GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of October 3 - 7, 2022

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"Run of the Mill" Ketamine vs Esketamine for Depression

Comparative Efficacy of Racemic Ketamine and Esketamine for Depression: A Systematic Review and Meta-Analysis

Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis [published correction appears in *J Affect Disord*. 2020 Nov 20:]. *J Affect Disord*. 2021;278:542-555. doi:10.1016/j.jad.2020.09.071

KEY TAKEAWAY: Racemic ketamine is more effective than intranasal esketamine for the treatment of depression.

STUDY DESIGN: Systematic review and meta-analysis of 24 RCTs (N=1,877)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Depression is a very common and serious concern in primary care. Ketamine has been shown to improve symptoms of depression and suicidality, but it does not have lasting effects, has a high level of abuse potential, and is administered intravenously. Intranasal esketamine can be delivered at lower doses and the delivery system is more practical for patients. Still, there are concerns about the efficacy and tolerability of esketamine.

PATIENTS: Adults with unipolar or bipolar depression

INTERVENTION: Intranasal esketamine

CONTROL: Intravenous racemic ketamine

PRIMARY OUTCOME: Depression, response to treatment, remission, suicidality, completion of treatment, and dropouts

METHODS (BRIEF DESCRIPTION):

- Patients 18 years old and older with unipolar or bipolar depression were included.
- Patients with other psychiatric conditions and pregnant and breastfeeding women were excluded from the review.
- A majority of participants were diagnosed with unipolar depression.
- Three trials tested the use of ketamine as a stand-alone treatment while all others tested ketamine as adjunct therapy to other psych medications.
- Six trials included patients without treatment resistant depression (TRD). All others only included those with TRD.

INTERVENTION (# IN THE GROUP): 980

COMPARISON (# IN THE GROUP): 1,011

FOLLOW UP PERIOD: 4 – 8 weeks

RESULTS:

- Racemic ketamine resulted in greater overall response than intranasal esketamine (RR 2.0; 95% CI, 1.6 to 2.6).
- Racemic ketamine resulted in greater remission rates than intranasal esketamine (RR 2.0; 95% CI, 1.5 to 2.7).
- There was no significant difference in change in depression score, suicidality, completion of treatment, dropouts, or dropouts due to adverse effects.

LIMITATIONS:

- Follow-up time was limited to four to eight weeks.
- Most studies excluded patients who had severe psychiatric conditions which may not reflect real-world scenarios.
- Inconsistent reporting of specific adverse events.
- Heterogeneity between the studies (i.e., using ketamine as monotherapy in some trials and ketamine as adjunct therapy in others).

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Perineal Massage for the Win! Evidence-Based Improvement of Perineal Outcomes in Vaginal Delivery

Perineal Massage During Labor: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Aquino CI, Guida M, Saccone G, et al. Perineal massage during labor: a systematic review and meta-analysis of randomized controlled trials. *J Matern Fetal Neonatal Med*. 2020;33(6):1051-1063. doi:10.1080/14767058.2018.1512574

KEY TAKEAWAY: Perineal massage during second stage of labor decreases risk of third- and fourth-degree perineal lacerations and increases likelihood of intact perineum during vaginal birth.

STUDY DESIGN: Meta-analysis of nine randomized controlled trials (RCTs; n=3,374)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Up to 85% of people who deliver vaginally experience perineal trauma, which can lead to increased blood loss, prolonged recovery, chronic perineal pain, dyspareunia, urinary and fecal incontinence, recto-vaginal fistula, and fear of labor among pregnant people. Many techniques meant to reduce perineal trauma risk have been studied, including warm compress, hands-on, the Ritgen maneuver, and various perineal massage techniques, often with conflicting evidence of effectiveness among studies.

