TOOLS FOR PRACTICE #360 | March 04, 2024

TOOLS FOR PRACTICE

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

Ketamine for Depression

CLINICAL QUESTION

What are the benefits and harms of ketamine/esketamine for depression?

BOTTOM LINE

Ketamine/esketamine appears effective for moderate-severe depression (helping 10-20% more people respond over placebo at 1-4 weeks). However, biases are very common and large effects are likely exaggerated. Adverse events are common (example: 20% more nausea/vomiting). Considerable uncertainty remains (treating mid/long-term, misuse risk, and long-term harms) and treatment is costly.

EVIDENCE

- 11 systematic reviews with meta-analyses (3-49 randomized controlled trials (RCTs), 703-3299 moderately-severely, mostly treatment-resistant, depressed patients) in last 3 years.[1-11] Typically, ketamine single-dose intravenously 0.5mg/kg over 40 minutes or esketamine intranasally 28mg (1-3 puffs) twice weekly (less frequent when stable). Results statistically significant unless noted.
- Efficacy:
    - Response rate (highest-quality review) versus placebo:[1]
        - Ketamine (4-7 RCTs, 185-202 patients):
            - Day 1: 27% versus 9%, number needed to treat (NNT)=6.
            - Day 28: Not statistically different (week 1-2 becomes non-significant).
        - Esketamine (5 RCTs, 1071-1117 patients):

        - Day 1: 27% versus 15%, NNT=9.
        - Day 28: 57% versus 42%, NNT=7.
      - Others found similar.[2-8,10]
    - Changes in depression scale:
      - Meta-analysis (3 RCTs, 703 patients):[4] MADRS depression scale (scale 0-60, ≤6 normal), baseline ≥28:
        - Mean improvement esketamine=18 versus placebo=14, difference=4 at 4 weeks. Minimal important difference[12]=3-6.
        - Other found similar[7] or statistics not clinically interpretable.[1-3,5,6,9,11]
- Versus active control:
  - Electroconvulsive Therapy (ECT): One RCT favored ECT (186 more-severe patients),[13] one favored ketamine (403 less-severe).[14]
  - Anti-depressant augmentation with esketamine versus quetiapine (150-300mg):[15] Remission (8 weeks), 27% versus 18%, NNT=11.
- Stopping: 297 esketamine responders (after 16 weeks) randomized to continue or placebo:[16]
  - At 18 weeks, relapse 26% (continued esketamine) versus 50% (discontinued/placebo), NNT=5.
- Adverse Events:
  - Esketamine: Dissociation (29% versus 4%); dizziness (32% versus 11%); nausea/vomiting (36% versus 15%); and more. Ketamine similar.[1]
  - Serious events (examples: mortality, substance misuse) inadequately studied.[17,18]
- Ketamine research issues: Mostly small/short, single-dose RCTs;[1,2,5-11] publication bias;[2,5,6] benefit halved in higher-quality RCTs;[5,6,11] unblinding common.[19]
  - RCT: 40 depressed patients given ketamine or placebo under-anesthesia. No difference in depression efficacy.[20]

CONTEXT

- Mechanism of action remains uncertain.[1,21-23]
- Guidelines:[23,24] Ketamine potential option for severe, treatment-resistant depression with awareness of risk mitigation, adequate delivery standards and uncertainty regarding medium/long-term management.
- Cost of intranasal esketamine:[25] $15,000-45,000/year. Ketamine generally in-hospital or related outpatient IV clinic.

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