GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 2 - Issue 37

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of September 12 - 16, 2022

SPOTLIGHT: Want Some Noninvasiveness? Try CT Over Invasive Coronary Angiography for Stable Chest Pain

- Cognitive Behavioral Therapy Prevents Depression When You Have Insomnia
- Is Less Always More? The Effects of Time-Restricted Eating on Weight Loss
- MDMA Enhanced Psychotherapy Reduces PTSD Symptoms

Want Some Noninvasiveness? Try CT Over Invasive Coronary Angiography for Stable Chest Pain

CT or Invasive Coronary Angiography in Stable Chest Pain
DISCHARGE Trial Group, Maurovich-Horvat P, Bosserdt M, et al. CT or Invasive Coronary Angiography in Stable Chest Pain. *N Engl J Med*. 2022;386(17):1591-1602. doi:10.1056/NEJMoa2200963

KEY TAKEAWAY: When diagnosing obstructive CAD, CT imaging does not increase the risk of major adverse cardiovascular events compared to ICA and is associated with lower procedure-related complications.
STUDY DESIGN: Multicenter, randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Computed tomography (CT) imaging is an accurate alternative diagnostic modality to invasive coronary angiography (ICA) in diagnosing obstructive coronary artery disease (CAD). Prior RCTs have demonstrated that initial CT imaging results in a lower number of invasive procedures and similar outcomes of hospitalization and revascularization as ICA. This study examined the effectiveness of CT and ICA on management of CAD by comparing the frequency of major cardiovascular events.

PATIENTS: Adults with stable chest pain and intermediate pretest probability of obstructive CAD
INTERVENTION: CT imaging
CONTROL: ICA
PRIMARY OUTCOME: Composite of major adverse cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke)
Secondary Outcome: Procedure related complications and angina pectoris

METHODS (BRIEF DESCRIPTION):

- Patients were at least 30 years old and were referred for ICA to one of the 26 European Centers.
  - Patients had stable chest pain with intermediate pretest probability (10–60%) of obstructive CAD.
  - The mean age of the patients was 60 ± 10 years.
  - 56% of the patients were women.
- Exclusion criteria were the receipt of hemodialysis, an absence of sinus rhythm, and pregnancy.
- Patients were randomly assigned to either CT or ICA with the use of web-based system, concealing the group assignment.
- Both patients and their clinicians were aware of the group assignments however the assessors were blinded.
- CT with at least 64 slice technology was performed and interpreted by board certified radiologists and ICA was performed per the guidelines by board-certified cardiologists
- Patient without obstructive CAD were discharged from the trial to their referring physician while patients with obstructive CAD were treated according to guidelines.
- For the primary outcome, complete follow up was achieved for 3,523 patients.

INTERVENTION (# IN THE GROUP): 1,833
COMPARISON (# IN THE GROUP): 1,834

FOLLOW UP PERIOD: 3.5 years

RESULTS:
Primary Outcome –

- CT testing did not increase the risk for major adverse cardiovascular events compared to ICA (hazard ratio 0.70; 95% CI, 0.46–1.1).

Secondary Outcomes –

- Major procedure related complications occurred more frequently in the ICA group (HR 0.26; 95% CI, 0.13–0.55; NNH=71).
- There was no difference in angina during the final four weeks of follow-up.

LIMITATIONS:

- Unblinded study as both clinicians and patients were aware of the group assignments.
- The incidence of non-diagnostic CT was 6% in this study.
- The study does not compare cost-effectiveness of CT and ICA.

Parth Shah, DO
Advocate Illinois Masonic Medical Center
Chicago, IL

Cognitive Behavioral Therapy Prevents Depression When You Have Insomnia

Prevention of Incident and Recurrent Major Depression in Older Adults with Insomnia: A Randomized Clinical Trial

Irwin MR, Carrillo C, Sadeghi N, Bjurstrom MF, Breen EC, Olmstead R. Prevention of Incident and Recurrent Major Depression in Older Adults with Insomnia: A Randomized Clinical Trial. *JAMA Psychiatry*. 2022 Jan 1;79(1):33-41. doi: 10.1001/jamapsychiatry.2021.3422.

KEY TAKEAWAY: Cognitive behavioral therapy for insomnia (CBT-I) is an effective method to prevent incident and recurrence of major depression in those with insomnia over 60 years old.

STUDY DESIGN: Assessor-blinded, parallel group, single site randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Insomnia occurs in 50% of older adults and has been associated with increased risk of depression. Preventative measures must be identified which can mitigate the incidence of depression in adults with insomnia. Sleep Education Therapy (SET) and CBT-I are two nonpharmacologic measures which show promise in this area.

