GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of November 13 - 17, 2023

SPOTLIGHT: Zuranolone Lifts Postpartum Depression

Zuranolone Lifts Postpartum Depression

Effects of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial

Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial [published correction appears in JAMA Psychiatry. 2022 Jul 1;79(7):740] [published correction appears in JAMA Psychiatry. 2023 Feb 1;80(2):191]. *JAMA Psychiatry*. 2021;78(9):951-959. doi:10.1001/jamapsychiatry.2021.1559

KEY TAKEAWAY: Oral zuranolone improves depression at 15 days in women with moderate to severe postpartum depression, with 22–24% greater response and remission rates compared to placebo with no significant adverse effects.

STUDY DESIGN: Phase 3, multi-site, double-blind, placebo-controlled, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Postpartum depression (PPD) is one of the most common medical complications during and after pregnancy. Approximately 13% of new female parents in the United States are affected by PPD. It is underdiagnosed and often goes untreated, with long-term maternal and infant morbidity. Zuranolone is an oral medication that targets the GABAergic pathway, prompting the current study of its efficacy and safety in the treatment of PPD.

PATIENTS: Women with moderate to severe postpartum depression

INTERVENTION: Zuranolone

CONTROL: Placebo

PRIMARY OUTCOME: Efficacy at 15 days

Secondary Outcome: Efficacy at three, nine, 21, and 45 days; safety and tolerability

METHODS (BRIEF DESCRIPTION):

- Randomization at a 1:1 ratio to receive zuranolone, 30 mg, or matching placebo capsules for two weeks.
- Women 18–45 years old (mean of 29.3 years) and six months or less postpartum were included.
  - 41% African American and 23% Latino
- Major depression diagnosis in the third trimester up to four weeks post-partum.
- Included patients had a Hamilton Depression Rating Score (HAMD-17) > 26 at the start of the trial.
- HAMD-17 is a standardized 52-point symptom scale measuring depression severity:
  - Normal: 0–7
  - Mild: 8–16
  - Moderate: 17–22
  - Severe: >24
- Primary efficacy outcome: Change from baseline HAMD-17 score at 15 days.
- Secondary efficacy outcomes: HAMD-17 scores at three, nine, 21, and 45 days.
  - HAMD-17 response (>50% improvement) and remission (score less than or equal to 7)
  - Clinical Global Impression Improvement (CGI-I) with scores from one (very much improved) to seven (very much worse)
- Safety and tolerability outcomes: Evaluated by comparing adverse events, vital signs, clinical laboratory evaluations, EKGs, and the Columbia Suicide Severity Rating Scale.

INTERVENTION (# IN THE GROUP): 76

COMPARISON (# IN THE GROUP): 77

FOLLOW-UP PERIOD: 45 days

RESULTS:

Primary Outcome –

- Zuranolone improved depression symptoms more than placebo at 15 days (Mean difference between groups –4 points; 95% CI, –6.9 to –1.5)

Secondary Outcome –

- Zuranolone improved the following compared to placebo:
  - Depression symptoms at all other days: three, nine, 21, and 45.
  - HAMD-17 response rates (72% vs 48%, OR 2.6; 95% CI, 1.3–5.2)
  - HAMD-17 remission rates (45% vs 23%, OR 2.5; 95% CI, 1.2–5.2)
  - CGI-I response at 15 days (72% vs 52%, OR 2.2; 95% CI, 1.1–4.3)
- Safety and tolerability outcomes: No difference in AE's (somnolence, headache, dizziness, nausea, diarrhea), vital signs, EKGs, clinical laboratory

findings, or suicidality between zuranolone and placebo.

LIMITATIONS:

- Generalizability: White women comprised 56% of the study population.
- Short follow-up period: The study ended after 45 days; the effectiveness of therapy is unknown after this point.
- The safety of breastfeeding was not assessed.

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Rejoice! Physical Activity and Exercise Improve Quantitative and Qualitative Factors in Type 2 Diabetes Patients

Movement is Improvement: The Therapeutic Effects of Exercise and General Physical Activity on Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Shah SZA, Karam JA, Zeb A, et al. Movement is Improvement: The Therapeutic Effects of Exercise and General Physical Activity on Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Diabetes Ther*. 2021;12(3):707-732. doi:10.1007/s13300-021-01005-1

KEY TAKEAWAY: Exercise and physical activity (including low-impact activities) significantly improve glycemic control as shown by a decrease in hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) levels, as well as a reduction in body mass index (BMI) and waist circumference.

