GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 4 - Issue 24

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of June 10 -14, 2024

SPOTLIGHT: Decisions, Decisions... The Best Pharmacological Options for Alcohol Use Disorder

Decisions, Decisions… The Best Pharmacological Options for Alcohol Use Disorder

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Pharmacotherapies for Adults with Alcohol Use Disorders: A Systematic Review and Network Meta-Analysis

Bahji A, Bach P, Danilewitz M, et al. Pharmacotherapies for Adults With Alcohol Use Disorders: A Systematic Review and Network Meta-analysis. *J Addict Med.* 2022;16(6):630-638. doi:10.1097/ADM.0000000000000992

KEY TAKEAWAY: In adult patients with alcohol use disorder (AUD), the four medications with the best evidence for improving both abstinence and reducing heavy drinking are acamprosate, disulfiram, baclofen, and oral naltrexone.

STUDY DESIGN: Systematic review and meta-analysis of 156 randomized clinical trials (RCTs) (N=27,334)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: To address limitations and knowledge gaps of previous AUD reviews and meta-analyses on the treatment of AUD, the authors employed a network meta-analysis (NMA), a statistical technique that can compare multiple treatments by combining direct and indirect evidence from a network of RCTs. NMA can help assess the comparative effectiveness of more than two treatments that a traditional meta-analysis cannot. There are currently many options for AUD, but many physicians may not be aware of the most effective options.

PATIENTS: Adults with AUD

INTERVENTION: Any medications used to treat AUD, either approved or off-label

CONTROL: Placebo, other medications, and non-pharmacological therapy

PRIMARY OUTCOME: Alcohol consumption (abstinence or reduction in heavy drinking), dropouts from trials, and dropouts from trials due to adverse events

METHODS (BRIEF DESCRIPTION):

- After determining eligibility (adults with AUD via DSM or other clinical criteria), there was a search of nine electronic databases for both published and unpublished studies for RCT or controlled trials that used medications with the goal of abstinence or reduction in heavy drinking.
- Two of the investigators independently reviewed each article for inclusion in the study.
  - The mean duration of the RCT was 12 weeks with a range of 4–52 weeks.
  - 74% of the participants were male with a mean age of 44 years old.
- Exclusions include nonadult samples, study designs other than randomized controlled, and studies shorter than a four-week duration.
- Interventions studied the most commonly used medications for AUD including oral naltrexone (50 mg/day), acamprosate (2–3 g/day), baclofen (30 mg/day), disulfiram (250–500 mg/day), topiramate, nalmefene, gabapentin, and extended-release naltrexone.
  - Several medication doses were not stated, and the frequency of dosing was not specified.
- Control groups included use of placebo, other medications (not used in the intervention group), and nonpharmacological/behavioral treatments.
  - Doses and frequency were not specified.
- Outcomes were measured in either improving abstinence or reducing heavy drinking.
  - Intention-to-treat principle was used for all outcomes.
- Network meta-analyses using random effects, frequentist models, and calculated summary rate ratios (RR) with 95% CIs were conducted.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 4–52 weeks

RESULTS:

Primary Outcome –

- The medications that significantly improved abstinence compared to placebo were:
  - Gamma-hydroxy-butyrate (RR 1.9; 95% CI, 1.0–3.5)
  - Baclofen (RR 1.8; 95% CI, 1.4–2.3)
  - Disulfiram (RR 1.7; 95% CI, 1.4–2.1)
  - Gabapentin (RR 1.7; 95% CI, 1.0–2.7)
  - Acamprosate (RR 1.3; 95% CI, 1.2–1.5)
  - Oral naltrexone (RR 1.2; 95% CI, 1.0–1.3)
- The medications that significantly reduced heavy drinking compared to placebo were:

