Transcranial Magnetic Stimulation (TMS)

TMS—the best intervention for treatment resistant major depressive disorder

- TMS is very safe and highly effective
- TMS is well tolerated
- The response to TMS is lasting

Repetitive Transcranial Magnetic Stimulation (rTMS)

- Results from over eight years of providing rTMS in private practice
- Indications and which patients respond the best
- Comparing FDA approved rTMS devices
- Future direction(s) for TMS

TMS is very safe and highly effective

- Mechanism of action
  - A changing magnetic field induces electrical current (Maxwell and Faraday)
  - MRI strength magnetic coil induces the magnetic energy that traverses the skull and into the cortex.
    - The time varying magnetic field induces current in the neurons of the superficial cortex that stimulates other neurons that are part of the circuit.
  - Role of neuroplasticity
    - Effects continue after stimulation is finished
    - rTMS affects cotical excitability with high frequency pulses increasing cortical excitability and low frequency pulses decreasing cortical excitability.

Focus is on location

- Left prefrontal cortex
  - Window into the Limbic System and associated circuits
    - Amygdala, hippocampus, mammillary bodies, etc.
  - Stimulation continues downstream
- Other areas are focus for study

Efficacy of rTMS

- Over 20 years of research and development
- More than 30 published randomized controlled trials
- Over a dozen Meta-analyses
- Over 11 years of clinical experience in the community
- Primary focus has been antidepressant treatment

Large scale studies of rTMS (N > 100)

- O’ Reardon, et. al., 2007. Industry sponsored (N = 301)
  - Randomized to either active arm or sham
  - Patients failed four previous antidepressants
  - Outcomes measured at 4 and 6 weeks using MADRAS and Ham-D
  - Active treatment superior to sham at 4 and 6 weeks (p = 0.038)
    - Response defined as > 50 % improvement from baseline
    - Response was Two fold higher after 4 weeks and Three fold higher at 6 weeks

Large scale studies of rTMS (N > 100)

- George, et. al., 2010
  - Randomized to active or sham
  - Active arm showed superiority at week 3 (14 % vs 5 %)
  - Open label extension for patients not previously responding
    - 41 % responded and 30 % remitted

Meta-analysis

- Level 1 evidence since randomized controlled trials are included
- More than 12 meta-analyses have been conducted since 2000
  - Majority show statistical superiority of rTMS to sham treatments
  - Effect sizes ranged from those showing 50 % to 80 % improvement in depression scores

Clinical Effectiveness of rTMS

- Pooled data of nonresearch samples show robust results
  - Carpenter et al (2012) pooled data from 42 clinical practices (N = 307)
    - Average of 2.5 to 3.4 previously failed medication trials
    - 58 % responded and 37.1 % remitted
  - Connolly et al (2012) (N =100)
    - Single academic practice
    - Similar results 50.6 % responded and 24.7 % remitted
    - Included patients who had failed ECT

Comparison with Electroconvulsive Treatment (ECT)

- ECT has had over 75 years of use and modifications
- rTMS has been FDA approved for 11 years
- ECT has faster response rate
- rTMS is non-invasive
- rTMS can help improve cognition whereas memory problems are a hallmark side effect of ECT
- Most Head to Head studies have showed ECT as more effective
  - Limited by sample size and variations on the rTMS protocols used

rTMS is Well Tolerated

- Proven safe and effective for decades
  - Only contraindication is presence of magnetic sensitive metal above shoulders
  - In some cases implanted stimulators may be a problem
- Transient discomfort to area of treatment
  - Stimulation to superficial neurons
  - Intense 4 second train of pulses at 10 Hz
  - Discomfort is diminished over time

rTMS is Well Tolerated

- Patients with migraine may have headaches
- Seizures are rare
  - Meta analysis by Bae et al (2007) estimate risk is 1.4 %
  - Increased risk with alcohol use, sleep deprivation, or some medications
- Imaging studies show no structural changes after rTMS
- Human histological study (Gates et al 1992) showed no histopathological changes to temporal lobe of one patient
- Meta analysis (N = > 3000) (Machii et al 2006) showed no cognitive deterioration

TMS response is long lasting

- Durability studies show vast majority of patient have over a year of lasting response
- My experience is that about 25 % of patients need another treatment within two to three years
- Majority of patients have not needed further rTMS and some have not had treatment for over 8 years
- Subsequent treatments have better and longer lasting response than the previous treatment

Results of over eight years experience providing TMS

- Well over 300 patients
- Results measured by PHQ-9 and Beck's Depression Inventory
  - 67 % have had robust response (average improvement was 11 points)
    - Within the group of patients 43 % achieved remission
- Most patients note improvement by the end of treatment but some take a month or more to recognize the improvement
  - Role of neuroplasticity
- One patient using the Deep TMS system had a seizure
  - Sleep deprived and taking Bupropion
  - He elected to continue treatment and continued using different device and had no further seizures

Indications for TMS and which patients respond the best

- FDA cleared for Major Depressive Disorder
  - Moderate to severe and failed one adequate medication trial
- Insurance carriers require at least 4 antidepressant failures
- Patients with concomitant Personality Disorders may not respond as well
- Duration of current Depressive episode may or many not be a factor

Comparison of TMS Devices

- Physical effects dependent on shape of magnetic coil
  - Figure eight shape is most common
    - First one developed
    - Neuronetics NeuroStar and MagStim devices
  - H-shaped coil
    - Brainsway device
    - Deeper stimulation with stronger pulses

Comparison of TMS Devices

- Southern Maine TMS experience
  - Six years using either Neuronetics or Brainsway devices
    - Three years each device with 100 patients treated with each device
  - Same patient selection criteria
    - MDD, failed at least 4 antidepressants
  - Same treating technicians and protocols

Comparison of TMS Devices

- Results
  - Less deep stimulation had the best results
    - About 10 % better results on PHQ-9
    - More patients could tolerate the treatment
  - Only patient to have a seizure in 8 years of treating patients was with the Deep TMS system
    - More patients dropped out of treatment with the Deep TMS treatment
    - Many moved to NeuroStar system and completed treatment

Future of TMS

- Early in the evolution of the treatment modality
  - Protocols for treating other conditions need development
    - Shapes of waveforms, pulse frequency, duration, location of treatment, etc.
- Conditions under investigation
  - Adolescent Major Depressive Disorder
  - Bipolar Depression
  - Obsessive Compulsive Disorder
  - Sustance Dependence
    - Tobacco, Opioids, others

Future of TMS

- Conditions under investigation (continued)
  - PTSD
  - Parkinson’s Disease
  - ADHD
  - Cognitive Impairment
  - Tinnitis
  - Auditory Hallucinations

Conclusion

- rTMS is at least the best initial intervention for Treatment Resistant Depression (TRD)
- rTMS is safe and effective
- rTMS is well tolerated and has no cognitive side effects
- Future improvements to the current state of the technology are ongoing
- Many more conditions will be treated by this modality in the future

References

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