GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of December 6 - 10, 2021

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Delayed-Release Psychotherapy: A New Approach to Preventing Relapse and Recurrence in Major Depressive Disorder

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Sequential Combination of Pharmacotherapy and Psychotherapy in Major Depressive Disorder: A Systematic Review and Meta-Analysis

Guidi J, Fava GA. Sequential Combination of Pharmacotherapy and Psychotherapy in Major Depressive Disorder: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2021; 78(3):261–269. doi:10.1001/jamapsychiatry.2020.3650

KEY TAKEAWAY: Sequential administration of psychotherapy after pharmacotherapy in the acute phase of a major depressive disorder (MDD) episode reduces the risk for relapse and recurrence.
STUDY DESIGN: Meta-analysis of 17 RCTs (N=2,283)
LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Residual symptoms and psychiatric comorbidities are associated with poor long-term outcomes in the treatment of MDD. The sequential model leverages psychotherapeutic strategies to target residual symptoms and psychiatric comorbidities at a time when psychotherapy is most likely to make a significant impact on a patient's overall, long-term well-being.

PATIENTS: Adults with MDD in remission
INTERVENTION: Cognitive behavioral therapy (CBT)
CONTROL: Treatment as usual, clinical management, psychoeducation, or active control conditions (mindfulness-based interventions)
OUTCOME: Relapse or recurrence of depression

METHODS (BRIEF DESCRIPTION):

- Comprehensive literature review of RCTs that examined sequential use of psychotherapy among patients with remitted MDD after acute-phase pharmacotherapy.
- Demographics:
  - Mean age: 46 years old
  - 69% female
- Exclusion Criteria: Psychotherapy was not primarily done face-to-face, first onset of depression was before 18 years old, other medical disorders
- Random effects model used for pooled results.
- Heterogeneity and publication bias were assessed.
- Meta-regression and sensitivity analysis were performed.

INTERVENTION (# IN THE GROUP): 1,208
COMPARISON (# IN THE GROUP): 1,075

FOLLOW UP PERIOD: 7 months–10 years

RESULTS:

- Sequential administration of psychotherapy reduced relapse and recurrence rates of MDD compared to controls (17 trials, N=1,208; RR 0.84; 95% CI, 0.74–0.94).
- Continuation, tapering, and discontinuation of pharmacotherapy did not significantly affect relapse and recurrence rates.
- Psychotherapy with pharmacotherapy reduced relapse and recurrence rates compared to active controls and treatment as usual (12 trials, N=1,276; RR 0.82; 95% CI, 0.71–0.95).

LIMITATIONS:

- Study designs varied widely across the RCTs, including sample size, treatment duration, and follow up.
- Exclusion criteria may limit generalizability.
  - Exclusion of virtual and telephone psychotherapy may not translate to COVID-era care.
- Data on racial breakdown of the study population not collected or highlighted.
- Efficacy of sequential psychotherapy compared to psychotherapy alone, pharmacotherapy alone, or simultaneous treatments were not studied.

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Reconsidering Caffeine Use During Pregnancy: Avoiding Caffeine Use During Pregnancy is No Small Thing

Association Between Maternal Caffeine Consumption and Metabolism and Neonatal Anthropometry

Gleason JL, Tekola-Ayele F, Sundaram R, et al. Association Between Maternal Caffeine Consumption and Metabolism and Neonatal Anthropometry: A Secondary Analysis of the NICHD Fetal Growth Studies-Singletons. *JAMA Netw Open*. 2021; 4(3): e213238.

KEY TAKEAWAY: Fetal growth can be adversely affected by the consumption of even small amounts of caffeine.
STUDY DESIGN: Longitudinal cohort study
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The American College of Obstetrics and Gynecology recommends limiting caffeine intake to <200 mg daily during pregnancy. However, it is unknown if any amount of caffeine is safe during pregnancy.

