GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of August 21 - 25, 2023

SPOTLIGHT: Acute Depression - Combination Pharmacotherapy Superiority

Acute Depression: Combination Pharmacotherapy Superiority

Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients with Acute Depression: A Systematic Review and Meta-analysis

Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2022;79(4):300-312. doi:10.1001/jamapsychiatry.2021.4313

KEY TAKEAWAY: Combination antidepressant pharmacotherapy results in superior treatment outcomes for acute depression in adults compared to monotherapy.

STUDY DESIGN: Systematic review and meta-analysis of 39 screened RCTs

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Acute depression is a common problem in adults in society today. Despite many antidepressant treatment options being available, the initial response to antidepressant monotherapy is approximately 60%, with a remission rate as high as 40%. While increasing antidepressant monotherapy dosing remains an option, dual therapy may provide a more beneficial outcome.

PATIENTS: Adults with depressive disorder

INTERVENTION: Using a combination of two antidepressants

CONTROL: Using antidepressant monotherapy

PRIMARY OUTCOME: Treatment efficacy

Secondary Outcome: Remission, response, change from baseline on a rating scale score, number of dropouts, and dropouts due to adverse effects

METHODS (BRIEF DESCRIPTION):

- The study followed Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for systematic reviews and closely adhered to Cochrane Collaboration recommendations.
- Searched using MEDLINE, PsycINFO, Embase, and the Cochrane Register of Controlled Trials databases for studies including adults (18+) with depressive disorder, being treated with either antidepressant monotherapy or combination therapy (two antidepressants) and measuring subsequent treatment effect (as defined by that study).
    - Studies focusing only on bipolar depression were excluded.
- Two reviewers carried out literature search, selection, data extraction, and evaluation of bias risk independently, following Cochrane Collaborations Handbook.
- Standardized Mean Difference (SMD) was calculated to assess primary outcome (treatment efficacy) across the 39 RCTs included in the systematic review/meta-analysis (and their respective methods of reporting this data).

INTERVENTION (# IN THE GROUP): 2,902

COMPARISON (# IN THE GROUP): 3,949

FOLLOW-UP PERIOD: 2–12 weeks

RESULTS:

Primary Outcome –

- Combination treatment was significantly superior in efficacy compared to monotherapy.
    - (Standardized mean difference [SMD] 0.31; 95% CI, 0.19–0.44)
- Individually, 31/38 studies suggested the superior efficacy of combination treatment.
- Combination therapy was associated with superior outcomes when analyses were restricted to studies with low bias risk, among non-responder populations, and when applied as first-line treatment.

Secondary Outcome –

- Combination therapy was significantly superior in remission (OR 1.5; 95% CI, 1.2–1.9), treatment response (OR 1.4; 95% CI, 1.2–1.7), and continuous change from baseline (SMD 0.38; 95% CI, 0.22–0.54), as compared to monotherapy.
- Low-risk studies showed differences in remission (OR 1.4; 95% CI, 1.1–1.9), response (OR 1.5; 95% CI, 1.1–1.9), and continuous change from baseline (SMD 0.34; 95% CI, 0.17–0.50).

LIMITATIONS:

- I^2 values indicated substantial heterogeneity of effects; however, this was expected given the large sample size.

- Results indicated possible reporting bias, though statistically significant results were still obtained when accounting for potential publication bias.
- It is conceivable that antidepressant discontinuation syndromes may have affected outcomes, though this is unlikely.

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Timing Matters: How Early Amniotomy Affects Time to Delivery Compared to Expectant Amniotomy

Early vs Expectant Artificial Rupture of Membranes Following Foley Catheter Ripening: A Randomized Controlled Trial

Gomez Slagle HB, Fonge YN, Caplan R, Pfeuti CK, Sciscione AC, Hoffman MK. Early vs expectant artificial rupture of membranes following Foley catheter ripening: a randomized controlled trial. *Am J Obstet Gynecol*. 2022;226(5):724.e1-724.e9. doi:10.1016/j.ajog.2021.11.1368

KEY TAKEAWAY: Amniotomy performed within one hour of Foley catheter expulsion following combined induction of labor with misoprostol leads to faster time to delivery, regardless of modality; faster time to vaginal delivery; and faster time to active labor in term pregnancy patients, compared to expectant amniotomy.

