

Novel treatments for resistant depression: ready for prime time?

Maureen O. Brown MD, MPH

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- 56 year old cab driver
- Long hx of depression, PTSD
- Much worse x 2 years, can't work
- Paranoia, auditory hallucinations
- Pervasive suicidal ideation
- Brief hospitalization 1 year ago
- Poor response/intolerance to 4 classes of antidepressants, 2 trials of augmentation, CBT

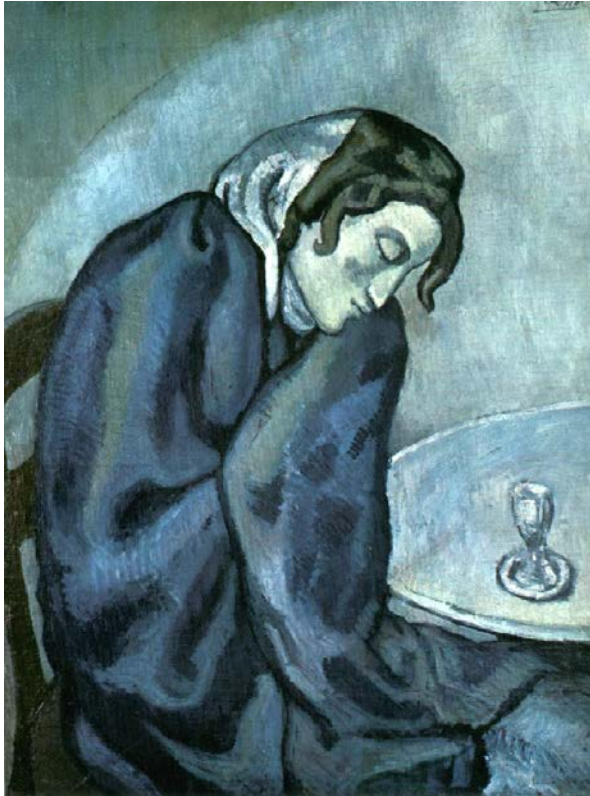


Objectives

- What is treatment resistant depression?
- What is Transcranial Magnetic Stimulation, and does it work?
- What about ketamine/esketamine?



What is Treatment Resistant Depression?



- No clear consensus re: definition
- No remission after adequate trials of 1-4 different antidepressants
- Response vs remission
- Rule out:
 - Inadequate dose
 - Non-adherence
 - Drug intolerance
 - Wrong diagnosis

How effective are antidepressants?



- 40-60% respond to initial drug after 6-8 wks
- 30% won't respond despite 4 drug trials
- ECT for resistant depression: 50-70% response, but high relapse rate



In MDD, 30-40% placebo response rate

- Refuses ECT
 - Stigma
 - Cost (\$, time)
 - General anesthesia
 - Cognitive impairment
 - High relapse rate



What is Transcranial Magnetic Stimulation (TMS)?

- 2008: FDA approved for treatment-resistant MDD
- Repetitive magnetic pulses
- Target: dorsolateral prefrontal cortex
- Protocols continue to evolve, with improved outcomes
- Continue antidepressant meds during/after tx
- Deep TMS approved in 2013



How is TMS delivered?



- No sedation, non-invasive
- 5x/week x 4-6 weeks
- Treatments take 20-40"
- Well-tolerated
 - headache
 - scalp discomfort
 - transient hearing loss
 - very rarely seizures
 - no cognitive impairment
- Remission evident by 4-6 weeks
- Consider maintenance TMS in responders

Relative Contraindications

- Hx of seizures, head injury, stroke or TIA
- Metallic implants in cephalic area
- Acute or chronic cardiac disease
- Deafness or hearing loss
- Metabolic or systemic disease
- Neurologic conditions: space occupying lesions, aneurysm, increased intracranial pressure

Does it work?

- NIMH(2010):
 - Multi-center, sham controlled RCT
 - Antidepressant-free, treatment-resistant MDD (n=190)
 - 15 sessions, +15 more for initial responders
 - Remission rate at 6 weeks: 15% vs 4%
- Brainsway (2015):
 - Industry-sponsored, multinational sham-controlled RCT
 - Anti-depressant free, MDD, failed 1-4 previous Rx trials (n=212)
 - 5 sessions/week x 4 wks of dTMS or sham coil, then 2x/week for 12 wks
 - Week 5 response rate: 38% vs 21%; remission rate 33% vs 15%
 - Week 16 response rate: 44% vs 26%; remission rate 32% vs 22% (n.s.)