STUDY DESIGN: Systematic review and meta-analysis of 26 RCTs (N=7,982)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Type 2 diabetes mellitus (T2DM) is a medical condition that continues to affect millions globally. Many patients live a sedentary lifestyle. There have been several studies examining the advantages of exercise on glycemic control via increased insulin sensitivity and improved glucose metabolism, but these have not been consolidated or quantified.

PATIENTS: Patients with T2DM

INTERVENTION: Exercise

CONTROL: Standard T2DM treatment

PRIMARY OUTCOME: HbA1C

Secondary Outcome: FBG, BMI, and waist circumference

METHODS (BRIEF DESCRIPTION):

- Patients had a mean age of 57 years old. Other demographics were not provided.
- Intervention groups: Aerobic exercise, resistance exercise, walking, yoga, nutrition plus exercise, anaerobic training, or any combination of the above with various frequencies throughout the week.
  - The average exercise session was about 45 minutes.
  - The mean exercise frequency was three days per week.
- Control groups: T2DM patients who had standard therapy (e.g., medication and counseling on diet and minimal physical activity).
- Outcome measurements: HbA1C levels, FSB, BMI, and waist circumference

INTERVENTION (# IN THE GROUP): 4,456

COMPARISON (# IN THE GROUP): 3,526

FOLLOW-UP PERIOD: Eight weeks to one year (mean follow-up of 22 weeks)

RESULTS:

Primary Outcome –

- Compared to control, exercise significantly reduced HbA1C levels (26 RCTs, N=2,456; mean difference [MD] –0.34; 95% CI, –0.50 to –0.19).

Secondary Outcome –

- Compared to control, exercise significantly decreased FBG levels (13 RCTs; N= 956; MD –1.3; 95% CI, –2.4 to –0.14).
- Compared to control, exercise significantly reduced BMI (13 RCTs; N=1,389; MD –0.96; 95% CI, –1.9 to –0.04).
- Compared to control, exercise significantly reduced waist circumference (10 RCTs; N=1,138; MD –2.6; 95% CI, –4.5 to –0.73).

LIMITATIONS:

- The most effective exercise regimen was unclear in the improvement of the primary and secondary outcomes.
- Unable to compare the different modalities of physical activities.
- Most outcome measures were disease-oriented labs and anthropometrics.

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LARCs: Don't Leave Labor and Delivery Without One!

Immediate vs Delayed Postpartum Insertion of Contraceptive Implant and IUD for Contraception

Sothornwit J, Kaewrudee S, Lumbiganon P, Pattanittum P, Averbach SH. Immediate versus delayed postpartum insertion of contraceptive implant and IUD for contraception. *Cochrane Database Syst Rev*. 2022;10(10):CD011913. Published 2022 Oct 27. doi:10.1002/14651858.CD011913.pub3

KEY TAKEAWAY: Immediate postpartum insertion of long-acting reversible contraception (LARC) improves the initiation rate of both contraceptive implants and IUDs by the first postpartum clinic visit. Immediate IUD insertion may reduce unintended pregnancy rates at 12 months but may increase IUD expulsion rates at six months.

STUDY DESIGN: Systematic review and meta-analysis of 16 randomized control trials (N = 2,609)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Clinicians commonly defer postpartum contraception to the first postpartum visit at six weeks, leaving an opportunity for unintended pregnancy. Insertion of LARCs prior to hospital discharge is convenient and may expand LARC use.

PATIENTS: Postpartum women, mostly over 18 years old

INTERVENTION: Immediate postpartum insertion of LARCs prior to hospital discharge

CONTROL: Delayed insertion of LARCs at 6–8 weeks postpartum

PRIMARY OUTCOME: LARC use at six and 12 months, unintended pregnancy rates at six and 12 months, duration of vaginal bleeding initially and at six months for implants, expulsion rates at six months for IUDs

METHODS (BRIEF DESCRIPTION):

- Investigators enrolled postpartum women who requested LARCs prior to hospital discharge after delivery, randomly assigning them to immediate vs delayed insertion groups. They assigned a total of 715 women to receive implants and 1,894 women to receive an IUD.
- They compared insertion of contraceptive implants or IUD insertion immediately (prior to hospital discharge) vs delayed insertion (at the 6-week clinic visit).
- They followed up with the patient at six months and 12 months, collecting data by medical record review.

