GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

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What's in this week's issue?

Week of November 29 - December 3, 2021

SPOTLIGHT: Depot to Go? Expanding Access to Injectable Contraception with Self-Administration

Depot to Go? Expanding Access to Injectable Contraception with Self-Administration

Self-Administration of Injectable Contraception: A Systematic Review and Meta-Analysis

Kennedy CE, Yeh PT, Gaffield ML, Brady M, Narasimhan M. Self-administration of injectable contraception: a systematic review and meta-analysis. *BMJ Glob Health*. 2019; 4(2):e001350. Published 2019 Apr 2. doi:10.1136/bmjgh-2018-001350

KEY TAKEAWAY: Self-administration of injectable contraception at home can lead to higher rates of contraceptive adherence compared to provider administration without an increase in safety concerns or unexpected pregnancies.

STUDY DESIGN: Systematic review and meta-analysis of 3 RCTs and 3 controlled cohort studies (N=3,851)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Injectable contraception, like Depot Medroxyprogesterone (DMPA), is an extremely common and efficacious form of birth control used by many women. While this medication is only administered every three months, the need for frequent clinic visits can be a significant barrier to contraceptive adherence for many women who desire pregnancy prevention. Self-administered injectable contraception may be a safe way to help eliminate barriers to contraceptive access and increase use of contraception for women around the world.

PATIENTS: Women of reproductive age

INTERVENTION: Self-administration of injectable contraception

CONTROL: Provider administration of injectable contraception

OUTCOME: Pregnancy, continuation rate of injectable contraception

Secondary Outcomes: Side effects, adverse events

METHODS (BRIEF DESCRIPTION):

- Systematic review of six peer-reviewed studies including 3 RCTs, 3 controlled cohort studies, and studies compared self-administration with provider-administrated injectable contraception on at least one outcome of interest.
- Risk of bias was assessed with the Cochrane Collaboration's tool (RCTs) or Evidence Project risk of bias tool (non-RCTs).
- Meta-analysis was conducted using random-effects models to generate relative risk (RR) of continuing injectable contraception and pregnancy in self-administered group compared to provider-administered group.

INTERVENTION (# IN THE GROUP): 1,925

COMPARISON (# IN THE GROUP): 1,926

FOLLOW UP PERIOD: 12 months

RESULTS: Primary Outcomes –

- Self-administration significantly increased likelihood of continuing contraception at 12 months compared to provider-administration (3 RCTs, N=1,263; RR 1.3; 95% CI, 1.2–1.4; 3 cohort studies, N=2,588; RR 1.2; 95% CI, 1.1–1.3).
- There were no differences in unintended pregnancies, with less than five pregnancies in each group.

Secondary Outcomes – There was no significant difference in side effects or adverse effects between two groups.

LIMITATIONS:

- The studies did not account for patient demographics beyond age and sex.
- The actual effect size was limited by low incidence of pregnancy.
- In one of the six studies, appointment reminders were sent to participants in the intervention group but not the participants in the control group.
- Only one of six studies included women less than 18 years old.

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Semaglutide to Aid in Weight Loss for Overweight or Obese Patients

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021; 384(11):989. doi:10.1056/NEJMoa2032183

KEY TAKEAWAY: Once weekly subcutaneous semaglutide injection plus lifestyle interventions are associated with clinically relevant weight loss.

STUDY DESIGN: Multisite, double-blind, randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Currently, clinical practice guidelines suggest pharmacotherapy for overweight and obese adults. Current options for medical management of overweight and obese individuals are limited by efficacy, cost, and safety.

PATIENTS: Overweight adults with comorbidities or obesity

INTERVENTION: Once weekly 2.4 mg semaglutide injections + lifestyle interventions

CONTROL: Placebo + lifestyle interventions

OUTCOME: Weight loss

Secondary Outcomes: Waist circumference, change in BMI, change in systolic blood pressure, change in functional status

METHODS (BRIEF DESCRIPTION):

- Participants were at least 18 years old from 16 countries that had unsuccessfully attempted to lose weight previously with a BMI ≥30 or a BMI ≥27 with comorbidities.
- The treatment group received weekly subcutaneous semaglutide injections for 68 weeks.
  - Dosage was titrated to 2.4 mg over the first eight weeks.
- The control group received matching placebo injections.
- Both the treatment and placebo groups received lifestyle interventions which included monthly counseling, a calorie-based diet, and physical activity.
- Change in body weight, as indicated by percentage, was measured over 68 weeks with targets at 5%, 10%, and 15% or more from baseline.
- Physical function was measured via the Weight on Quality of Life-Lite Clinical Trials Version and the 36-item Short Form Health Survey (SF-36).

INTERVENTION (# IN THE GROUP): 1,306

COMPARISON (# IN THE GROUP): 655

FOLLOW UP PERIOD: 68 weeks of treatment with 7 week follow up period

RESULTS:

Primary Outcome –

- The semaglutide group experienced more weight loss than the placebo group.
  - Greater mean weight change: Mean difference between the two groups –12% (95% CI, –13 to –12)
  - More likely to lose at least 5% of weight (86% vs 32%; *P*<.001)
  - More likely to lose at least 10% of weight (69% vs 12%; *P*<.001)
  - More likely to lose at least 15% of weight (51% vs 4.9%; *P*<.001)

Secondary Outcomes –

- The semaglutide group had a greater decrease in weight circumference than the placebo group (–14 cm vs –4.1 cm; MD –9.4 cm; 95% CI, –10 to –8.5).
- The semaglutide group had a greater decrease in BMI than the placebo group (–5.5 vs –0.92; MD –4.6; 95% CI, –5.0 to –4.3).