PATIENTS: Patients in active labor

INTERVENTION: Perineal massage during second stage of labor

CONTROL: Usual care (no perineal massage)

PRIMARY OUTCOME: Third- or fourth-degree perineal lacerations

Secondary outcomes: Intact perineum, episiotomy, first- or second-degree perineal lacerations, other lacerations

METHODS (BRIEF DESCRIPTION):

- Studies compared perineal trauma outcomes between people in the second stage of labor who did and did not receive perineal massage during pushing or between and during pushing.
- Perineal massage was performed by a midwife or similar provider using two lubricated fingers inserted into the vagina applying posterior pressure in a sweeping motion for an average of 5–15 minutes of total massage time.
- No other interventions were performed in included studies, including hands-on, warm compress, Ritgen maneuver or perineal massage prior to the second stage of labor.
- Study populations were similar, with average age and BMI under 30, primiparous and multiparous women with singleton gestation and cephalic presentation undergoing attempt at spontaneous vaginal delivery at or near term >36 weeks gestation.

INTERVENTION (# IN THE GROUP): 1,725

COMPARISON (# IN THE GROUP): 1,649

FOLLOW UP PERIOD: Immediate postpartum

RESULTS:

Primary Outcome –

- Perineal massage significantly reduced risk of third- or fourth-degree laceration compared to usual care (5 trials, N=2,487; relative risk [RR] 0.49; 95% CI, 0.25–0.94).

Secondary Outcomes –

- Perineal massage increased the likelihood of intact perineum compared to usual care (9 trials, N=3,374; RR 1.4; 95% CI, 1.0–1.9).
- Perineal massage reduced the risk of episiotomy compared to usual care (9 trials; N=3,374; RR 0.56; 95% CI, 0.38–0.82).
- No significant difference in risk of first- or second-degree lacerations between perineal massage group and no massage.

LIMITATIONS:

- Generalizability of these results may be limited given these were uncomplicated pregnancies with spontaneous vaginal delivery in young healthy patients.
- Only five of nine studies reported the primary outcome (third- or fourth-degree lacerations).
- Blinding was not possible given the nature of the intervention.

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A Low Carb Diet for Crohn's Remission?

A Randomized Trial Comparing the Specific Carbohydrate Diet to a Mediterranean Diet in Adults with Crohn's Disease

Lewis JD, Sandler RS, Brotherton C, et al. A Randomized Trial Comparing the Specific Carbohydrate Diet to a Mediterranean Diet in Adults With Crohn's Disease [published correction appears in Gastroenterology. 2022 Aug 26]. *Gastroenterology*. 2021;161(3):837-852.e9. doi:10.1053/j.gastro.2021.05.047

KEY TAKEAWAY: A selective carbohydrate diet was not more effective than the Mediterranean diet for achieving Crohn's disease remission.

STUDY DESIGN: Randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Many patients with Crohn's disease prefer non-pharmacologic therapies including dietary approaches to control their symptoms. Prior studies have demonstrated efficacy of the Mediterranean diet (MD) for achieving symptom remission, and some studies have suggested decreased inflammation with the specific carbohydrate diet (SCD). This study aimed to directly compare the effects of the MD and SCD on Crohn's disease remission.

PATIENTS: Adults with mild-to-moderate Crohn's disease

INTERVENTION: Specific carbohydrate diet (SCD)

CONTROL: Mediterranean diet (MD)

PRIMARY OUTCOME: Symptomatic remission at six and 12 weeks

Secondary outcomes: Fecal calprotectin response and CRP response at six weeks

METHODS (BRIEF DESCRIPTION):