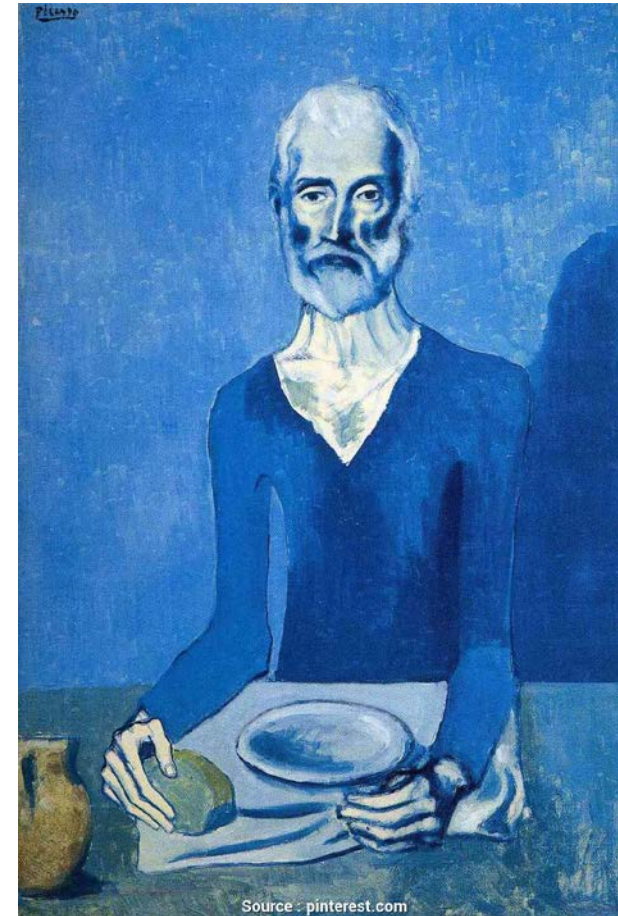
Who responds best to TMS?

- Positive predictors:
 - Less severe depression, shorter duration
 - Hx of previous response to TMS
 - Concomitant antidepressant Rx
- Negative predictors:
 - Short acute treatment (5-15 sessions)
 - Drug naïve patients
 - Elderly
 - Long duration of current episode
 - Psychotic depression



What about ketamine?

- Off-label use, sub-anesthetic doses
- OK with most antidepressants (avoid benzos)
- Antidepressant effects: rapid, robust but transient
- Contraindicated if psychotic features
- Adverse effects:
 - Transient increase in BP, pulse (BP>180/110, or HR>110, in 30%)
 - Transient dissociative or psychotomimetic effects
 - Headache, nausea, dizziness, anxiety



Does ketamine work?

- Studies small, no long-term follow-up
- Pooled analysis, n=172, unipolar or bipolar MDD, placebo control, *single* dose:
 - Response at 2 hours 51% vs 2%
 - At 1 day, 53% vs 7%
 - 7 days, 31% vs 7%; 14 days 11% vs 0%
 - Remission peaked at 30% at 1d, 3% at 14d
- Efficacy vs placebo, 2x/wk x 2 wks (n=35):
 - Response 69% vs 15%, remission 38% vs 8%



What is Esketamine?

- FDA approved in 2019
- Restricted availability, administered in medical office, 2+ hours observation
- Dose 56-84mg, intranasal (4-6 sprays)
- 2x/week x 4 weeks, then weekly x 4 weeks, then q1-2 weeks
- Give with oral antidepressant
- Very limited number of providers in King County



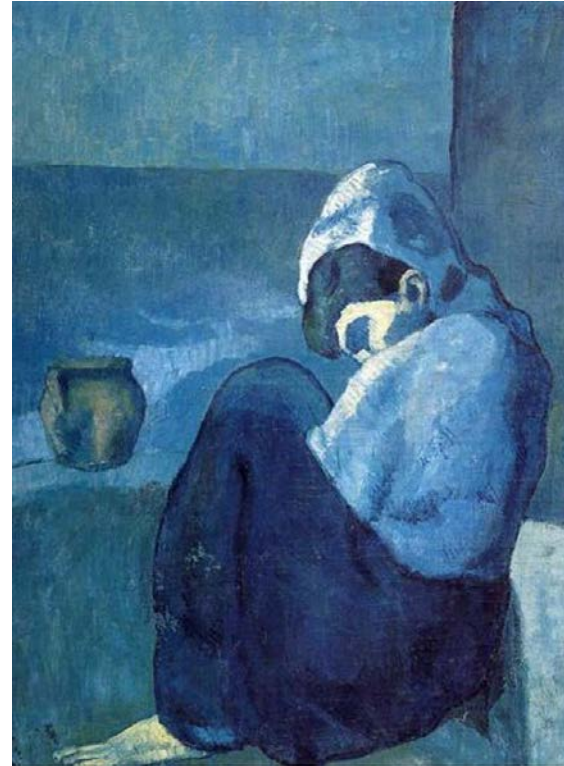
Does Esketamine work?

- Very limited data!
- 1 (+) short-term RCT (28 d, n=342)
 - 70% F, mean age 46
 - Response 54% vs 39%
 - Remission 39% vs 31%
- 1 long-term maintenance RCT
 - Variable duration, Qw or Qow, up to 80+wks
 - Remitters (n= 176): relapse 27% vs 45%, median 153 vs 33 days
 - Responders (n=121): relapse 26% vs 58%, median 635 vs 88 days



What's next?

- Ongoing TMS protocol modifications
- Trans-cranial direct current stimulation
- Psilocybin-assisted treatment: 2018 FDA approval of further testing for refractory depression





Next steps?

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