STUDY DESIGN: Single-site, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Labor induction is currently performed in approximately 30% of pregnancies, with evidence that the labor induction rate is still rising. Higher labor induction rates increase the risk of failure and the need for cesarean delivery. Labor interventions, such as amniotomy, have been shown to reduce cesarean delivery rates. Amniotomy has been shown to decrease the time to delivery, but there is no consensus on the best timing of amniotomy during labor induction. Currently, data on the timing of amniotomy during labor induction is limited.

PATIENTS: Pregnant people undergoing a combination Foley catheter and misoprostol induction of labor

INTERVENTION: Amniotomy within one hour of complete Foley catheter ripening

CONTROL: Expectant management following complete Foley catheter ripening

PRIMARY OUTCOME: Reduction in time to delivery regardless of modality

Secondary Outcome: Rate of cesarean delivery, time to active labor, and delivery within 12 to 24 hours

METHODS (BRIEF DESCRIPTION):

- 160 patients with a singleton pregnancy on labor and delivery from a single teaching hospital in Newark, Delaware undergoing cervical ripening with misoprostol with a Foley catheter at term were enrolled and randomized.
  - Aged 25–32
  - Between 38- and 40-weeks' gestation
- Exclusions: Patients with known uterine scars, fetal demise, major fetal congenital anomalies, HIV/HepC infection before labor induction.
  - Other exclusions: HELLP syndrome or eclampsia; category III FHT; growth restriction <10th percentile with elevated, absent, or reversal of flow in umbilical artery; and growth restriction <5th percentile with elevated, absent, or reversal of flow in umbilical artery.
- The intervention included early artificial rupture of membranes, defined as an amniotomy performed within one hour of Foley catheter expulsion or expectant management following Foley catheter expulsion.
- Induction started with an intravaginal 25-µg misoprostol tablet concurrently placed with a Foley catheter.
  - Extra 25-µg doses were provided at 3-hour intervals for a maximum of 24 hours.
  - Oxytocin titration to achieve regular contractions was used once a subsequent dose of misoprostol was deemed contraindicated or after Foley catheter expulsion.
- Cervical checks were performed within one hour of Foley catheter expulsion; patients were then randomized to early vs expectant amniotomy.
  - Early amniotomy included an immediate repeat cervical exam followed by an amniotomy.
  - Expectant amniotomy involved an immediate repeat cervical exam followed by a decision on the timing of amniotomy being made, with the earliest occurring four hours from Foley expulsion at the next cervical examination.

INTERVENTION (# IN THE GROUP): 79

COMPARISON (# IN THE GROUP): 81

FOLLOW-UP PERIOD: No identified follow-up period

RESULTS:

Primary Outcome –

- There was a reduction in time to delivery for patients who underwent amniotomy within one

hour of Foley catheter expulsion compared to patients who underwent expectant management.
    - (Median interquartile range [IQR] 11 hours; 95% CI, 6.3–17) for early amniotomy vs (20 hours; 95% CI, 13–26) for expectant management.
- There was a reduction in time to vaginal delivery for patients who underwent amniotomy within one hour of Foley catheter expulsion compared to patients who underwent expectant management.
    - (Median interquartile range [IQR] 10 hours; 95% CI, 5.1–13) for early amniotomy vs (17 hours; 95% CI, 11–21) for expectant management.

Secondary Outcome –

- There was a reduction in time to active labor for the early amniotomy group vs expectant group.
    - (Median [IQR] 6.7; 95% CI, 4.1–9.2) vs (14; 95% CI, 10–18)
- The rate of delivery within 24 hours was significantly higher for the early amniotomy group vs the expectant group.
    - (n [%]; 68 [86.1%] vs 57 [70.4%]; p=.03)
- The rate of delivery within 12 hours was significantly higher for the early amniotomy group vs the expectant group.
    - (47 [60%] vs 18 [20.2%]; p<.001)
- No significant difference in the rate of cesarean delivery between groups.

LIMITATIONS:

- The study population was limited to a single center, so data generalizability is limited.
- Study providers and participants were not blinded, with the potential for biased distribution of obstetrical interventions.

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Hydrochlorothiazide Does Not Prevent Kidney Stone Recurrence

Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Dhayat NA, Bonny O, Roth B, et al. Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence. *N Engl J Med*. 2023;388(9):781-791. doi:10.1056/NEJMoa2209275

KEY TAKEAWAY: Treatment with HCTZ did not differ from placebo in preventing the recurrence of kidney stones.

STUDY DESIGN: Double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Kidney stones have a high risk of recurrence. Data on the efficacy of thiazide diuretics for preventing recurrent kidney stones is limited.

