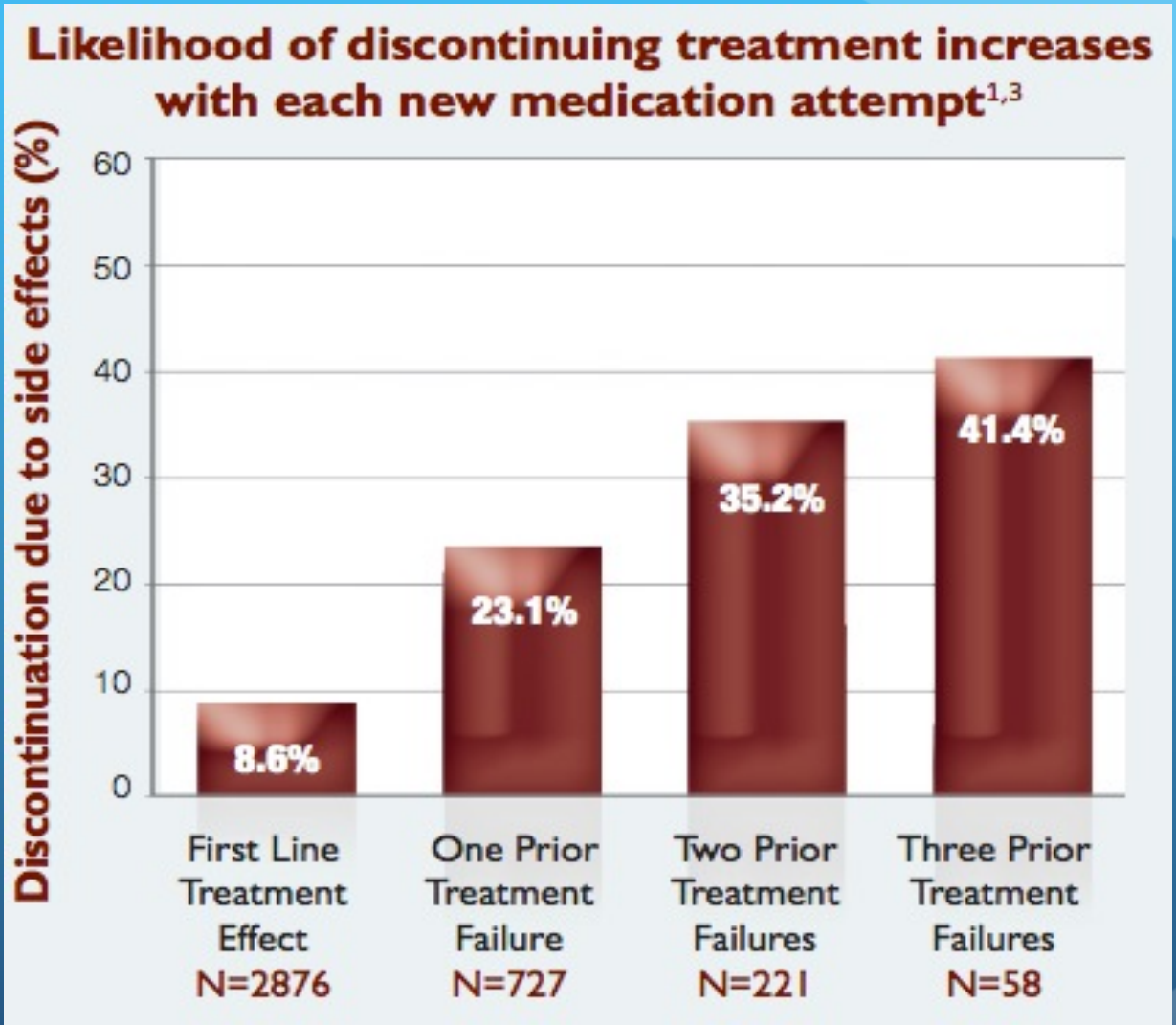
TOLERABILITY OF ANTIDEPRESSANT DRUGS STAR*D, Continued



Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*

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NON-INVASIVE BRAIN STIMULATION

