Neuromodulation Therapies for Depression at UNC

Robert K. McClure, M.D.
Associate Clinical Professor
UNC Department of Psychiatry

Disclosure of Potential Conflicts of Interest:

Goals:

(A.) Transparency

(B.) Clarity

(C.) Accuracy

Potential Conflicts of Interest:

(1.) 2002-2005: Speaker's bureau, Jannsen and Pfizer, Abbott consultation fee.

(2.) 2005: travel/lodging reimbursement for attendance at conferences sponsored by Medtronics, and Neuronetics.

(3.) UNC Chapel Hill School of Medicine requires annual report of each faculty member's financial relationship(s) with any commercial interests. Accepting reimbursement equal to or exceeding 10% of their annual salary is subject to review. No reimbursement has approached this level.

(4.) Centers for Medicaid and Medicaire Services (CMS) see

https://www.cms.gov/openpayments/collects information over the past decade from applicable manufacturers and group purchasing organization (GPOs) . **I have no conflicts of interest.**

Indications *Not* Approved by the FDA ("Off-Label" Use):

(1.) Ketamine is not FDA-approved for treatment of MDD or BPAD so the treatment of depression is "off-label".

(2.) Transcranial Magnetic Stimulation (TMS) is FDA approved for the treatment of MDD*.

(3.) ECT devices are FDA-approved (grandfathered)

(3.) Deep brain stimulation (DBS) for treatment-refractory Obsessive Compulsive Disorder (OCD) is FDA approved under a humanitarian device exemption, but is not FDA approved for the treatment of MDD or BPAD.

“A Neuromodulation Therapy is….”

(1.) A pharmacologic agent or medical device used to

(2.) Correct abnormal function of neuronal circuits

(3.) Implicated in a psychiatric condition

UNC Neuromodulation therapies *(increasing invasiveness):*

(1.) Ketamine Infusion

(2.) Transcranial Magnetic Stimulation (TMS)

(3.) Electroconvulsive Therapy (ECT)

(4.) Vagal Nerve Stimulation (VNS)

(5.) Deep Brain Stimulation (DBS) for OCD but not MDD or BPAD

Ketamine Meta-Analysis Results:

(McGirr et al, 2015)

1) Ketamine was associated with higher rates of:

a) **clinical remission** relative to (saline or midazolam) at 24 h (OR 7.06), 3 days (OR 3.86) and 7 days (OR 4.00)

b) **clinical response** at 24 h (OR 9.10), 3 days (OR 6.77), and 7 days (OR 4.87).

2) A standardized mean difference (assumed a conservative estimation of r = 0.7.) = **0.90** in favor of ketamine observed at 24 h, based on depression rating scale scores.

3.) Group comparisons revealed greater efficacy in unipolar depression compared to bipolar depression (1.07 v. 0.68).*

Ketamine Meta-Analysis Results:

(Coyle and Laws, 2015):

1) Effect sizes were significantly larger for repeat than single infusion at 4 h, 24 h and 7 days, but the small number of studies at 12–14 days post infusion failed to reach significance.
2) For single infusion studies, effect sizes were large and significant at 4 h, 24 h and 7 days.
3) A discrepancy in peak response time depending upon primary diagnosis: 24 h for MDD, and 7 days for BD.
4) The majority of published studies have used pre–post comparisons so further placebo-controlled studies would help to clarify the effect of ketamine over time.

Benefits and Risks of Ketamine

Benefits: 40-50% response rate; IV only; very rapidly acting; systemic side effects only during treatment; outpatient; no seizure.

Risks: psychomimetic side effects; elevated blood pressure and pulse (treatable); pain during IV; Medicaire and insurers not reimbursing; repeated treatments; short duration of therapeutic effects.

