GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of August 26 - 30, 2024

SPOTLIGHT:
Zuranolone: A 14-Day Rapid Acting Treatment for Postpartum Depression

- Shorter Course, Lower Cost: Rifampicin for Pulmonary Tuberculosis?
- OMT as a Complement to Medical Therapy in GAD
- Can a New Intervention Prevent the Cognitive Decline of Dementia?

Zuranolone: A 14-Day Rapid Acting Treatment for Postpartum Depression

Zuranolone for the Treatment of Postpartum Depression

Deligiannidis KM, Meltzer-Brody S, Maximos B, et al. Zuranolone for the Treatment of Postpartum Depression. *Am J Psychiatry.* 2023;180(9):668-675. doi:10.1176/appi.ajp.20220785

KEY TAKEAWAY: Treatment with oral zuranolone in women with severe postpartum depression (PPD) demonstrated rapid improvement in depressive symptoms.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, parallel-group, phase three trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Depression during pregnancy or the postpartum period is frequently underdiagnosed and untreated, but expedient, effective management is essential to reduce adverse maternal and fetal outcomes. While selective serotonin reuptake inhibitors (SSRIs) are currently the main treatment for PPD, achieving a response to these medications can take up to 12 weeks. Zuranolone, a neuroactive steroid and positive modulator of the $GABA_A$ receptor, is investigated in this study as an oral, once-daily, 14-day treatment for more rapid therapy for PPD.

PATIENTS: Women with PPD

INTERVENTION: Zuranolone

CONTROL: Placebo

PRIMARY OUTCOME: Depression severity

Secondary Outcome: Change in depression severity up to 45 days, safety and tolerability

METHODS (BRIEF DESCRIPTION):

- Women 18–45 years old with an episode of severe major depression during the third trimester of pregnancy or ≤4 weeks postpartum, and who were ≤12 months postpartum were enrolled at one clinical site.
- Those with a history of psychotic disorders, bipolar disorder, attempted suicide, or risk of suicide were excluded.
- Women were required not to breastfeed during the study.
- Participants had a mean age of 31 years old, 22% identified as Black, 38% identified as Hispanic, 15% were taking baseline antidepressant medication, and most had onset of symptoms within four weeks of delivery.
- 200 patients were initially enrolled and randomized in a 1:1 ratio, with 196 participants who self-administered either oral zuranolone 50 mg/day or placebo once daily each evening for 14 days.
- A smartphone platform visually confirmed medication compliance.
- Participant responses to validated screening tools were collected at baseline and on days three, 15, 28, and 45. Change from baseline was also measured.
- The Hamilton Depression Rating Scale (HAM-D) ranks 17 items to assess depression severity. Scores range from 0–52 with higher scores indicating more severe depression. A score of 0–7 is indicative of no depression while severe depression is a score of ≥25.
- Clinical Global Impressions Severity (CGI-S) scores rank the severity of illness from 1–7 with higher scores indicating worse illness. A score of one is indicative of no illness while a score of seven is indicative of being extremely ill.

INTERVENTION (# IN THE GROUP): 98

COMPARISON (# IN THE GROUP): 98

FOLLOW-UP PERIOD: 45 days

RESULTS:

Primary Outcome –

- Zuranolone showed significant improvement in depressive symptoms compared to placebo, based on the change in HAM-D score from baseline to day 15 (least squares mean [LSM] difference –4.0; 95% CI, –6.3 to –1.7).

Secondary Outcome –

- The zuranolone group showed significantly greater improvement in the change in HAM-D scores compared with the placebo at day three (LSM difference –3.4; 95% CI, –5.4 to –1.4), day 28 (LSM difference –2.9; 95% CI, –5.4 to –0.5), and day 45 (LSM difference –3.5; 95% CI, –6.0 to –1.0).
- Change from baseline in CGI-S scores was greater at day 15 in the zuranolone group compared to placebo (LSM difference –0.6; 95% CI, –0.9 to –0.2).