BRIGHT LIGHT THERAPY:

- Both Seasonal and Non-Seasonal Depression
- Can be helpful in pregnancy
- Estimated 40-60% positive response but need more rigorous larger-scale studies
- Rare, mild nausea, headaches
- May trigger mania in patients with bipolar disorder

10,000 Lux, UV Shielded, Diffused

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NON-INVASIVE BRAIN STIMULATION

CES:

- FDA-Cleared Since 1978
- Safety shown over 30 years, though precautions for pregnancy are on FDA label
- More evidence for pain, insomnia and anxiety relief
- Reports "positive outcomes" on depression, but more rigorous research and evidence needed

CRANIAL ELECTROTHERAPY STIMULATION

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NON-INVASIVE BRAIN STIMULATION

TMS :

- FDA Cleared 2008
- **TMS MONOTHERAPY (Not with medications)** after one prior failed drug attempt:
  - Response: 54%
  - Remission: 33%
- **TMS AS ADD-ON (in the field)**
  - Significantly better results
- **6 MONTH RELAPSE RISK IN TMS RESPONDERS MAINTAINED ON ONE MEDICATION:** 11% (with 85% benefitting after TMS reintroduction)

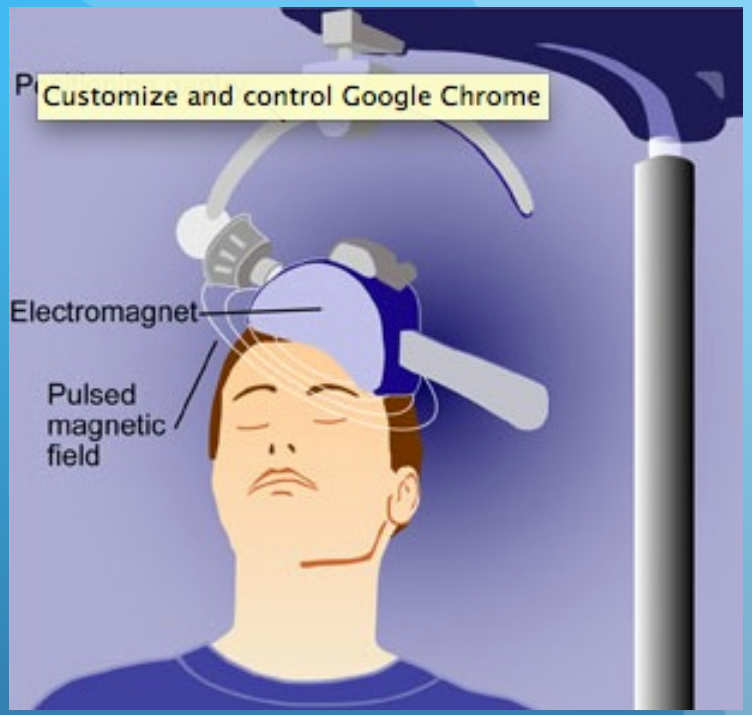

Image from NIMH

TRANSCRANIAL MAGNETIC STIMULATION

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TMS THERAPY: SAFETY

- No systemic side effects
- No adverse effect on cognition
- Most common adverse event is transient scalp discomfort
  - Less than 5% of patients discontinued due to adverse events
- Clinical studies of non-pregnant population – no seizures
  - (over 10,000 treatments)
- Seizure risk with TMS: (0.003% per treatment; 0.1% per patient).
  - Compared to risk of seizure with fluoxetine (0.1%); bupropion SR (0.1%); TCA's (0.4% - 2%)
- Long-term safety demonstrated

Janicak, et al. *J Clin Psychiatry*, 2008; Janicak, et al. *Brain Stimulation*, 2010.