PATIENTS: Pregnant women
INTERVENTION: Caffeine consumption
CONTROL: No caffeine consumption
OUTCOME: Fetal growth

METHODS (BRIEF DESCRIPTION):

- Participants had singleton pregnancies at 8 to 13 weeks' gestation.
- Participants were excluded if they smoked or had a history of chronic conditions.
- Two methods were used in determining the impact of caffeine consumption on fetal growth.
  - Self-reported caffeine consumption: Participants reported the types and amounts of caffeine containing beverages they consumed in the week prior to being interviewed. The amount of caffeine consumed was calculated based on average caffeine content of each beverage.
    - Participants were categorized according to their reported caffeine consumption: No caffeine, 1-50 mg caffeine daily, >50 mg caffeine daily
  - Plasma caffeine levels:
    - Caffeine levels were measured in blood obtained from participants at the time of enrollment.
    - Caffeine levels were divided into quartiles: Q1 <28 ng/mL, Q2 28–157 ng/mL, Q3 157–659 ng/mL, Q4 >659 ng/mL
- Following delivery, the following outcomes were measured: weight; length; head, abdominal, arm, and thigh circumferences; skin fold; fat mass
- β (Beta coefficient) is the change in the parameter being measured produced by a change of one standard deviation in the intervention studied. In this study β is the change produced in a studied fetal measurement associated with each SD in caffeine exposure.

INTERVENTION (# IN THE GROUP): 1,182
COMPARISON (# IN THE GROUP): 873

FOLLOW UP PERIOD: Through delivery

RESULTS:

Self-Reported Caffeine Consumption –

- Neonates of women that reported consuming >50 mg/d compared to neonates of women reporting no caffeine intake had significantly lower:
  - Birthweight (β = −66 g; 95% CI, −121 to −10)
  - Arm circumference (β = −0.17 cm; 95% CI, −0.31 to −0.02)
  - Thigh circumference (β = −0.32 cm; 95% CI, −0.55 to −0.09)
- There was no statistical significance in length or head circumference.

Plasma Caffeine Levels –

- Neonates born to women with the highest plasma caffeine level compared to neonates born to women with the lowest plasma caffeine levels had significantly lower:
  - Birth weight (β = −84 g; 95% CI, −146 to −23)
  - Length (β = −0.44 cm; 95% CI, −0.78 to −0.12)
  - Head circumference (β = −0.28 cm; 95% CI, −0.47 to −0.09)
- The birthweights of neonates born to mothers in quartile 2 or quartile 3 of caffeine consumption did not statistically differ from the neonates born to mothers with the lowest plasma caffeine levels.

LIMITATIONS:

- There was low correlation between self-reported caffeine consumption and plasma caffeine levels.
- Reported caffeine consumption and caffeine levels were only evaluated once during pregnancy.

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Brush that Pain Off Your Shoulder with Home-Based Exercises

Effects on Shoulder Pain and Disability of Teaching Patients with Shoulder Pain a Home-Based Exercise Program: A Randomized Controlled Trial

Santello G, Rossi DM, Martins J, Libardoni TC, de Oliveira AS. Effects on shoulder pain and disability of teaching patients with shoulder pain a home-based exercise program: a randomized controlled trial. *Clin Rehabil*. 2020; 34(10):1245–1255. doi:10.1177/0269215520930790

KEY TAKEAWAY: Home-based exercise programs and patient education significantly decrease patient self-reported pain levels.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Physical therapy is effective for shoulder pain and impingement, but the efficacy of home-based exercise programs is not well studied. This study aimed to determine if a home program could improve function and patient quality of life.

PATIENTS: Adults with >3 months of rotator cuff tendinopathy

INTERVENTION: Home-based program

CONTROL: Conservative measures

OUTCOME: Self-reported shoulder pain and disability

Secondary Outcomes: Change in pain intensity, quality of life, and medication intake for pain relief

METHODS (BRIEF DESCRIPTION):

- Adults from Brazil with rotator cuff tendinopathy, a medical referral form for PT, and self-reported shoulder pain lasting for more than three months were recruited at a public health center.
- The experimental group received 90 minutes of instructions on stretching, strengthening, and joint mobility exercises to be performed ≥3 times per week for 2 months.
  - Exercises that produced pain were skipped.
- The control group was given verbal education on their shoulder pain and instructions to massage their necks, use ice, and avoid heavy lifting.
- Primary outcome was measured using SPADI (range 0–100) where a lower score indicated better function and less pain.
- Secondary outcomes (pain intensity, medication use) were measured with 0–10 numeric pain rating scale.
- Effect size (Cohen's *d*) interpretation:
  - <0.5 = small effect size
  - 0.5–0.8 = moderate effect size
  - >0.8 = large effect size
- 36-Item Short Form Health Survey, measuring quality of life, and the Chronic Pain Self-Efficacy Scale Description were also administered.