  - Disulfiram (RR 0.19; 95% CI, 0.10–0.35)
  - Baclofen (RR 0.72; 95% CI, 0.57–0.91)
  - Acamprosate (RR 0.78; 95% CI, 0.70–0.86)
  - Oral naltrexone (RR 0.81; 95% CI, 0.73–0.90)
- The medications that had significant drop-out rates were:
  - Nefazodone (RR 2.1; 95% CI, 1.4–3.1)
  - Aripiprazole (RR 2.0; 95% CI, 1.4–2.9)
  - Carbamazepine (RR 1.9; 95% CI, 1.0–3.3)
  - Calmefene (RR 1.2; 95% CI, 1.0–1.4)
- The medications that had the least drop-out rates were:
  - Baclofen (RR 0.83; 95% CI, 0.70–0.97)
  - Pregabalin (RR 0.63; 95% CI, 0.43–0.94)
- The medications that caused more drop-out rates due to adverse events compared to placebo were:
  - Nalmefene (RR 3.3; 95% CI, 2.3–4.5)
  - Fluvoxamine (RR 3.1; 95% CI, 1.6–5.9)
  - Topiramate (RR 2.9; 95% CI, 1.4–3.5)

LIMITATIONS:

- Studies with different treatment settings, medication dosing, study duration, AUD severity, comorbidities, treatment goals, and delivery of behavioral cointerventions were combined.
- High-quality studies were mixed with lower-quality studies.
- Publication bias and selective reporting are potential limitations.

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Chronic Geriatric Pain: Are GABA Agonists Superior to Opioids?

Comparative Effectiveness of Pain Control Between Opioids and Gabapentinoids in Older Patients with Chronic Pain

Kim E, Raji MA, Westra J, Wilkes D, Kuo YF. Comparative effectiveness of pain control between opioids and gabapentinoids in older patients with chronic pain. *Pain*. 2024;165(1):144-152. doi:10.1097/j.pain.0000000000003006

KEY TAKEAWAY: In elderly patients with chronic pain, gabapentinoids (GABA) were related to a greater decrease in pain interfering with activities than opioids, in a dose-dependent manner.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Chronic pain is common in the United States, affecting approximately 20% of the population, and even more common in geriatric patients. Physician preference has been shifting from opioids to GABA due to the risks of overuse and side effects of opioids.

PATIENTS: Medicare beneficiaries with chronic pain

INTERVENTION: Gabapentinoids

CONTROL: Opioids

PRIMARY OUTCOME: Pain reduction

Secondary Outcome: Dose-dependent changes

METHODS (BRIEF DESCRIPTION):

- Medicare beneficiaries with a diagnosis of chronic pain and no prior GABA or opioid use in the past year were included.
- Those beneficiaries with less than 30 days of GABA or opioid use or no home health assessments before or after treatment began were excluded.
- GABA daily dosage was as follows:
  - Low: <600 mg
  - Intermediate: 600 to <1200 mg
  - High: ≥1200 mg
- Opioids daily dosage was as follows:
  - Low: <50 morphine milligram equivalents (MME)
  - Intermediate: 50 to <90 MME
  - High: ≥90 MME
- Pain-related activity interference was assessed on a 0–4 scale, with 4 indicating maximum interference.
- Pre-treatment pain scores were taken from assessment closest to drug prescription within 0–60 days.
- Post-treatment pain scores were derived from assessment closest to drug prescription within 8–60 days.
- Comparison was made between both groups on pre-post change in:
  - Pain-related activities interference score
  - Less-than-daily pain interference in activity
- Results were adjusted based on demographics and health comorbidities.

INTERVENTION (# IN THE GROUP):

- Low dosage: 2,096
- Intermediate dosage: 881
- High dosage: 231

COMPARISON (# IN THE GROUP):

- Low dosage: 2,542
- Intermediate dosage: 197
- High dosage: 107

FOLLOW-UP PERIOD: Up to 60 days after intervention initiation

RESULTS:

Primary Outcome –

- GABA reduced pain interference in activity more than opioids (adjusted difference –0.10 points, *P*=.01).
- After adjusting for patient demographics and comorbidities, the GABA group improved in less-than-daily pain interference compared to the opioid group (odds ratio [OR] 1.3; 95% CI, 1.2–1.5).
- When excluding patients with neuropathic pain, diabetes, or stroke, the odds of less-than-daily pain interference between groups were not statistically significant (OR 1.2; 95% CI, 1.0–1.5).