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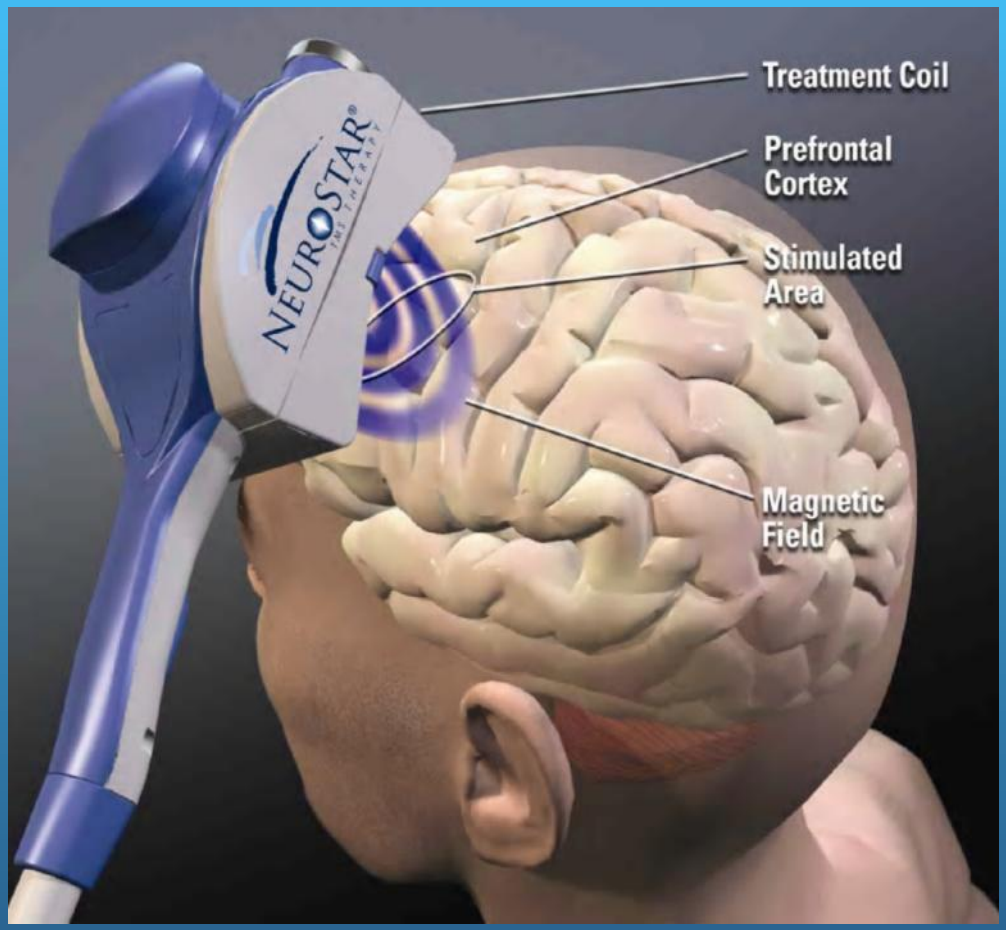
HOW TMS WORKS



- MRI-strength magnetic field pulses induce neuronal electrical currents & firing, causing:
  - Release of neurotransmitters
  - Changes in neural network activity
  - Changes in activity of deeper structures
  - Clinical effects

Faraday (1839) *Experimental Research in Electricity*. Vol 1; Barker (1991) *J Clin Neurophysiol*; Barker (1985) *Lancet*