- Adult patients with Crohn's disease were recruited across 37 study sites in the United States. Inclusion criteria were adults with mild to moderate Crohn's disease, defined by a short Crohn's Disease Activity Index (sCDAI) score between 175 and 400. sCDAI is a weighted index including three patient-reported symptoms: number of mostly liquid bowel movements per day, severity of abdominal pain (assessed from none to severe), and general well-being (assessed from generally well to terrible).
- Patients were randomized to the specific carbohydrate diet (SCD) or Mediterranean diet (MD). The SCD was high in fresh fruits and vegetables except starchy vegetables and did not allow grains, processed meats, milk, or sweeteners other than honey or saccharin. Participants were provided with all meals for the first six weeks and instructed to follow this diet on their own for an additional six weeks.
- Remission was defined by an sCDAI score less than 150, in the absence of initiation or increase of any Crohn's disease medications.
- Secondary outcomes were fecal calprotectin level <250 ug/g and reduction by >50% among participants with a baseline >250 ug/g, C-reactive protein <5 mg/L and >50% reduction from baseline among participants with a baseline > 5 mg/L.

INTERVENTION (# IN THE GROUP): 99

COMPARISON (# IN THE GROUP): 92

FOLLOW UP PERIOD: 12 weeks

RESULTS:

- At six weeks, symptomatic remission in patients were achieved similarly in both the SCD and MD arm (47% vs 44%, respectively; *P*=.77).
- At 12 weeks symptomatic remission in patients were also achieved similarly in both the SCD and MD arm (42% vs 40%, respectively; *P*=.87).
- There were no significant differences in fecal calprotectin or CRP response between the SCD and MD groups at six weeks.

LIMITATIONS:

- Short follow up of 12 weeks may have been inadequate.
- Patients were not able to be blinded.
- Small sample size.
- Limited diversity of participants (91% White, 63% female).

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Pharmacologic Treatment Options for Alzheimer-Type Dementia

Benefits and Harms of Prescription Drugs and Supplements for Treatment of Clinical Alzheimer-Type Dementia

Fink HA, Linskens EJ, MacDonald R, et al. Benefits and Harms of Prescription Drugs and Supplements for Treatment of Clinical Alzheimer-Type Dementia. *Ann Intern Med*. 2020;172(10):656-668. doi:10.7326/M19-3887

KEY TAKEAWAY: It is unclear if pharmacologic treatment improves behavioral and psychological symptoms of Alzheimer-type dementia.

STUDY DESIGN: Systematic review and meta-analysis of 66 studies [55 evaluating non-BPSD outcomes and 12 of evaluating BPSD outcomes, with some overlap studied in both] (N= 5,202)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: 10% of the older U.S. population is affected by dementia. The most common cause is Alzheimer-type dementia. Advanced dementia can lead to behavioral and psychological symptoms. Dementia not only lowers quality of life of those affected but burdens caregivers and increases institutionalizations.

PATIENTS: Patients with Clinical Alzheimer-type Dementia (CATD)

INTERVENTION: Prescription drugs or supplements

CONTROL: Placebo

OUTCOME: Cognition, function

METHODS (BRIEF DESCRIPTION):

- Study was developed and followed a standardized protocol where reviewers of studies for selection were verified by another reviewer using Risk of Bias and Strength of Evidence.
- Patients: Living in a nursing home and follow-up duration for at least 24 weeks
- Interventions: Cholinesterase inhibitors, Memantine, Supplements, Antipsychotic drugs, Antidepressant drugs, Antiseizure drugs
- Control: Placebo
- Outcomes:
  - Cognitive: global screen, global multidomain, memory, executive, language, attention
  - Functional, quality of life, and behavioral symptoms

INTERVENTION (# IN THE GROUP):

- Donepezil: 1,399
- Rivastigmine: 1,448

COMPARISON (# IN THE GROUP): 2,355

FOLLOW UP PERIOD: At least 24 weeks

RESULTS:

- Donepezil slightly reduced the worsening of cognitive decline and function over about six months, but differences compared to placebo were of uncertain clinical importance (12 trials, n=2,460; SMD 0.35; confusion 95% CI -3.5 to 1.9).
- Isolated statistical evidence for high dose citalopram for agitation symptoms however insufficient evidence and above recommended dose without adequate research on harms with higher than recommended doses.