INTERVENTION (# IN THE GROUP):

- Implants: 361
- IUDs: 954

COMPARISON (# IN THE GROUP):

- Implants: 354
- IUDs: 940

FOLLOW-UP PERIOD: Six and 12 months

RESULTS:

Primary Outcome –

- Immediate insertion increases initiation rates compared to delayed insertion.
  - Implants (Relative risk [RR] 1.48; 95% CI, 1.11–1.98)
  - IUD's (RR 1.27; 95% CI, 1.07–1.51)

Secondary Outcome –

- Immediate insertion does not change utilization compared to delayed insertion.
  - Implants:
    - Six months (RR 1.16; 95% CI, 0.80–1.50)
    - 12 months (RR 0.98; 95% CI, 0.93–1.04)
  - IUDs:
    - Six months (RR 1.02; 95% CI, 0.65–1.62)
    - 12 months (RR 0.86; 95 % CI, 0.50–1.47)
- Immediate contraceptive implant insertion does not change unintended pregnancy rates compared to delayed insertion.
  - Six months (RR 0.20; 95% CI, 0.01–4.08)
  - 12 months (RR 1.82; 95% CI, 0.38–8.71)
- Immediate insertion of an IUD reduces unintended pregnancy rates compared to delayed insertion at 12 months (RR 0.26; 95% CI, 0.17–0.41).
- Implants do not increase vaginal bleeding in the first six weeks, (+2.98 days; 95% CI, –2.71 to 8.66 days) three months, or six months.
- Immediate insertion increases IUD expulsion rates at six months compared to delayed insertion (RR 4.55; 95% CI, 2.52–8.19).

LIMITATIONS:

- Many outcomes were based on studies with moderate to very low certainty evidence.

- Selection bias is possible because studies included only postpartum participants who requested LARCs.

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Battle of the Blues: Ketamine vs ECT in the Fight Against Refractory Depression Without Psychosis

Ketamine vs ECT for Nonpsychotic Treatment-Resistant Major Depression

Anand A, Mathew SJ, Sanacora G, et al. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. *N Engl J Med*. 2023;388(25):2315-2325. doi:10.1056/NEJMoa2302399

KEY TAKEAWAY: Ketamine performed equally as well as electroconvulsive therapy (ECT) in the treatment of refractory treatment-resistant depression without psychosis in patients who failed two or more antidepressants.

STUDY DESIGN: Open-label, randomized, noninferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: ECT is a well-known treatment option for medication-resistant major depression without psychosis, but it has many limitations. Ketamine is a suggested alternative on the rise, but its efficacy compared to ECT needs to be studied.

PATIENTS: Adult patients with treatment-resistant major depression

INTERVENTION: Ketamine

CONTROL: ECT

PRIMARY OUTCOME: Treatment response

Secondary Outcome: Quality of life, cognitive function

METHODS (BRIEF DESCRIPTION):

- The study was an open-label, randomized, non-inferiority trial with a noninferiority margin of –10 percentage points.
    - The patients responding to the ketamine treatment would be no more than 10% less than those responding to ECT.
- Patients had nonpsychotic treatment-resistant depression after failing two or more antidepressants.
- Patients were randomly assigned in a 1:1 ratio to receive either ketamine or electroconvulsive therapy (ECT).
- Prescribed medication was continued throughout the trial period.
- The initial treatment phase lasted for three weeks, with follow-up assessments at one, three, and six months.
- The primary outcome was treatment response, defined as a reduction of 50% or more from baseline in the score of the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR).
- Secondary outcome measures included assessments of quality of life and cognitive function. One of these measures was the Montgomery-Asberg Depression Rating Scale (MADRS).

INTERVENTION (# IN THE GROUP): 200

COMPARISON (# IN THE GROUP): 203

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Ketamine was found to be non-inferior in terms of treatment response to ECT at three weeks (55% vs 41%, respectively; difference 14%; 95% CI, 3.9–24).

Secondary Outcome –

- Ketamine did not improve quality of life and cognitive function (MADRS) compared to ECT (51% vs 41%, respectively; difference 9.3%; 95% CI, 0.9–19.4).