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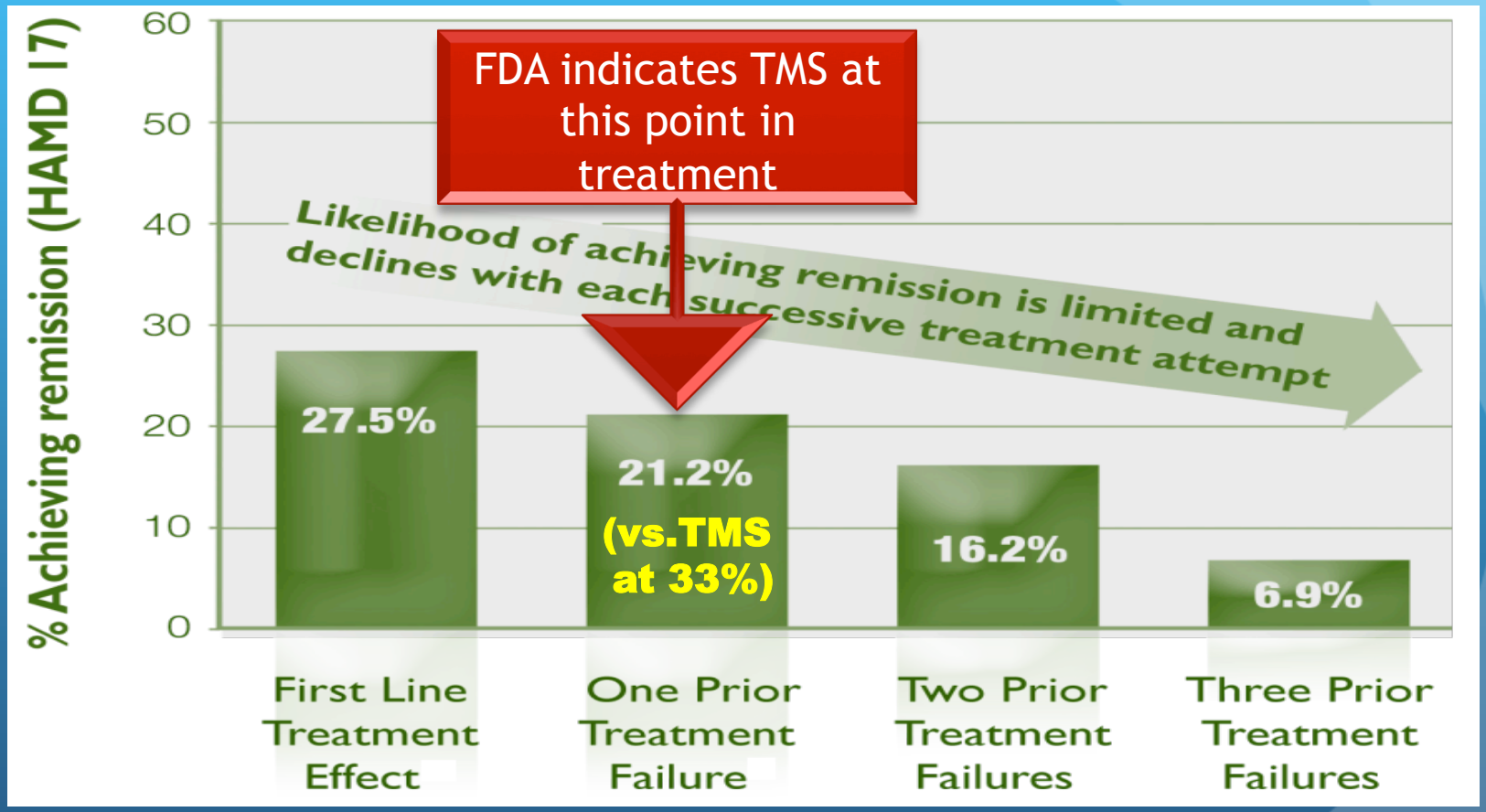
Standard FDA-Protocol TMS MONOTHERAPY
on FDA-Indicated Population
Shows better efficacy at achieving remission than Medication
(With One Prior Medication failure)



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OVERVIEW OF EVIDENCE SUPPORTING ANTIDEPRESSANT EFFECTS OF TMS

- > 30 controlled clinical research studies published on TMS
- 3-Part clinical study by Neuronetics qualifying TMS for FDA Approval for indicated population with 1 prior med failure (1/2 response; 1/3 remission with TMS Monotherapy)
- *Independent* NIMH Study supporting industry Findings
- Recent Meta-analyses supporting increased use of TMS in psychiatric practice
- TMS centers' experiences demonstrate superior efficacy using more updated, individualized treatment parameters on broader population
- Ongoing clinical outcome studies continue to support efficacy and safety in even broader than indicated population failure (1/2 response; 1/3 remission)

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TMS IN PREGNANCY: OPEN-LABEL CASE SERIES PILOT STUDY

Kim D, et al J Women's Health 2011

An Open Label Pilot Study of Transcranial Magnetic Stimulation for Pregnant Women with Major Depressive Disorder