PATIENTS: Age 18 or older with at least two episodes of kidney stones in the past 10 years

INTERVENTION: HCTZ 12.5 mg, 25 mg, or 50 mg

CONTROL: Placebo

PRIMARY OUTCOME: Recurrence of kidney stone

METHODS (BRIEF DESCRIPTION):

- Patients 18+ years old with a median age of 49 enrolled at 12 centers in Switzerland.
  - 20% of participants were women, and 95% were White.
- Exclusion criteria: Patients with secondary causes of kidney stones or those receiving drugs interfering with kidney stone formation.
- Participants were randomized to 12.5mg HCTZ daily, 25mg HCTZ daily, 50mg HCTZ daily, or matching placebo.
- End point: Recurrence was defined as the visible passage of a stone with or without symptoms or radiologic recurrence with the appearance of new stones on CT or the enlargement of preexisting stones.
- Efficacy was evaluated to treat the population with analyses stratified to episodes of kidney stones within 10 years before the randomization of groups.
- Clinical follow-up visits three months after randomization and yearly thereafter.
  - All patients also had a telephone visit every three months.

INTERVENTION (# IN THE GROUP): 105 (12.5 mg), 108 (25 mg), 101 (50 mg)

COMPARISON (# IN THE GROUP): 102 (placebo)

FOLLOW-UP PERIOD: Yearly for three years, with telephone visits every three months

RESULTS:

Primary Outcome –

- The symptomatic or radiologic recurrence of kidney stones was similar in each group.
  - 12.5mg (59%), 25mg (56%), 50mg (49%)
  - No differences compared to placebo (59%)
- There was no evidence of a dose-response effect.

Secondary Outcome –

- There was no difference in the secondary outcome of symptomatic recurrence.

LIMITATIONS:

- Women were underrepresented in the study.
- Most patients were White.
- The follow-up was limited to three years.
- It is unknown if patients received lifestyle modification advice.
- Baseline rates of hypercalciuria were not noted.
- It is unknown whether the allocation was concealed.

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To Bleed or Not to Bleed? That is the Question.

Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia

van Baarle FLF, van de Weerdt EK, van der Velden WJFM, et al. Platelet Transfusion before CVC Placement in Patients with Thrombocytopenia. *N Engl J Med*. 2023;388(21):1956-1965. doi:10.1056/NEJMoa2214322

KEY TAKEAWAY: Prophylactic platelet transfusion in thrombocytopenic patients decreased post-catheter placement-related bleeding events. Withholding platelet transfusion did not meet the margin for noninferiority.

STUDY DESIGN: Multi-center, single-blinded randomized, non-inferiority control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Central venous catheter placement is a common procedure done in an estimated 18% of hospitalized patients. Few high-quality studies are available assessing the risk of bleeding following ultrasound-guided CVC placement in patients with thrombocytopenia. With the scarcity of platelets available, whether prophylactic platelet transfusion is necessary for thrombocytopenic patients, and at which threshold needs to be determined.

PATIENTS: Thrombocytopenic patients receiving central venous catheter placement

INTERVENTION: Platelet transfusion

CONTROL: No platelet transfusion

PRIMARY OUTCOME: Decreased Grade 2 to 4 bleeding post-catheter placement

Secondary Outcome: Decreased Grade 3 to 4 bleeding post-catheter placement

METHODS (BRIEF DESCRIPTION):

- Included patients with thrombocytopenia with platelet counts of 10,000 to 50,000 per cubic millimeter within 24 hours prior to CVC placement.
- Patients were in either the hematology unit or the intensive care unit.
- Randomized 1:1 with one unit platelet transfusion or no transfusion prior to CVC placement.
- CVC was placed according to clinical practice guidelines at each site and with ultrasound guidance.
- CVC must be in place for at least 24 hours.
- Subsequent CVC placements could be included but only if greater than 24 hours after the previous placement.
- The primary outcome was Grade 2 to 4 catheter-related bleeding events within 24 hours of CVC placement.
- Noninferiority margin was 3.5 for the relative risk.
- Secondary outcomes included Grade 3 to 4 (major) catheter-related bleeding events.