LIMITATIONS:

- ECT: Started with unilateral and switched to bilateral for inadequate response, possibly affecting response rate.
- More ECT sessions might increase response, but most received 6–9.
- The open-label design could influence response.
- No study on the maintenance treatment's long-term effects.
- No placebo group was included in the trial.
- Treatment method flexibility introduces outcome variability.
- Follow-up involves prescribed treatment and introducing confounding factors.
- Results may not generalize to psychosis or different settings.

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Let's Stop the Bleeding

Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

Gallos I, Devall A, Martin J, et al. Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage. *N Engl J Med*. 2023;389(1):11-21. doi:10.1056/NEJMoa2303966

KEY TAKEAWAY: The E-MOTIVE intervention, a calibrated drape for early detection of postpartum hemorrhage (PPH) and a first response treatment bundle, reduces the risk of severe maternal PPH, laparotomy for PPH, and maternal death from PPH.

STUDY DESIGN: Cluster randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Postpartum hemorrhage (PPH) is one of the leading causes of maternal death in the world. Early detection and consistent intervention strategies help to address some of the challenges associated with PPH. The E-MOTIVE intervention consists of a calibrated drape for measuring blood loss and a framework for the management of PPH to address these challenges.

PATIENTS: Patients delivering vaginally

INTERVENTION: E-MOTIVE intervention

CONTROL: Usual care

PRIMARY OUTCOME: Severe postpartum hemorrhage (>1,000 mL of blood loss), postpartum laparotomy, maternal death from bleeding

METHODS (BRIEF DESCRIPTION):

- Cluster randomized trial of 39 hospitals across Kenya, Nigeria, South Africa, and Tanzania.
- The study included a seven-month baseline period with usual care for postpartum hemorrhage.
- In a randomized 1:1 sequential manner the control group received usual care management and the intervention group started using trial intervention E-MOTIVE management (allowed two months for transition).
- Intervention trial E-MOTIVE management consisted of a calibrated drape for measuring blood loss and a framework for PPH to address these challenges.
- Usual care management consisted of blood loss measured visually and interventions in accordance with their local and national guidelines.

INTERVENTION (# IN THE GROUP): 101,104

COMPARISON (# IN THE GROUP): 109,028

FOLLOW-UP PERIOD: 14 months

RESULTS:

Primary Outcome –

- The E-MOTIVE intervention decreased the risk for the composite primary outcome compared to usual care (RR 0.40; 95% CI, 0.32–0.50).
- PPH was detected more with the E-MOTIVE intervention than with usual care (RR 1.6; 95% CI, 1.4–1.8).
- Severe PPH (>1,000 mL of blood loss) was detected more in the usual care group than in the E-MOTIVE intervention group (RR 0.4; 95% CI, 0.31–0.49).
- There was no difference between the two groups for maternal death (RR 0.73; 95% CI, 0.38–1.7).

LIMITATIONS:

- There was clinical information such as postnatal hemoglobin and maternal anemia that were not evaluated in this study due to study design.
- It was difficult to assess maternal death directly associated with bleeding due to confounding factors. There may have been under and/or over-reporting.
- The trial was conducted in low and middle-income countries. Further research is needed to apply the intervention in high-income countries.
- The drapes used in the control hospital were transparent so providers would have been able to see the blood collecting in the drape. This could have influenced their actions.

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One More Week or To Deliver? Investigating the Risk of Fetal Death and Morbidity by Birth Percentile

Risks of Stillbirth, Neonatal Mortality, and Severe Neonatal Morbidity by Birthweight Centiles Associated with Expectant Management at Term

Hong J, Crawford K, Odibo AO, Kumar S. Risks of stillbirth, neonatal mortality, and severe neonatal morbidity by birthweight centiles associated with expectant management at term. *Am J Obstet Gynecol.* 2023;229(4):451.e1-451.e15. doi:10.1016/j.ajog.2023.04.044

KEY TAKEAWAY: Delivery of infants with BW < 3rd centile between 37+0 to 37+6 weeks gestational age (GA) is associated with the best outcomes in balancing the risks of neonatal morbidity and risk of stillbirth with expectant management. For infants with birthweight (BW) in the 3rd to 10th percentile best outcomes were seen with delivery at 38+0 to 38+6 weeks GA and for infants in other percentiles 39+0 weeks GA.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: At term, SGA babies are at risk of stillbirth which is inversely related to the infant's birth weight. However, preemptive early delivery must be weighed against the risk of neonatal morbidity and long-term adverse outcomes that are related to early-term delivery.