- During the treatment course, adverse events were reported by 60% (N=59) in the zuranolone group and 42% (N=41) in the placebo group.
    - The most common adverse event was somnolence.
- Dose reduction was required for 16% (N=16) receiving zuranolone and 1.0% (N=1) receiving placebo.

LIMITATIONS:

- The study only included patients with severe PPD, and the representation of patients from outside the US was low.
- The population of those with PPD was homogenous, excluding those with later postpartum onset, who may have different symptom severity and medication response.
- As the zuranolone group reported more adverse events, this could have impacted the blinding of the study.
- Long-term safety and tolerability remain unknown given the short follow-up period.
- The effect of zuranolone on lactation is unknown, as study participants were not allowed to breastfeed.
- There was a high placebo response, possibly related to frequent study visits.

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Shorter Course, Lower Cost: Rifampicin for Pulmonary Tuberculosis?

Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

Jindani A, Atwine D, Grint D, et al. Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis. *NEJM Evid.* 2023;2(9):EVIDoa2300054. doi:10.1056/EVIDoa2300054

KEY TAKEAWAY: A shorter course of four-month high-dose rifampicin is not as effective for pulmonary tuberculosis resolution as the standard six-month regimen.

STUDY DESIGN: Randomized, single-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Globally, approximately 10 million people are affected by tuberculosis (TB), and over 10% of them die from it despite the availability and efficacy of rifampicin, isoniazid, ethambutol, and pyrazinamide. This may be due to the long duration of the current standard dose of six months leading to nonadherence due to high costs and incomplete treatment. Prior studies explored the efficacy of four months of rifapentine and moxifloxacin. This study assesses the efficacy of four months of rifampicin which is cheaper and more readily available.

PATIENTS: Patients with newly diagnosed TB

INTERVENTION: Four months of rifampicin

CONTROL: Six months of rifampicin

PRIMARY OUTCOME: Noninferiority determined by unfavorable outcomes

Secondary Outcome: Per-protocol analysis of primary efficacy outcome, conversion status of sputum culture at eight and 12 weeks, adverse events

METHODS (BRIEF DESCRIPTION):

- Adults ≥18 years old with newly diagnosed TB by positive sputum Xpert MTB/RIF with rifampicin-sensitivity who had not had more than one week of treatment from Botswana, Uganda, Guinea, Nepal, Pakistan, and Peru were included.
- Patients were blinded and randomized to one of the following treatments:
  - Four months daily rifampicin 1,200 mg/d and isoniazid + ethambutol and pyrazinamide for the first two months (SR1).
  - Four-month daily rifampicin 1,800 mg/d and isoniazid + ethambutol and pyrazinamide for the first two months (SR2).
  - Six months daily rifampicin 10 mg/kg and isoniazid + ethambutol and pyrazinamide for the first two months
- Medication was distributed by an on-site pharmacist or nurse.
- Unfavorable outcomes included death due to TB, loss of follow-up, withdrawal from trial, a complete change of medication regimen secondary to adverse effects, and positive sputum culture after the completed medication regimen.
- The noninferiority margin was defined as eight percentage points.

INTERVENTION (# IN THE GROUP):

- 1,200 mg/d rifampicin: 192
- 1,800 mg/d rifampicin: 195

COMPARISON (# IN THE GROUP): 191

FOLLOW-UP PERIOD: 18 months

RESULTS:

Primary Outcome –

- Four months of 1,800 mg/d rifampicin was inferior to standard dosing (adjusted risk difference [aRD] 6.3; 90% CI, 1.1–12).
  - Four months of 1,200 mg/d was also inferior (aRD 3.1; 90% CI, –1.6 to 7.9).