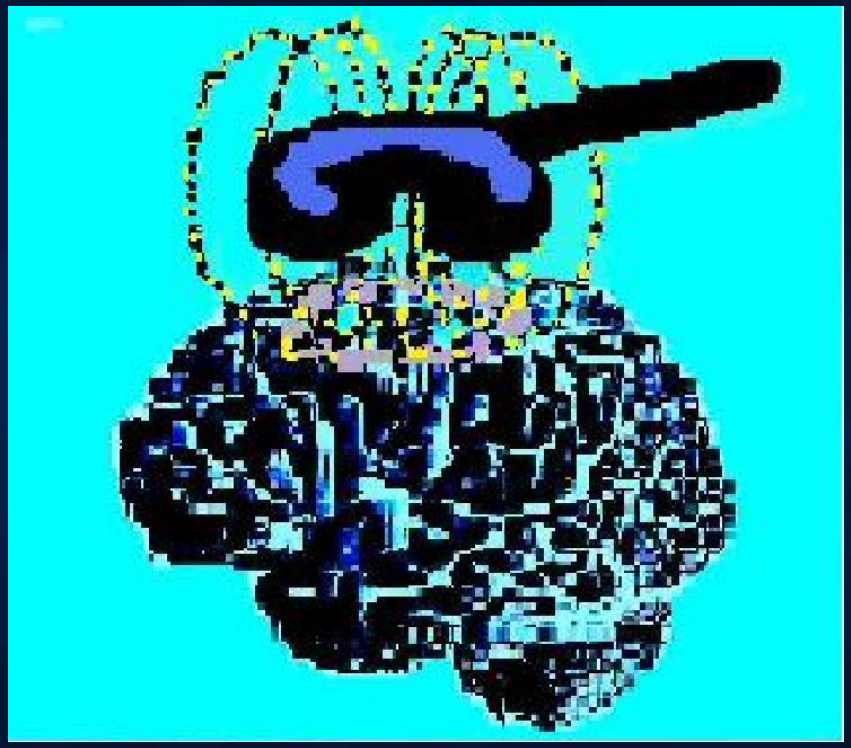
Transcranial Magnetic Stimulation (TMS):

Electromagnetic induction:

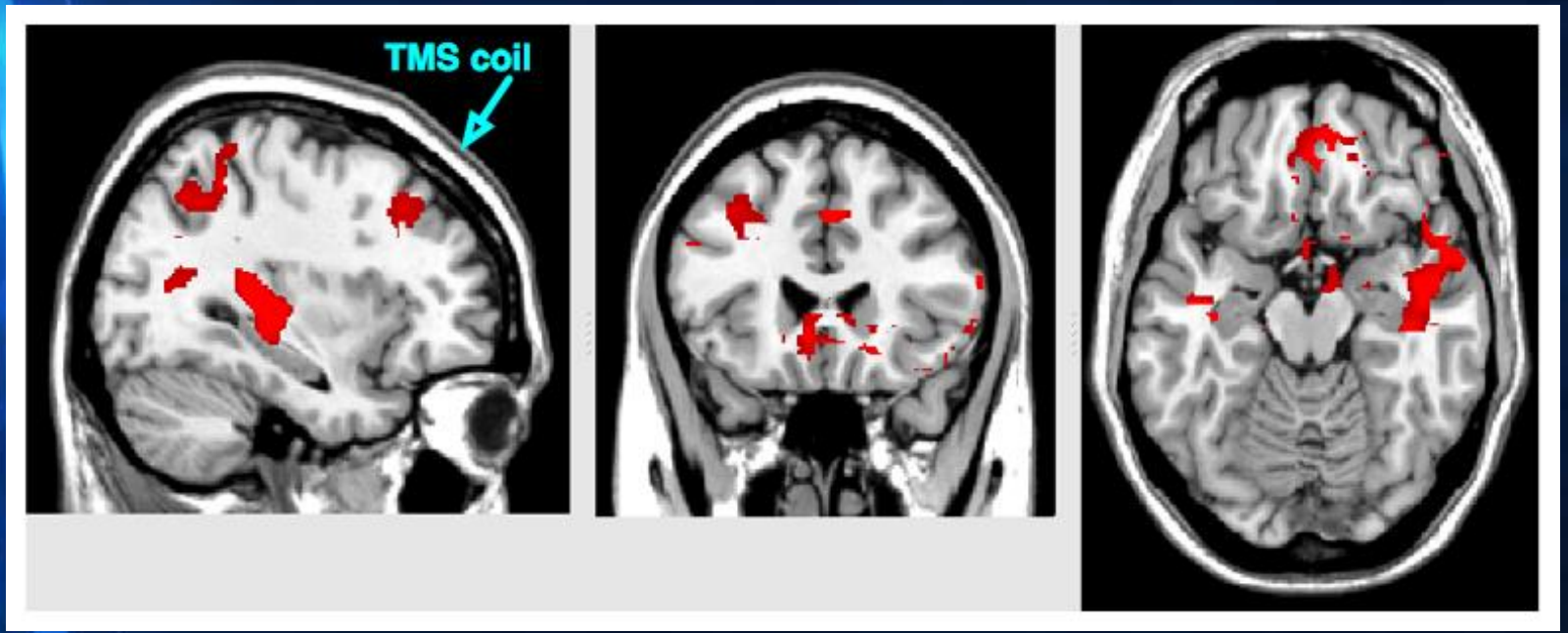
Faraday's Law: a magnetic field induces an electrical current in a perpendicular direction.