PATIENTS: Adults over 60 years old with insomnia

INTERVENTION: CBT-I (5 components: cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation)

CONTROL: SET (5 components: sleep hygiene, sleep biology, characteristics of healthy sleep, stress biology, impact on sleep)

PRIMARY OUTCOME: Incident or recurrence of depressive disorder

Secondary Outcome: Sustained remission of insomnia

METHODS (BRIEF DESCRIPTION):

- Patients: >60 years older within a 15-mile radius around UCLA
- The mean age was 70.2 for the CBT-I group and 69.9 for the SET group.
- Participants had insomnia per DSM-4 Criteria. Exclusion criteria: depression in the last 12 months per DSM-4 or DSM-5 criteria, sleep disordered breathing, or co-occurring psychiatric disorders.
- For eight weeks, the treatment group received weekly 120-minute sessions of CBT-I.
- The comparison group received 120-minute group sessions of SET weekly for eight weeks.
- Time to major depressive disorder was measured via structured clinical interview from the DSM-5 every six months for 36 months during the trial period as well as monthly telephone PHQ-9 screening. PHQ-9 scores ranged from 0 to 27 with 10 being a positive score and higher numbers indicating more severe depression.
- Durable remission of insomnia was measured via DSM-5 criteria every six months during the 36-month period.

INTERVENTION (# IN THE GROUP): 156

COMPARISON (# IN THE GROUP): 135

FOLLOW UP PERIOD: 36 months

RESULTS:

Primary Outcome:

- CBT-I decreased the rate of depression compared to SET (HR 0.51; 95% CI, 0.29–0.88; NNT=8).

Secondary Outcome:

- CBT-I improved sustained remission rates of insomnia as compared to SET (26% vs 10%, respectively; β=0.56; 95% CI, 0.07–1.04).

LIMITATIONS:

- The generalizability is limited given the small geographic area and inherent selection bias.
- Predominantly White participants.

Samuel Castles, MD
Alaska Family Medicine Residency
Anchorage, AK

Is Less Always More? The Effects of Time-Restricted Eating on Weight Loss

Calorie Restriction with or without Time-Restricted Eating in Weight Loss

Liu D, Huang Y, Huang C, et al. Calorie Restriction with or without Time-Restricted Eating in Weight Loss. *N Engl J Med*. 2022; 386(16):1495–1504.

KEY TAKEAWAY: Time-restricted eating was not more effective in reducing body weight, body fat, or metabolic risk factors than daily calorie restriction in obese patients.
STUDY DESIGN: Randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Time-restricted eating, also known as intermittent fasting, is a popular weight-loss strategy. This regimen most commonly restricts eating to an 8- or 12-hour eating window per 24 hours. A major draw to this eating regimen is the simplicity of it and the lack of food restriction. Although studies have shown that time-restricted eating can result in overall weight reduction in obese patients, long-term efficacy is still undetermined.

PATIENTS: Obese adults
INTERVENTION: Time-restricted eating
CONTROL: Daily calorie restriction
PRIMARY OUTCOME: Net difference between baseline body weight and end of trial body weight
Secondary Outcomes: change in waist circumference, body fat, body lean mass, metabolic risk factors (levels of plasma glucose, insulin sensitivity, serum lipids, and blood pressure)

METHODS (BRIEF DESCRIPTION):

- 139 obese adults from Guangzhou, China were recruited from the general public (118 completed study; drop-out rate of 15%).
  - In this study, obesity is defined as a BMI between 28-45 kg/m^2.
  - Patients were 18 to 75 years old.
- The daily calorie requirements for all participants consisted of:
  - Men: 1,500 to 1,800 kcal/day (40–55% carbohydrates, 15–20% protein, 20–30% fat)
  - Women: 1,200 to 1,500 kcal/day (40–55% carbohydrates, 15–20% protein, 20–30% fat)
  - These calorie restrictions accounted for about 75% of the participants daily caloric intake at baseline.
- Time-restricted eating regimen consisted of eating the restricted calorie amount between 8:00 am to 4:00 pm.
  - Only noncaloric beverages were allowed outside that eating window.
- Trial personnel (observers) were blinded to which participants were assigned to which intervention.
- Daily-calorie restriction regimen had no eating time restrictions.
- All participants received bi-monthly in-person dietary counseling, follow-up phone calls and messages by trained health coaches. Dietary information booklets and a daily dietary log were also provided.
- Outcome measurements were taken by multiple modalities including:
  - iDXA scan, CT scan, and transient elastography to assess fat mass throughout the body.
  - Standard methods were used to assess the metabolic risk factors.
  - The 12-item Short-Form Health Survey Questionnaire assessed quality of life.