- **SUBJECTS:**
  - 20 cases 18-39 years old, 14-34 weeks gestational age
  - If on antidepressant medications, doses remained constant 2 weeks before TMS and throughout the duration of TMS
  - No other significant psychiatric, biochemical problems, or epilepsy
- **Pre-TMS:**
  - Maternal-Fetal Specialist screening
- **TREATMENT:**
  - Twenty 10-minute sessions of 1 HZ TMS localized to *Right* DLPFC
  - No Sham (completely open); No control.
- **POST DELIVERY:**
  - Delivery records, major malformations, NICU admissions were evaluated

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RESULTS – TMS IN PREGNANCY: OPEN LABEL STUDY

- 10 of 13 subjects were acceptable (3 excluded)
- 100% compliance of TMS treatment
- 70% (7) responded to TMS treatment (at least 50% improvement of HDRS-17 scores)
- 30% (3) remitted
- For all scales, there was no significant difference between subjects who were on or off medications
- No serious maternal adverse events
  - Most common adverse event: Mild headache
- No Adverse pregnancy or neonatal outcomes or NICU admissions

CONCLUSION:
Promising BUT not conclusive due to small sample size and open label uncontrolled conditions.

RECOMMENDATIONS:
Larger, randomized, sham-controlled study

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WHAT INCREASES THE RISK OF SEIZURE DURING PREGNANCY?

- Pregnancy itself does not increase the risk of seizure in non-epileptic patients.
- Must monitor for conditions that predispose to seizures:
  - Sleep deprivation
  - Nausea and vomiting, and subsequent dehydration.
  - Diabetic Hypoglycemia (blood sugar can be checked)
  - Preeclampsia 2-8% of pregnancies (usually 20-24 weeks gest)
- Pre-existing epilepsy: Preferable to consider ECT or TMS in hospital setting

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QUESTIONS THAT BEG RESEARCH ON TMS & PREGNANCY:

- TMS ***before*** conception to reduce medication or depression exposure?
- Does TMS affect the HPA Axis in a detrimental way in pregnancy? Especially oxytocin and thyroid hormones?
- Does TMS cause any other maternal-fetal risks or exposures?
- If so, what are the risks compared to ECT, medications or the condition of depression itself?

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TMS EFFICACY IN POSTPARTUM POPULATION

- Efficacy likely similar to general population but clearly needs further study
- TMS Case Studies/Reports:
  - One open-label (n=9) study demonstrated successful TMS treatment of MDE
    - 8 out of 9 achieved remission after 4 weeks
    - 7 of 8 maintained remission after 6 months without addition of medications (1 being lost to follow-up)
  - Successful treatment of rapid cycling during pregnancy/ postpartum

Garcia et al, Brain Stimulation, 2010
Cohen et al, brain Stimulation, 2008

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MORE INVASIVE BRAIN STIMULATION

ECT :

- 80-90% Response
- Generalized Anesthesia Risks
- Usually Temporary: Confusion, Amnesia, Muscle and Head aches, Temporary Dependence on Caregivers/Drivers

Image from NIMH

ELECTROCONVULSIVE THERAPY

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MORE ON ECT

- "GOLD STANDARD" IN PSYCHIATRY
- RESPONSE 80-90%
- RISK OF RELAPSE WHILE ON COMBO MEDS DURING 6 MONTHS POST-SUCCESSFUL ECT: 40- 50%
- Virtually all ECT patients will relapse if no ECT or medication continuation therapy is used

Prudic J, et al. J ECT. 2013.
Kellner CH. J ECT 2013.

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MATERNAL RISKS IN ECT

18 maternal ECT-Related Complications out of 339 case reports of ECT use in pregnancy between 1942 and 2007

-status epilepticus,
-hematuria
-uterine contractions and/or preterm labor,
-vaginal bleeding,
-abdominal pain, and
-placental abruption

Anderson EL, Reti IM. Psychosom Med. 2009

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PREGNANCY/FETAL RISKS WITH ECT

11 ECT-associated fetal complications out of 339 cases of ECT use in pregnancy between 1942 and 2007:

- Most Common was transient fetal arrhythmia (n=8).
- Only one fetal death due to status epilepticus.