Clinical application:

A magnetic field induces electrical current in the Neurons of the brain.



TMS Effects: **Left prefrontal TMS results in activation of neurons at site of stimulation, and at cortical and subcortical regions connected by synapses**



Benefits and Risks of TMS

Benefits: 30-50% response rate; no systemic side effects; outpatient; no seizure, Medicaire and insurers reimbursing.

Risks: pain during treatment; weekday treatments; ECT more for refractory depression, seizure risk, maintenance; MRI

Electroconvulsive Therapy (ECT)

Benefits: >50% efficacy in refractory MDD; covered by Medicaire and insurers

Risks: anesthesia; 1/10,000-20,000 mortality rate; short and long term memory; side effects (headache, nausea, muscle pain), and major inconvenience

Vagus Nerve Stimulation (VNS)

Benefits: 30-40% efficacy in refractory MDD.

Risks: Invasive, surgical adverse events; MRI exclusion

Ketamine Treatment Centers of North Carolina

6 Years and 1,000 Patients...Thoughts on Treating Depression and Anxiety With Ketamine

Steven P. Levine, M.D.

History

- Ketamine is a dissociative anesthetic first developed by Parke Davis in 1962.
- “Buddy drug” during the Vietnam war.
- 1st randomized controlled trial in depression published in 2000, but awareness of antidepressant properties since the 70’s.
- 1st report of antidepressant potential of an NMDA receptor antagonist in 1959.

Indications

- Major Depression
- Bipolar Depression
- PTSD
- OCD
- Fibromyalgia

Contraindications

- Current mania
- Current psychosis or history of psychotic disorder
- Uncontrolled hypertension or unstable cardiac illness
- Current substance abuse