INTERVENTION (# IN THE GROUP): 29

COMPARISON (# IN THE GROUP): 30

FOLLOW UP PERIOD: 2 months

RESULTS:

Primary Outcomes –

- Home exercise decreased shoulder pain and dysfunction compared to conservative measures (number needed to treat [NNT]=1; 95% CI, 1.0–1.4).
  - SPADI between group difference = 40 points (*d*=1.6).
  - 90% of intervention group vs 7% of control group had SPADI scores <20.

Secondary Outcomes –

- The exercise group needed pain medication less often than the conservative measures group (OR 6.4; 95% CI, 2.1–20).
- The groups had no significant difference in quality of life or pain intensity ratings.

LIMITATIONS:

- Small sample size.
- Majority women.
- Baseline SPADI was higher in the control group (65 vs 61).
- Short follow up.

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How Low Can We Go? Intensive Blood Pressure Control for Older Patients

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

Zhang W, Zhang S, and Deng Y etal. Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. *N Engl J Med*. 2021 Aug 30. doi: 10.1056/NEJMoa2111437.

KEY TAKEAWAY: Intensive blood pressure therapy reduces the incidence of stroke, acute coronary syndrome (ACS), and acute decompensated heart failure (ADHF) compared to standard blood pressure therapy in patients 60 to 80 years old. However, intensive blood pressure therapy increases the risk for hypotension.

STUDY DESIGN: Multicenter non-blinded randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Studies on blood pressure control in the elderly have demonstrated cardiovascular benefits from intensive blood pressure control. However, questions remain regarding a practical goal systolic blood pressure. This study investigates a specific blood pressure target of 110–129 mmHg in the elderly, with the goal of reducing cardiovascular risk, as well as risk of iatrogenic hypotension.

PATIENTS: Older Chinese adults with hypertension

INTERVENTION: Intensive blood pressure control (110–129 mmHg)

CONTROL: Standard blood pressure control (130–150 mmHg)

OUTCOME: Composite of stroke, ACS, ADHF, coronary revascularization, atrial fibrillation, and death from cardiovascular causes

Secondary Outcomes: Individual components of the composite outcome, death from any cause, major adverse cardiovascular events, and renal outcomes

Safety Outcomes: Hypotension, dizziness, syncope, and fainting

METHODS (BRIEF DESCRIPTION):

- Patients 60–80 years old (mean 66 years) with high blood pressure (systolic blood pressure 140–190 mmHg) were recruited from 42 clinical sites in China.
  - Patients with history of hemorrhagic or ischemic stroke were excluded.
- Treatment group: Intensive blood pressure group received Olmesartan 20 mg oral once daily and Amlodipine 5–10 mg oral once daily initially then HCTZ with adjusted doses if needed to achieve target systolic blood pressure.
  - Comparison group: Received standard therapy.
  - To reach blood pressure goals, the treatment group required an average of 1.9 medications and the control group required 1.5.
- Automated blood pressure devices were used for home monitoring, paired with an app that uploaded data.
- The composite of cardiovascular outcomes and secondary outcomes were determined by face-to-face physician visits via a standardized questionnaire at 1, 2, and 3 months then every 3 weeks for 4 years.
- During the 4th interim analysis, the trial prematurely concluded.

INTERVENTION (# IN THE GROUP): 4,243

COMPARISON (# IN THE GROUP): 4,268

FOLLOW UP PERIOD: 3.3 years

RESULTS:

Primary Outcome –

- Intensive blood pressure therapy reduced the risk for the composite outcome compared to standard therapy (3.5% vs 4.6%, respectively; HR 0.74; 95% CI, 0.6–0.92).