PATIENTS: Singleton pregnancies with delivery after 37+0 weeks

INTERVENTION: 37+0 to 40+6 weeks GA

CONTROL: 40+6 weeks GA

PRIMARY OUTCOME: Stillbirths including any antenatal or intrapartum fetal deaths, neonatal mortality, severe morbidity

METHODS (BRIEF DESCRIPTION):

- Singleton pregnancies from 2000–2018 in Queensland, Australia with delivery between 37+0 and 40+6 weeks were reviewed with 948,895 singleton births assessed.
- BW was stratified into > 3rd, <3rd to 10th, 10th to 25th, 25th to < 90th, and > 90th percentile.
- Neonatal morbidity was defined as admission to the NICU, severe acidosis (pH< 7) at birth, significant neonatal resuscitation at birth, or Apgar score < 4 at five minutes.
- Per 10,000 pregnancies/births, the rates of stillbirth, mortality, and severe neonatal morbidity were calculated by BW centiles and GA.
- Relative risk (RR) of mortality and expectant management between GA of delivery were calculated and stratified by BW centiles.
- Expectant management was defined as waiting another week before delivery.
- Composite risk of mortality with expectant management (the sum of the probability of stillbirth for the week the fetus remains in utero plus the probability of neonatal death when birth occurs in the following week) was compared with rates of neonatal mortality and severe neonatal morbidity to determine if the risk of mortality was higher with birth or with expectant management.

INTERVENTION (# IN THE GROUP): 813,077

COMPARISON (# IN THE GROUP): 135,804

FOLLOW-UP PERIOD: 28 days after birth

RESULTS:

Primary Outcome –

- The rate of stillbirth increased with GA, with a marked increase after 40 weeks GA.
- For BW < 3rd percentile, there was a > 10-fold increase in stillbirth.
  - 10/1,000 pregnancies at 37+0 to 37+6 weeks (95% CI, 6.2–15)
  - 106.4/10,000 pregnancies at 40+0 to 40+6 weeks (95% CI, 75–147)
- The risk of stillbirth increased with GA for all BW percentiles. Infants in the lower BW categories were more significantly affected.
  - 38+0 to 38+6 weeks: (RR 1.6; 95% CI, 1.2–2.0)
  - 39+0 to 39+6 weeks: (RR 2.6; 95% CI, 2.0–3.3)
  - 40+0 and 40+6 weeks: (RR 11; 95% CI, 8.7–13)
- Infants born with weights > 90th percentile had a non-significant risk of stillbirth.
  - 38+0 to 38+6 weeks: (RR 1.3; 95% CI, 0.76–2.3)
  - 39+0 to 39+6 weeks: (RR 1.6; 95% CI, 0.94–2.7)
  - 40+0 to 40+6 weeks: (RR 4.3; 95% CI, 2.8–6.8)
- Across all BW percentiles, rate, and RR of severe morbidity were highest at 37+0 to 37+6 GA and lowest at 39+0 to 39+6 GA.

- Neonates with BW < 3rd percentile had the highest severe neonatal morbidity at 37+0 to 37+6 weeks GA 715/10,000 pregnancies (95% CI, 601.7–842.3).

- After 38+0 GA, the absolute risk difference between expectant management compared to birth was highest for BW < 3rd centile and 3rd to 10th centile.
- Composite mortality risk of expectant management was highest with BW < 3rd centile at 28.3/10,000 pregnancies at 37+0 to 37+6 weeks (95% CI, 25.1–31.8) drastically to 125.2/10,000 pregnancies at 40+0 to 40+6 weeks (95% CI, 118.4–132.3).

LIMITATIONS:

- Data quality was dependent on correct coding and data entry.
- Impact of mother's chronic disease on analyzed data.
- Women with hypertension, and diabetes, and who smoked during pregnancy had higher rates of stillbirth, mortality, and morbidity.
- Inability to determine if a planned birth at a gestational age was made solely because of fetal size or if other maternal or infant factors were causative.

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