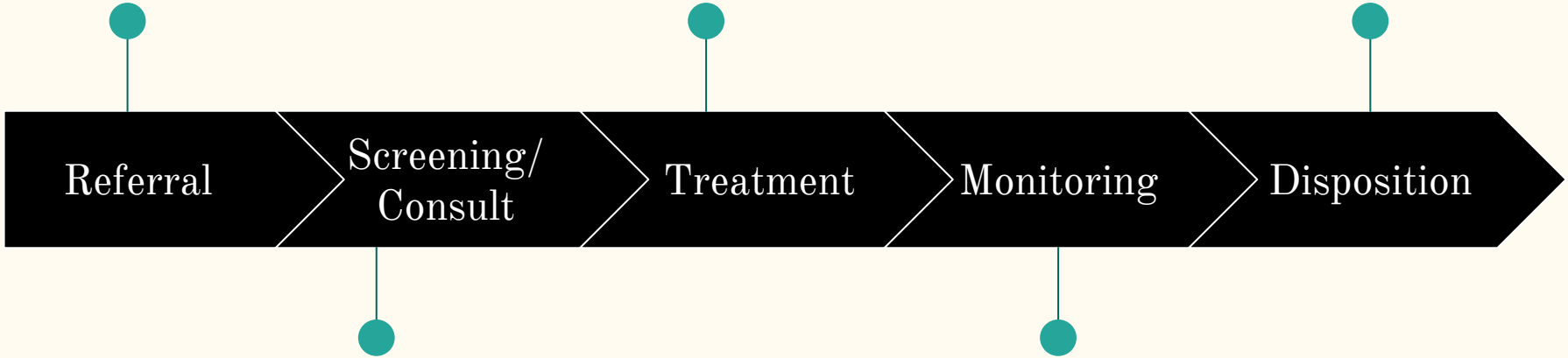
Ketamine Treatment Centers Numbers

- 3 open locations: Princeton, NJ; Denver, CO; Baltimore, MD
- Raleigh, NC opens June 15th, 2016
- Total patient treated = 1,000+ (>8,000 infusions)
- Primary diagnoses: 60% MDD, 15% bipolar depression, 15% PTSD, 10% OCD. Multiple comorbidities, including GAD and personality d/o diagnoses.
- Overall response rate approximately 70% following 1-2 infusions.
- Approximately 50% of responders will achieve remission at some point during treatment.
- 0 known suicides following treatment in a highly vulnerable population.

Primarily referred by psychiatrists/therapists- KTC serves consultant/liaison role

0.5 mg/kg IV over 40 min, 10-20% dose titrations as needed

Periodic maintenance ketamine (q3wks - qyear) vs. oral medication/therapy



Inclusion/Exclusion criteria; H&P; preparing patients is key

Assessments at 24hrs post acute tx, weekly during maintenance - scales +phone

Office Environment

1. Private rooms with white noise machines to block ambient sound.
2. Low stimulation and minimal background activity or distraction.
3. Warm and safe environment.
4. Most patients choose to listen to music.

Adverse Events

Medical

Acute:

Occasional mild nausea, mitigating by closing one's eyes.

Mild, transient elevations of heart rate and blood pressure.

Dreamlike, dissociative experience may be part of the mechanism, **not** an AE

Long-term (up to 5 years): None.

Psychological

With minimal preparation, a small percentage will experience anxiety/panic.

Well-prepared patients will almost always have a pleasant, interesting, or productive experience.

Maintenance

- Initial series of 6 infusions (3 per week for 2 weeks, or 3 per week, then 2 per week, then 1).
- 1st maintenance dose 2-3 weeks later.
- Ongoing maintenance schedule determined by duration of sustained response.
- Psychotherapy is critical.
- May consider augmenting/extending response with oral medication (lithium, dextromethorphan/quinidine, etc) or neuromodulation (TMS, tDCS).

What is the true mechanism of action (how does it work)?

- NMDA receptor antagonist?
- AMPA receptor activation?
- How important are serotonergic, noradrenergic, sigma-1, u-opioid targets?
- Anti-inflammatory?
- The dissociative experience?

Who should be offering this?

- Psychiatrists
- Anesthesiologists
- Ketamine Treatment Centers of North Carolina combines the expertise of psychiatrists and anesthesiologists

What are appropriate dose parameters?

- 0.5 mg/kg IV over 40 min is relatively arbitrary, but best studied
- Anecdotal vs. evidence-based protocols
- Therapeutic window? Pre-clinical (animal) studies suggest that increasing the dose above a threshold may be ineffective.

Where do we go from here?

- Practice guidelines and possibly a registry are coming.
- Where will funding come from for further research to establish best practices?
- Self-reporting measurement tools for rapidly-acting treatments?
- What will be the role of ketamine in 5 years once multiple ketamine-like products in the pipeline come to market?

References

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