INTERVENTION (# IN THE GROUP): 188

COMPARISON (# IN THE GROUP): 185

FOLLOW-UP PERIOD: Immediately after CVC placement, one hour after CVC placement, 24 hours after CVC placement

RESULTS:

Primary Outcome –

- Patients who received a prophylactic platelet transfusion have fewer Grade 2 to 4 catheter-related bleeding events than the no transfusion group (4.8% vs 12%; absolute risk difference 7.1%; 90% CI, 1.3–1.8).
    - Withholding transfusion did not meet the margin for inferiority for relative risk (relative risk [RR] 2.5; 90% CI, 1.3–4.7).

Secondary Outcome –

- There was no difference in major bleeding events (Grade 3 to 4) between the transfusion and no transfusion groups (2.1% vs 4.9%; RR 2.4; 95% CI, 0.75–7.9).

LIMITATIONS:

- The study was only conducted in the Netherlands.
- They utilized ultrasound guidance only, which may not be available in lower-income countries.
- This was a single-blind trial.
- There was no follow-up of platelet counts after the transfusion, so patients may have needed more than one transfusion prior to CVC placement.

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When Less is More: Targeted Statin Management

Treat-to-Target or High-Intensity Statin in Patients with Coronary Artery Disease: A Randomized Clinical Trial

Hong SJ, Lee YJ, Lee SJ, et al. Treat-to-Target or High-Intensity Statin in Patients with Coronary Artery Disease: A Randomized Clinical Trial. *JAMA*. 2023;329(13):1078-1087. doi:10.1001/jama.2023.2487

KEY TAKEAWAY: The treat-to-target strategy and immediate high-intensity statin therapy are similar as far as cardiac events; however, treat-to-target does increase the amount of laboratory draws a patient undergoes.

STUDY DESIGN: Multisite randomized noninferiority trial

LEVEL OF EVIDENCE: STEP 3 (downgraded as participants were not blinded)

BRIEF BACKGROUND INFORMATION: Guidelines on statin therapy recommend immediate treatment with high-intensity statin without a tailored treatment to a target goal. Though this approach may simplify treatment, it may overlook compliance factors such as patient-specific side effects and tolerance of high-dose medication. This study investigates major cardiac and cerebrovascular outcomes for both strategies.

PATIENTS: Adults with coronary artery disease

INTERVENTION: Treat to target statin therapy

CONTROL: High-intensity statin

PRIMARY OUTCOME: Major adverse cardiac and cerebrovascular events

Secondary Outcome: New onset diabetes, end-stage renal disease (ESRD), elevated creatinine or elevated liver enzymes, discontinuation of the study drug, and patients requiring additional non-statin agents

METHODS (BRIEF DESCRIPTION):

- Patients >19 years old with coronary artery disease were recruited from 12 centers in South Korea.
  - Participants had stable, acute coronary artery disease or acute coronary syndrome.
- Patients with myopathy, limited life expectancy of <3 years, or alcohol use disorder were excluded.
- The mean age was 65, with 27.9% female and a mean BMI of 27.9 kg/m2.
  - The baseline LDL in the target-to-treat strategy group was 46 mg/dL and 47 mg/dL in the immediate high-intensity group.
  - Baseline HDL levels in both groups were 47 mg/dL.
- The treat-to-target group received a statin which was titrated to the lowest possible dose to maintain LDL <70 mg/dL.
  - Medications included rosuvastatin 10-20 mg, Atorvastatin 20-40 mg.
  - The comparison group received rosuvastatin 20 mg or atorvastatin 40 mg by mouth daily.
- The primary composite outcome of cardiac and cerebrovascular events was measured as the composite score of all-cause death, myocardial infarction, stroke, or revascularization at three years (assessed at six weeks, and three-, six-, 12-, 24-, and 36-month visits).
- The secondary outcomes of new-onset diabetes, ESRD, laboratory abnormalities, and drug discontinuation were measured via health assessments at six weeks and three, six, 12, 24, and 36 months, and with lab draws at six weeks, and 12, 24, and 36 months.
- The expected cardiovascular event endpoint was 12%, and a noninferiority threshold of 3% was chosen to reflect no difference between therapy groups.
- A blinded clinical committee was responsible for categorizing each event.

INTERVENTION (# IN THE GROUP): 2,108

COMPARISON (# IN THE GROUP): 2,106

FOLLOW-UP PERIOD: 36 months

RESULTS:

Primary Outcome –

- Cardiac and cerebrovascular events occurred in the treat-to-target group less frequently than in the high-intensity group.
  - (8.1% vs 8.7% respectively; percent absolute difference –0.60%; 95% CI, –infinity to 1.1; meeting the noninferiority threshold)

Secondary Outcome –

- New-onset diabetes, aminotransferase or creatine kinase elevation, ESRD, or discontinuation of statin were similar between the two groups.