Secondary Outcome –

- Per protocol, the analysis was similar to the primary outcome analysis.
- Conversion of culture at week eight was lowest in the control group with 86%, and highest in the 1,200 mg group with 93% (no statistical analysis was performed).
- Conversion of culture at week 12 was lowest in the 1,200 mg group and equivalent in the 1,800 mg with 98% and the control group at 98% (no statistical analysis was performed).
- There was no increase in grade three and four adverse events among high-dose rifampicin groups compared to control:
  - 1,200 mg (percentage point difference 0.5; 95% CI, –3.3 to 4.2)

- 1,800 mg (percentage point difference 0.4; 95% CI, –3.3 to 4.2)

LIMITATIONS:

- The study excluded participants with positive human immunodeficiency virus (HIV) and diabetes mellitus (DM).
- The study did not collect rifampicin levels from participants.
- The study did not have growth indicator tube cultures available at all sites.

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OMT as a Complement to Medical Therapy in GAD

Effect of Osteopathic Manipulative Therapy on Generalized Anxiety Disorder

Dixon L, Fotinos K, Sherifi E, et al. Effect of Osteopathic Manipulative Therapy on Generalized Anxiety Disorder. *J Am Osteopath Assoc.* 2020;120(3):133-143. doi:10.7556/jaoa.2020.026

KEY TAKEAWAY: Osteopathic manipulative therapy (OMT) may be an effective complement to traditional medical therapy for generalized anxiety disorder (GAD).

STUDY DESIGN: Nonrandomized, non-controlled study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Despite the standard of care, GAD can be difficult to treat. Thus, alternative modalities to treat GAD are increasingly relevant. This article studied the effect of OMT on GAD.

PATIENTS: Individuals with moderate to severe GAD

INTERVENTION: Five OMT sessions

CONTROL: Not applicable

PRIMARY OUTCOME: Anxiety symptoms

METHODS (BRIEF DESCRIPTION):

- Patients 18–65 years old with a primary diagnosis of moderate to severe GAD based on Hamilton scoring criteria, who did not achieve remission rates after at least eight weeks of standard treatment Hamilton A (HAM-A) score >20 at screening were included in the study.
- Exclusion Criteria: Drug or alcohol dependence, pregnancy, changes in medication use during study, suicide risk, and serious disease or illness.
- Participants were initially screened with both the mini international neuropsychiatric interview and HAM-A scoring criteria to rate their anxiety.
- Participants received five sessions of OMT (muscle energy, myofascial release, cranial, balanced ligamentous tension [BLT], and visceral) during an 8–9 week period.
- The HAM-A was used to assess symptoms during and after the study, with 30 being the highest score indicating severe anxiety. The Intolerance of Uncertainty Scale (IUS) and Beck Anxiety Index (BAI) were also used to assess anxiety symptoms.
- The study looked at the mean change on the HAM-A, IUS, and BAI scales before and after OMT, utilizing paired sample t-tests in observed cases.

INTERVENTION (# IN THE GROUP): 26

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- OMT decreased anxiety symptoms compared to baseline:
  - HAM-A score (t_{25}=15, P<.0001)
  - IUS score (t_{25}=4.2, P<.0001)
- There was no significant decrease in anxiety symptoms when assessed with BAI (t_{25}=0.022, P=.98).

LIMITATIONS:

- The study lacked a control group and was not blinded.
- The reference did not study the effects of particular OMT techniques.
- A relatively small sample size of 26.

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Can a New Intervention Prevent the Cognitive Decline of Dementia?

Effect of Personalized Risk-Reduction Strategies on Cognition and Dementia Risk Profile Among Older Adults: The SMARRT Randomized Clinical Trial

Yaffe K, Vittinghoff E, Dublin S, et al. Effect of Personalized Risk-Reduction Strategies on Cognition and Dementia Risk Profile Among Older Adults: The SMARRT Randomized Clinical Trial. *JAMA Intern Med.* 2024;184(1):54-62. doi:10.1001/jamainternmed.2023.6279

KEY TAKEAWAY: Personalized interventions aimed toward identified risk factors for poor cognition and dementia may improve overall cognition.