Secondary Outcome –

- An intermediate dose of GABA reduced pain interference in activity more than opioids (adjusted difference –0.4, *P*=.001).
- GABA improved less-than-daily pain interference more than opioids in the following groups:
  - Low dose (OR 1.2; 95% CI, 1.03–1.3)
  - Intermediate dose (OR 2.6; 95% CI, 1.8–3.7)
  - High dose (OR 3.8; 95% CI, 2.0–7.4)

LIMITATIONS:

- The generalizability of the findings was limited to Medicare beneficiaries.
- Medication adherence was not accounted for since medication use was measured with filled prescriptions.
- Physical activity level, socioeconomic status, and other interventions were not included variables.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Bright Days and Dark Nights Independently Improve Mood

Day and Night Light Exposure Are Associated with Psychiatric Disorders: An Objective Light Study in >85,000 People

Burns, A.C., Windred, D.P., Rutter, M.K. et al. Day and night light exposure are associated with psychiatric disorders: an objective light study in >85,000 people. *Nat. Mental Health* 1, 853–862 (2023). https://doi.org/10.1038/s44220-023-00135-8

KEY TAKEAWAY: Increased daytime and decreased nighttime light exposure reduces the risk of developing mental health disorders.

STUDY DESIGN: Quantitative cross-sectional cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Spending time outdoors is associated with better overall mental health. Bright light exposure during the day supports a healthy circadian rhythm. Disruptions in the amount of daytime and nighttime light exposure may be correlated with the development of certain mental disorders and overall mood quality.

PATIENTS: Adults ≥18 years old

INTERVENTION: Levels of light exposure

CONTROL: Not applicable

PRIMARY OUTCOME: Risk of major depressive disorder (MDD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), bipolar disorder, psychosis, and self-harm

Secondary Outcome: Depression, anxiety, and PTSD symptom severity, overall wellbeing

METHODS (BRIEF DESCRIPTION):

- Participants were recruited through the UK National Health Service patient registries between 2006–2010.
  - The median participant age was 63 years old, with approximately 57% female and 43% male.
- From 2013–2015, participants were given an accelerometer with an embedded ambient light sensor to wear on their dominant wrist for seven days. Participants were instructed to continuously wear the device over their clothing throughout the day as they conducted their normal activities. The device quantitatively measured light exposure through Lux, a standardized unit that measures light level intensity.
- Information from each participant's light exposure profile was extracted to obtain average daytime and nighttime exposure timeframes. Daytime hour exposure times were from 0730 to 2030 while nighttime hours exposure was from 0030 to 0600.
- From 2016–2017, participants were asked to complete an online mental health questionnaire (MHQ) based on the DSM4 criteria for MDD, GAD, PTSD, bipolar disorder, psychosis, and self-harm.
- Participant symptom severity was also assessed using the PHQ-9 score for depression, the GAD-7 score for anxiety, the PCL-6 score for PTSD, and an overall well-being score, which asked about the participant's happiness.
- 86,772 participants had sufficient data obtained from their accelerometer and light sensor device, however, only 61,466 of those participants completed the MHQ.
- Results were adjusted for the participant's age, sex, ethnicity, photoperiod (duration between sunrise and sunset), employment, and physical activity.

INTERVENTION (# IN THE GROUP): 61,466

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- Increased light exposure at night was associated with higher odds of:
  - MDD (odds ratio [OR] 1.3; 95% CI, 1.2–1.4)
  - Self-harm (OR 1.3; 95% CI, 1.1–1.4)
  - GAD (OR 1.2; 95% CI, 1.1–1.4)
  - PTSD (OR 1.3; 95% CI, 1.2–1.5)
  - Psychosis (OR 1.2; 95% CI, 1.1–1.3)
  - Bipolar disorder (OR 1.2; 95% CI, 1.0–1.4)
- Increased light exposure during the day was associated with lower odds of:
  - MDD (OR 0.81; 95% CI, 0.76–0.87)
  - Self-harm (OR 0.76; 95% CI, 0.67–0.87)
  - PTSD (OR 0.82; 95% CI, 0.73–0.92)
  - Psychosis (OR 0.69; 95% CI, 0.61–0.79)
- There was no association between increased daytime light exposure and GAD or bipolar disorder.

Secondary Outcome –

- Increased nighttime light exposure was associated with greater depressive symptoms, anxiety symptoms, PTSD symptoms, and less well-being.
- Increased daytime light exposure was associated with less depressive symptoms, anxiety symptoms, PTSD symptoms, scores, and greater well-being.