Secondary Outcomes –

- Intensive therapy specifically reduced the risk of the following compared to standard therapy:
  - Major Adverse Cardiac Events (HR 0.72; 95% CI, 0.56–0.93)
  - Stroke (HR 0.67; 95% CI, 0.47–0.97)
  - ACS (HR 0.67; 95% CI, 0.47–0.94)
  - ADHF (HR 0.27; 95% CI, 0.08–0.98)
- No significant difference in risk of coronary revascularization, atrial fibrillation, death from cardiovascular causes, and renal outcomes were observed.

Safety Outcomes –

- Intensive therapy increased the risk for hypotension compared to standard therapy (RR 1.3; 95% CI, 1.0–1.7).
- The risk for dizziness, syncope, and fainting were not statistically different.

LIMITATIONS:

- The study only included those with knowledge and access to technology.

- Patients with a history of stroke were excluded from this study.
- Investigators and patients were aware of trial group assignments.
- Data and safety monitoring committee recommended trial be stopped early on basis of clear CV benefit in intensive therapy group (trial was stopped with median follow up of 3.3 years).
- One event per patient was used in analysis, however, it is possible that patients had multiple events that were not included in this study.

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Lower Blood Pressure Targets Reduce Cardiovascular Events

Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes

Flint AC, Conell C, Ren X, et al. Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes. *N Engl J Med*. 2019; 381(3):243–251. doi: 10.1056/NEJMoa1803180.

KEY TAKEAWAY: Both systolic and diastolic hypertension independently influence the risk of adverse cardiovascular events, regardless of the definition of hypertension (≥140/90 or ≥130/80), thus affirming the importance of diastolic blood pressure (BP), and additionally, validating the lower BP threshold.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: In previous studies, such as the Framingham Heart Study, it has been argued that treatment for hypertension could improve with measurement of systolic BP only. Additionally, the American College of Cardiology-AHA risk estimation tool does not consider diastolic BP when determining cardiovascular risk. Overall, the relationship between systolic and diastolic BP and CV outcomes remains unclear and was complicated by the recent changes to the hypertension guidelines with two different BP thresholds (≥140/90 mmHg vs ≥130/80 mmHg).

PATIENTS: Adult patients

INTERVENTION: Mean blood pressure ≥130/80 mmHg

CONTROL: Mean blood pressure ≥140/90 mmHg

OUTCOME: Composite of myocardial infarctions (MI), ischemic strokes, and hemorrhagic strokes

METHODS (BRIEF DESCRIPTION):

- BP measurements were analyzed over an 8-year period.
  - BP measurements included up until an outcome event occurred.
- Patients were observed if they developed the composite outcome.
- Bivariate and multivariable cox survival analysis of the composite outcome was performed which were controlled for covariates (age, sex, race, BMI, coexisting conditions [DM, CAD, hypercholesterolemia, HF, hx of CVA, smoking status]).
- SBP and DBP measurements were standardized to z scores to allow for comparison.

INTERVENTION (# IN THE GROUP): 533,353

COMPARISON (# IN THE GROUP): 118,159

FOLLOW UP PERIOD: 8 years

RESULTS:

- Higher SBP was associated with a higher risk for the composite outcome.
  - ≥140 mmHg vs <140 mmHg: HR 1.18 (95% CI, 1.17–1.18)
  - ≥130 mmHg vs <130 mmHg: HR 1.18 (95% CI, 1.17–1.19)
- Higher DBP was associated with a higher risk for the composite outcome.
  - ≥90 mmHg vs <90 mmHg: HR 1.06 (95% CI, 1.06–1.07)
  - ≥80 mmHg vs <80 mmHg: HR 1.08 (95% CI, 1.06–1.09)
- Diastolic hypertension was associated with a higher risk for the composite outcome.
  - SBP <140 mmHg and DBP ≥90 mmHg: HR 1.7 (95% CI, 1.5–1.8)
  - SBP <130 mmHg and DBP ≥80 mmHg: HR 1.5 (95% CI, 1.0–2.2)
- Estimate of risk of composite outcome (based on logistic-regression model):
  - 160 mmHg average SBP: 4.8%
  - 96 mmHg average DBP: 3.6%
  - 136 mmHg average SBP: 1.9%
  - 81 mmHg average DBP: 1.9%

LIMITATIONS:

- Death was not reported as a primary outcome.
- The population used may not apply to specific subpopulations since it included a generally healthy population.

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