STUDY DESIGN: Unblinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding and small sample size)

BRIEF BACKGROUND INFORMATION: Dementia, with its many forms, is a common and feared illness experienced by older adults. Medication trials are underway for new treatments, but research has not demonstrated the benefit of a dementia prevention approach from a risk reduction standpoint. This study set to evaluate whether addressing modifiable risk factors through personalized coaching could improve overall cognition.

PATIENTS: Older adults with risk factors for dementia

INTERVENTION: Individualized coaching sessions

CONTROL: Mailed education materials

PRIMARY OUTCOME: Cognition

Secondary Outcome: Risk factors, quality of life

METHODS (BRIEF DESCRIPTION):

- Adult members of Kaiser Permanente Washington in Seattle, 70–89 years old with at least two of eight risk factors for dementia identified on electronic health records (physical inactivity, uncontrolled hypertension, poor sleep, prescription medications with adverse effects on cognition, depressive symptoms, uncontrolled diabetes, social isolation, tobacco use) were included in the study.
- Exclusion criteria included members who had fewer than two risk factors, lived in a skilled nursing facility, received hospice care, were already diagnosed with dementia, and those with other chronic medical and mental health conditions.
- Participants had a mean age of 75 years old with no significant differences between groups in gender, race, education, comorbidity index, and risk factors of physical inactivity, uncontrolled hypertension, poor sleep, risky medications, depression, uncontrolled diabetes, social isolation, and smoking.
- Patients were stratified by age (70–79 years old and 80–89 years old) and randomized into the following groups:
  - The intervention group received 45-minute health coaching sessions every 4–6 weeks for three months, then 20-minute sessions every six weeks for 15 months.
    - Sessions were given by health coaches and nurses to set goals aimed at addressing risk factors and reinforcing protective factors.
  - The control group received 1–2 pages of mailed education about reducing dementia risk every three months.
- All patients underwent an in-person baseline visit using a modified neuropsychological test battery.
- Outcomes were measured every six months for two years.
- The primary outcome measured the composite score on the modified neuropsychological test battery (Cognitive Abilities Screening Instrument [CASI] telephone test, revised Wechsler Memory Scale Logical Memory test, Digit Span test, and Category Fluency and Phonemic Fluency tests) with higher scores indicating improved cognition.
- Secondary outcomes regarding change in risk factors included the Rapid Assessment of Physical Activity for older adults (higher score indicates more activity), steps per day, blood pressure, the Pittsburgh Sleep Quality Index (lower score indicates better sleep), use of Beers criteria prescription medications, the Center for Epidemiologic Studies Depression Scale (low score indicating fewer symptoms), hemoglobin A1C, the Patient-Reported Outcomes Measurement Information System (PROMIS) satisfaction form, and self-reported smoking.

- Quality of Life was measured by the PROMIS Global Health measure for physical health, mental health, social health, pain, and fatigue.
- Outcomes were reported as an average treatment effect (ATE) of the standard deviation (SD) of change in composite scores, standardized at a mean of zero and SD of one.

INTERVENTION (# IN THE GROUP): 82

COMPARISON (# IN THE GROUP): 90

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- Personalized health coaching improved cognition more than control (within-group change 0.32 vs 0.18, respectively; ATE 0.14; 95% CI, 0.03–0.25).

Secondary Outcome –

- Personalized health coaching improved risk factors more than control (ATE 0.11; 95% CI, 0.01–0.20).
- There was no significant difference in quality of life between the two groups.
- Similar rates of serious adverse events were reported during the study in both the intervention and control groups (24 vs 23, respectively), deemed unrelated to the interventions.

LIMITATIONS:

- All patients in the study were from one healthcare facility.
- Participants were not blinded to the intervention.
- The clinical benefit of the change in cognitive scores is uncertain.
- The COVID-19 pandemic changed the in-person assessments to telephone assessments.
- Clinics with greater diversity were oversampled to achieve greater diversity.
- Social interactions were limited during the COVID-19 pandemic and social isolation was one of the risk factors measured.
- The durability of the intervention's effect is uncertain.

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