LIMITATIONS:

- The psychiatric questionnaire was performed an average of 1.9 years after the accelerometer was worn. This assumes the person is living the same lifestyle when they answer the questions as when they wore the device to collect the data.
- Observational, cross-sectional study design inhibits the determination of causality. The outcomes are strictly based on correlation.
- The sensor was wrist-mounted and did not collect light data at the ocular level. This wrist-mounted accelerometer/sensor only provides a course estimate of the light sensed at the retina.
- True darkness could not be distinguished from device coverage, which could contribute to errors in the light exposure measurements.

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Can We Use Smartphones to Help Diagnose Obstructive Sleep Apnea Based on Breathing Sounds?

In-Home Smartphone-Based Prediction of Obstructive Sleep Apnea in Conjunction with Level 2 Home Polysomnography

Han SC, Kim D, Rhee CS, et al. In-Home Smartphone-Based Prediction of Obstructive Sleep Apnea in Conjunction With Level 2 Home Polysomnography. *JAMA Otolaryngol Head Neck Surg*. 2024;150(1):22-29. doi:10.1001/jamaoto.2023.3490

KEY TAKEAWAY: Smartphone-based prediction of obstructive sleep apnea (OSA) is becoming comparable to standard in-lab polysomnography testing, allowing for greater access to diagnosis.

STUDY DESIGN: Diagnostic study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: OSA is a disease noted by frequent/repetitive episodes of upper airway obstruction associated with a multitude of negative health outcomes. The standard method for diagnosis is via in-lab polysomnography (PSG). The various devices and tools used to help diagnose this condition without the full use of a sleep lab/center are emerging. Given the ubiquity of smartphones, sound-based home diagnostic assessment is an area of interest.

PATIENTS: Adults with or without sleep apnea who slept alone

INTERVENTION: Smartphone apnea-hypopnea index (AHI) predictive app

CONTROL: Sound-based assessment for OSA in the setting of a level two in-home unattended PSG

PRIMARY OUTCOME: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the predictive model based on the recorded breathing sounds

METHODS (BRIEF DESCRIPTION):

- Each participant had a level two at-home PSG study performed while also using a smartphone recording app.
  - Each participant had the same brand of PSG equipment.
- Data from the PSG was evaluated by sleep technologists and then reviewed by a sleep specialist.
- Two smartphones provided to each participant (iOS and Android OS) were placed between 50 cm and 100 cm from their head during sleep.
- The recording app used was the default recording app on each phone.
- The recorded sounds were analyzed with the AI prediction model, which was trained using over 1,000 level one in-lab PSG audio data, 297 smartphone audio data from level one PSG, and a compilation of 22,500 home environment noises.
- The data was analyzed and utilized a binary system to categorize into various AHI cutoffs.

INTERVENTION (# IN THE GROUP): 101

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- With AHI cut-off values of five, 15, and 30 (mild, moderate, severe OSA, respectively):
  - iOS sensitivity of 93%, 91%, and 93%
  - iOS specificity of 84%, 94%, and 94%
  - iOS accuracy of 89%, 93%, and 94%
  - iOS PPV of 86%, 88%, and 74%
  - iOS NPV of 92%, 96%, and 99%
  - Android sensitivity of 92%, 90%, and 93%
  - Android specificity of 84%, 94%, and 94%
  - Android accuracy of 88%, 93%, and 94%
  - Android PPV of 86%, 87%, and 72%
  - Android NPV of 91%, 96%, 99%
- Strong correlation for AHI detection from home PSG to iOS (r=.96; 95% CI, 0.94–0.97).
- Strong correlation for AHI detection from home PSG to Android OS (r=.95; 95% CI, 0.93–0.97).

LIMITATIONS:

- The study was unable to account for sleeping position(s).
- The study was only performed on a small sample size of Korean participants.
- Level two PSG (performed at home) underdiagnoses OSA compared to sleep lab studies.