1.6% miscarriage risk

Anderson EL, Reti IM. Psychosom Med. 2009

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WHEN TO USE ECT:

<u>Particularly effective for:</u>

- Catatonia.
- Rapidly worsening/destructive/life-threatening/malnourishing/self-neglectful
  - bipolar or unipolar depressions,
  - psychotic depressions,
  - Psychoses
  - and manias.

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ECT IN PREGNANCY

- APPROPRIATE WHEN RISKS OF CONDITION OUTWEIGH THE RISK OF ECT & ANESTHESIA (Determined on a Case-By-Case Basis)

- OB/GYN, Anesthesiologist and Psychiatrist Monitoring before, during and post-ECT
  - Maternal-Fetal Monitoring for blood pressure, hypoxia, contractions, fetal movement, etc.

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INVASIVE BRAIN STIMULATION

VNS

- 30% Response; 15% Remission over 6-12 months
- Surgical, hoarseness, shortness of breath, nausea, pain, and anxiety

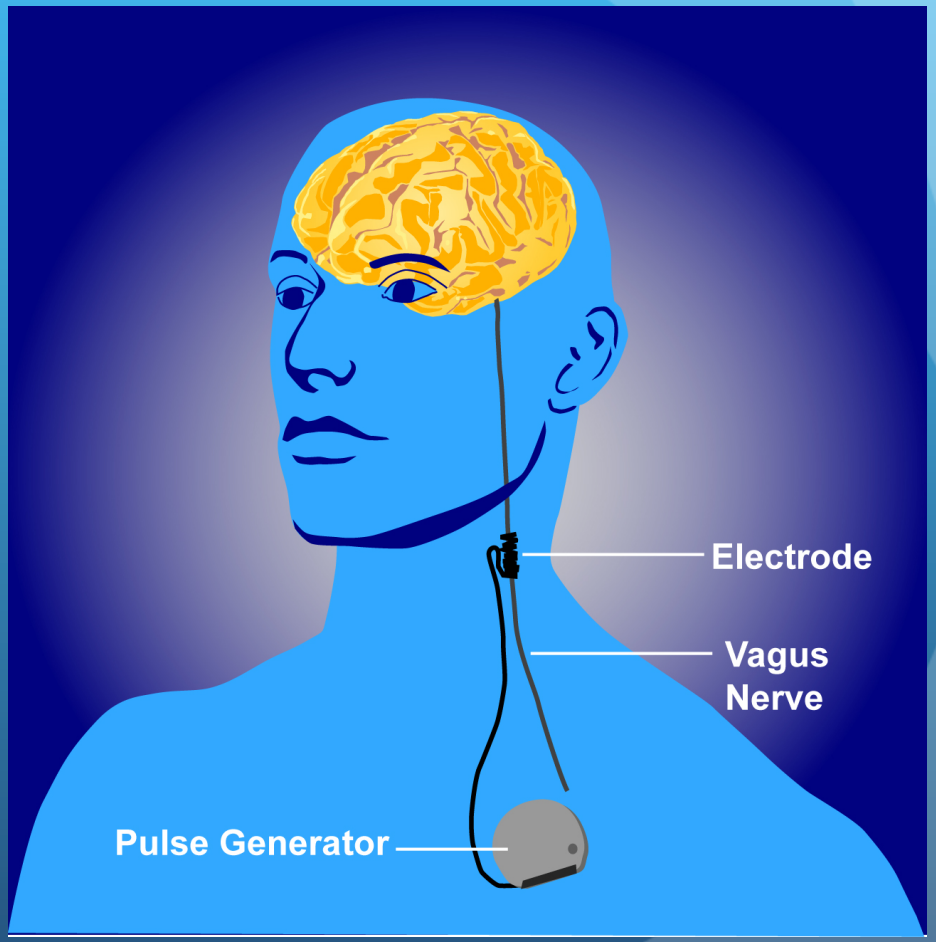

Image from NIMH

VAGUS NERVE STIMULATION

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Thank you!

Any Questions?

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