INTERVENTION (# IN THE GROUP): 69
COMPARISON (# IN THE GROUP): 70

FOLLOW UP PERIOD: 12 months

RESULTS:
Primary Outcome:

- There was no significant difference in weight loss after 12 months between the two groups (net difference –1.8 kg; 95% CI, –4.0 to 0.4).

Secondary Outcomes:

- There was no significant difference found between groups for waist circumference, BMI, body fat, body lean mass, blood pressure, quality of life, or metabolic risk factors.

LIMITATIONS:

- Patient population only consisted of adults from Guangzhou, China which may limit generalizability.
- Energy expenditure was not assessed throughout trial.
- Obese adults with comorbid cardiovascular disease and/or diabetes were excluded from the study which limits generalizability.

Stephanie Meier, DO
Advocate Illinois Masonic Medical Center
Chicago, IL

MDMA Enhanced Psychotherapy Reduces PTSD Symptoms

MDMA-Assisted Therapy for Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study

Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study. *Nature Medicine*. 2021; 27(6):1025-1033. doi:10.1038/s41591-021-01336-3

KEY TAKEAWAY: MDMA-assisted therapy is a safe and efficacious treatment in reducing symptoms of severe PTSD.

STUDY DESIGN: Randomized, double-blinded, placebo-controlled phase three study (15 centers in 3 countries)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: PTSD is a highly disabling mental condition often accompanied by other psychiatric co-morbidities. Despite its high personal, social, and economic cost current treatment modalities have shown limited effectiveness in treating PTSD. Previous case-reports and phase two RCTs have shown promising results and benefits of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy compared to placebo and psychotherapy.

PATIENTS: Adults with PTSD

INTERVENTION: MDMA-assisted psychotherapy

CONTROL: Placebo and psychotherapy

PRIMARY OUTCOME: Frequency and intensity of PTSD symptoms

Secondary Outcomes: Depression and disability

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: Adult military veterans and non-veteran patients at study sites in the U.S. (n=77), Canada (n=9), and Israel (n=5) meeting DSM-5 PTSD criteria with symptom duration of at least six months, and CAPS-5 severity score of at least 35.
  - CAPS-5 scores reflect frequency and intensity of PTSD symptoms. Scores of greater than 10 indicate mild PTSD, those greater than 22 moderate PTSD, and those 35 or greater indicate severe PTSD.
- Study members underwent supervised discontinuation of psychiatric medication.
- Enrollees were randomized 1:1 to intervention or control groups.
- All participants received three 90-minute preparatory sessions conducted by a two-therapist team.
- Both groups received three experimental sessions of manualized therapy lasting eight hours, spaced four weeks apart.
  - The intervention group received MDMA in a single divided dose of 80–180 mg (depending on tolerability and patient choice) with each session.
  - The control arm received placebo with each session.
- Experimental sessions were followed by three 90-minute integrative sessions, including the morning after each experimental session and subsequent sessions weekly.
- CAPS-5 and Sheehan Disability Scale (SDS) scores were assessed three weeks after each of the first two experimental sessions and at the study endpoint.

INTERVENTION (# IN THE GROUP): 46

COMPARISON (# IN THE GROUP): 44

FOLLOW UP PERIOD: 18 weeks

RESULTS:

Primary Outcome:

- MDMA-assisted psychotherapy improved PTSD symptom severity and frequency compared to placebo and psychotherapy (between-group difference 12; effect size 0.91; 95% CI, 0.44–1.4).

Secondary Outcomes:

- MDMA-assisted psychotherapy improved depression symptoms more than the placebo and psychotherapy group (effect size 0.67; 95% CI, 0.22–1.1).
- MDMA-assisted psychotherapy did not affect disability compared to placebo and psychotherapy (effect size 0.43; 95% CI, –0.01 to 0.88).

LIMITATIONS:

- Participation limited due to the COVID-19 pandemic.
- Lacked racial and ethnic diversity, with enrollment skewed to white and female participants.
- Study limited to participants who had access to referrals from treatment providers, word of mouth, or viewed print and internet advertisements, and who then initiated contact with study sites.
- Time-demanding five-part training process for therapists and intense psychological therapy for patients.
- No follow up beyond 18 weeks.
- Subjective effects of MDMA may complicate blinding of study participants.
- Physiological effects such as vital signs and their

monitoring may have limited therapist blinding.
- Exclusion of comorbid psychiatric disorders limits applicability.
- Study not directly applicable to scope of family medicine practice.

Yuri Brito, MD
Montana Family Medicine Residency
Billings, MT