LIMITATIONS:

- Additional, high-quality studies are needed before the results can be deemed to be clinically significant.
- Other cholinesterase inhibitors vs placebo confusion changes were not reported.
- Additional comparisons for behavioral and psychological symptoms of dementia (BPSD) vs non-BPSD outcomes were found to be insufficient.
- Harms and side effects were not reported in enough studies.
- No standardization of Alzheimer diagnosis in subjects chosen in each study.
- Longer treatment time needed especially for BPSD trials.

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Cognitive Behavioral Therapy Improves Sleep for Older Adults with Insomnia

Efficacy of Cognitive Behavioral Therapy for Insomnia in Geriatric Primary Care Patients

Hinrichsen GA, Leipzig RM. Efficacy of cognitive behavioral therapy for insomnia in geriatric primary care patients. *J Am Geriatr Soc*. 2021;69(10):2993-2995. doi:10.1111/jgs.17319

KEY TAKEAWAY: Cognitive Behavioral Therapy for Insomnia (CBT-I) may be an effective intervention for insomnia in patients over 75 years old.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Insomnia is common in geriatric adults; however, most insomnia medications are inappropriate for geriatric patients due to adverse effects. CBT-I is an established treatment for insomnia in most adults; however, efficacy data for older patients is limited.

PATIENTS: Older adults with insomnia

INTERVENTION: CBT-I

CONTROL: Pre-treatment baseline scores before CBT-I treatment

PRIMARY OUTCOME: Depression, anxiety, insomnia, daytime sleepiness, time to sleep onset, total sleep time, unintended early wake time

METHODS (BRIEF DESCRIPTION):

- There were 29 patients (66–92 years old; mean age=77) referred from a large geriatric primary care practice in New York. Patients met diagnostic criteria for insomnia without other sleep disorders and were cognitively intact.
- Participants underwent a baseline assessment to include:
  - Depression symptoms using the Patient Health Questionnaire-9 (PHQ-9; 0 to 27 points with higher scoring indicating increased severity).
  - Anxiety symptoms using the Generalized Anxiety Disorder-7 (GAD-7; 0 to 21 points with higher scoring indicating increased severity).
  - Insomnia using the Insomnia Severity Index (ISI; 0 to 28 points with higher scoring indicating increased severity).
  - Daytime sleepiness using the Epworth Sleepiness Scale (ESS; 0 to 24 points with higher scoring indicating increased severity).
  - Insomnia as measured by patient-recorded sleep diary.
- Weekly CBT-I sessions were provided until participants reported two weeks of sustained improvement (mean number of sessions required was 6.1).
- Upon completion of intervention, participants were given repeat administration of study measures.
- Paired t-tests were used to compare baseline and post-intervention data.
- Effect sizes were calculated using Cohen's d.

INTERVENTION (# IN THE GROUP): 29

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW UP PERIOD: 1-2 weeks following completion of protocol and sustained improvement

RESULTS:

CBT-I improved the following areas compared to baseline:

- Depression: 4.2 vs 2.3 (*P*=.020, effect size 0.5)
- Anxiety: 5.9 vs 2.9 (*P*=.001, effect size 0.71)
- Insomnia severity: 16 vs 5.7 (*P*<.001, effect size 2.2)
- Daytime sleepiness: 6.4 vs 4.9 (*P*=.013, effect size 0.5)
- Time to fall asleep: 46 vs 22 minutes (*P*<.001, effect size 0.91)
- Time awake after falling asleep: 41 vs 14 minutes (*P*<.001, effect size 0.8)
- Waking earlier than intended: 29 vs 11 minutes (*P*=.001, effect size 0.7)
- Percentage of intended time spent sleeping: 75% vs 88%; (*P*<.001, effect size 1.4)
- CBT-I did not improve total time asleep.

LIMITATIONS:

- The study cohort was largely homogeneous (mostly White and well-educated participants), limiting its generalizability and applicability across other groups.
- With no control group, improvements could be attributed to some other characteristic of this cohort rather than their participation in CBT-I.

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