- The composite of the secondary outcomes of new-onset diabetes, aminotransferase or creatinine kinase elevation, and ESRD was lower in the target to treat vs the high-intensity therapy group.
    - (6.1% vs 8.2% respectively; percent absolute difference –2.1%; 95% CI, –3.6 to –0.50%)
- Patients receiving adjunctive non-statin therapy were 20% in the target-to-treat group and 11% in the high-intensity statin group.

LIMITATIONS:

- This homogenous population in South Korea may not apply to other clinic populations.
- The study was not blinded to participants or providers.
- The study was funded by pharmaceutical companies.
- A lower-than-expected event rate (expected 12% vs actual 8.1%–8.7%) may indicate the noninferiority threshold was inaccurate or the study was underpowered.

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Prenatal Antidepressant Exposure Not Associated with Neurodevelopmental Disorders in Controlled Analyses

Association of Antidepressant Use During Pregnancy with Risk of Neurodevelopmental Disorders in Children

Suarez EA, Bateman BT, Hernández-Díaz S, et al. Association of Antidepressant Use During Pregnancy with Risk of Neurodevelopmental Disorders in Children [published online ahead of print, 2022 Oct 3]. *JAMA Intern Med*. 2022;182(11):1149-1160. doi:10.1001/jamainternmed.2022.4268

KEY TAKEAWAY: Antidepressant use in pregnancy does not increase the risk of neurodevelopmental disorders in children when controlled for confounding factors.

STUDY DESIGN: Cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Antidepressant use during pregnancy has been associated with neurodevelopmental disorders in some studies. However, these results may not adequately control for confounding factors, including genetic and environmental factors.

PATIENTS: Pregnant individuals and their children

INTERVENTION: In utero antidepressant exposure from gestational week 19 until delivery

CONTROL: No in-utero antidepressant exposure from gestational week 19 until delivery

PRIMARY OUTCOME: Any neurodevelopmental disorder diagnosis

METHODS (BRIEF DESCRIPTION):

- Healthcare utilization data from the Medicaid Analytic eXtract (MAX; 2000-2014) and the IBM MarketScan Research Database (MarketScan; 2003-2015) was used to identify pregnant individuals and their children.
  - 1.93 million pregnancies in MAX and 1.25 million pregnancies in MarketScan were included.
- Children were followed from birth until outcome diagnosis, disenrollment, death, or end of study (maximum 14 years).
- Pregnant individuals were identified if they filled at least one antidepressant prescription from 19 weeks until delivery.
- The children of individuals who used antidepressants from gestational week 19 until delivery were compared to the children of those who did not.
- Multiple analyses were completed to adjust for confounding, including Adjusted, High dimensional propensity score (HDPS) adjusted, Discontinuer referent, and Sibling analysis.
  - The Sibling analysis was considered the most fully adjusted.
- Children's health information was monitored for diagnosis of any neurodevelopmental disorder.
- Children's health information was monitored for diagnosis of autism spectrum disorder, attention-deficit/hyperactivity disorder, specific learning disorders, developmental speech/language disorder, developmental coordination disorder, intellectual disability, and behavioral disorders.

INTERVENTION (# IN THE GROUP): 145,702

COMPARISON (# IN THE GROUP): 3,032,745

FOLLOW-UP PERIOD: 14 years or until relevant diagnosis, disenrollment, or death

RESULTS:

Primary Outcome –

- Exposure to antidepressants in late pregnancy increased the risk of any neurodevelopment disorder in the unadjusted, adjusted, HDPS, and discontinuer referent analyses.
  - (HR 1.1; 95% CI, 1.1–1.2)
- There was no significant difference in the adjusted sibling analysis.
  - (HR 0.97; 95% CI, 0.88–1.1)
- These outcomes were largely consistent over varying antidepressant classes and in-utero drug exposure windows.

LIMITATIONS:

- Pregnant individuals were assumed to be actively taking any prescribed anti-depressants.
- Diagnoses occurring at age 15 or later or after loss to follow-up were not monitored.
- It is possible that, in the absence of universal screening, some neurodevelopmental disorders were missed.
- Strong crude associations between antidepressant exposure in utero and neurodevelopmental

disorders were found and may be clinically relevant, although not present on fully-adjusted analyses.

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