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Psilocybin for Depression: Comparision with First-Line Treatment

Trial of Psilocybin Versus Escitalopram for Depression
Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of Psilocybin versus Escitalopram for Depression. *N Engl J Med.* 2021;384(15):1402-1411. doi:10.1056/NEJMoa2032994

KEY TAKEAWAY: Psilocybin and escitalopram showed similar efficacy in reducing depressive symptoms at six weeks.

STUDY DESIGN: Double-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and short duration of study)

BRIEF BACKGROUND INFORMATION: Early studies of psilocybin are suggestive of a robust antidepressant effect with just one or two doses. This may offer advantages over selective serotonin reuptake inhibitor (SSRI) medications which have a delayed onset of action and can be limited by side effects. However, there is a lack of randomized controlled trials comparing psilocybin to established depression treatments. This phase two, double-blind, randomized controlled trial compared psilocybin versus escitalopram for the treatment of depression over six weeks.

PATIENTS: Adults with depression

INTERVENTION: Psilocybin

CONTROL: Escitalopram

PRIMARY OUTCOME: Change in depressive symptom score

METHODS (BRIEF DESCRIPTION):

- Participants 18–80 years old were recruited through both formal (trial networks) and informal (social media) means.
- Inclusion criteria included patients with moderate-to-severe depression as determined by the cutoff score on the Hamilton Depression Scale (completed during the initial screening call) and confirmed by the patient's physician.
- Exclusion criteria included personal or immediate family history of psychosis, history of suicide attempts, previous use of escitalopram (previous use of psilocybin allowed), contraindication to SSRIs or undergoing MRI imaging, medical condition making the patient unsuitable for the trial (assessed by physician), pregnancy, known or suspected psychiatric condition that could compromise rapport between the patient and the trial mental health providers.
- Participants discontinued preexisting psychiatric medications at least two weeks and any psychotherapy at least three weeks before starting a trial medication.
- Participants were predominantly middle-aged (psilocybin group mean age 43 years old vs escitalopram group mean age 39 years old), male (psilocybin group 63% vs escitalopram group 69%), White (psilocybin group 93% vs escitalopram group 83%), university educated (psilocybin group 73% vs escitalopram group 79%), and had moderate severity depression (psilocybin group baseline Quick Inventory of Depressive Symptomatology Self-report [QIDS-SR-16] mean score of 15 vs escitalopram group mean score of 16).
- Intervention group: Participants received psilocybin 25 mg initially and at three weeks, with daily placebo otherwise for six weeks.
- Control group: Participants were administered a single dose of 1 mg psilocybin, assumed to have minimal effects, followed by a daily dose of 10 mg escitalopram for three weeks; subsequently, they received a re-dose of 1 mg psilocybin and the escitalopram dosage was increased to 20 mg daily, continuing for six weeks.
- Participants received psychological support from two assigned mental health professionals the day before, during, and after each psilocybin dosing.
- The primary outcome was a change in depressive symptom score on the QIDS-SR-16. Scores range from 0–27 with higher scores indicating more severe depression.
- Secondary outcomes included response (≥50% score decrease) and remission (score of ≤5) on the QIDS-SR-16.

INTERVENTION (# IN THE GROUP): 30

COMPARISON (# IN THE GROUP): 29

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- There was no difference in depressive symptoms between the two groups (mean difference [MD] –2.0; 95% CI, –5.0 to 0.9).

Secondary Outcome –

- 70% of patients in the psilocybin group met the criteria for response vs 48% of patients in the escitalopram group, however, this was not significantly different (between-group difference 22%; 95% CI, –3 to 48).
- 57% of patients in the psilocybin group met the criteria for remission vs 28% of patients in the escitalopram group (between-group difference 28%; 95% CI, 2–54).

LIMITATIONS:

- There was no placebo arm, so conclusions about the effects of either treatment regimen alone are limited.
- The effectiveness of blinding was not evaluated; if ineffective, it may have introduced expectancy effects among participants and trial staff that confounded results.
- The six-week period of follow-up may have limited the observed antidepressant efficacy in the escitalopram group.
- Generalizability is limited because the study sample was small and self-selected with most patients expressing a preference to be in the psilocybin arm.
- Generalizability is further limited by most patients in the sample having moderate depressive symptoms and the sample being relatively socio-demographically homogeneous (predominantly White, male, university-educated, and employed).

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