Adverse Effects (no statistical analysis conducted) –

- Those in the semaglutide and placebo group reported adverse events at 90% vs 87% respectively.
- The most common adverse effect was gastrointestinal disorders (nausea, vomiting, diarrhea, or constipation) and was predominantly seen in the semaglutide group than those receiving placebo (74% vs 48%).
- Discontinuation occurred more in the semaglutide group than the placebo group, 7.0% vs 3.1% respectively, mainly due to GI events.

LIMITATIONS:

- The participants' demographics skewed towards white and female.

- Enrolled participants may be inherently more motivated towards weight loss than the general population.

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The views expressed in this GEM are the author's and do not reflect the official policy of the U.S. Army, Tripler Army Medical Center, or the U.S. government.

Does Melatonin Work for Most of Our Middle-Aged Primary Care Patients?

Efficacy of Melatonin for Sleep Disturbance in Middle-Aged Primary Insomnia: A Double-Blind, Randomised Clinical Trial

Xu H, Zhang C, Qian Y, et al. Efficacy of melatonin for sleep disturbance in middle-aged primary insomnia: a double-blind, randomised clinical trial. *Sleep Med*. 2020; 76:113–119. doi:10.1016/j.sleep.2020.10.018.

KEY TAKEAWAY: Melatonin supplementation decreased early wake times but had no effect on objective sleep parameters.

STUDY DESIGN: Randomized double-blind, placebo-controlled parallel study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Insomnia has a worldwide prevalence of 10%–40% with several adverse consequences. Several studies have shown that melatonin may help regulate sleep rhythm in the elderly, but no studies have been done on middle-aged populations.

PATIENTS: Chinese individuals 45–60 years old with primary insomnia

INTERVENTION: Melatonin (3 g)

CONTROL: Placebo

OUTCOME: Sleep onset latency

Secondary Outcome: Subjective sleep quality

METHODS (BRIEF DESCRIPTION):

- Participants were from the Tianlin, Xuhui district in Shanghai.
- All had primary insomnia by DSM-IV criteria.
- Exclusion criteria included those with medical conditions that could interfere with sleep, treatment, major psychiatric illness, or alcoholism.
- Participants were given 3 mg of fast-acting melatonin or identical appearing placebo an hour before bed, the following were measured at baseline and on the last treatment day:
  - Sleep onset latency: The time from lights off at 22:30 to sleep onset in minutes measured by overnight polysomnography (PSG)
  - Early wake time: The time from lights-on at 6:30 when PSG was stopped minus wake-up time measured in minutes
  - PSG, Pittsburg Sleep Quality Index (PSQI), insomnia severity index (ISI) and Epworth Sleepiness Scale (ESS)
  - Sleep parameters were reported as a difference in change in minutes (calculated as change in melatonin group subtracted from the change in placebo group).

INTERVENTION (# IN THE GROUP): 51

COMPARISON (# IN THE GROUP): 46

FOLLOW UP PERIOD: Four weeks

RESULTS:

Primary Outcome –

- There was no statistically significant difference in sleep onset latency in participants taking melatonin compared to placebo (52 minutes; 94% CI, –41 to 149).

Secondary Outcomes –

- Early wake time improved in the melatonin group (–31 minutes; 95% CI, –54 to –7)
- There was no statistically significant difference in subjective sleep quality.

LIMITATIONS:

- A longer study period is needed to understand the long-term effects of melatonin.
- Only one dose of melatonin was studied.
- Levels of participants' endogenous melatonin were unknown.
- Results may only be applicable to those within China and the specific age range.

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Aspirin: Not as Benign as We Thought

Effect of Aspirin on Cancer Incidence and Mortality in Older Adults

McNeil JJ, Gibbs P, Orchard SG, et al. Effect of Aspirin on Cancer Incidence and Mortality in Older Adults. *J Natl Cancer Inst*. 2021; 113(3):258–265. doi:10.1093/jnci/djaa114

KEY TAKEAWAY: 100 mg of aspirin daily is not associated with an increased risk for new cancers, but is associated with an increased risk of cancer mortality and metastatic cancer in the elderly.

STUDY DESIGN: Randomized, double-blind, placebo-controlled study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Many patients take "baby aspirin." Previous studies examined potential benefits from daily low dose aspirin, including colorectal cancer incidence, however the populations studied were generally younger and short–term cancer risk was not affected. However, the ASPREE trial found higher all-cause mortality.

PATIENTS: Adults over 65 years old without cardiovascular disease, dementia, or physical disability

INTERVENTION: 100 mg aspirin daily

CONTROL: Placebo

OUTCOME: Fatal and non-fatal cancers

METHODS (BRIEF DESCRIPTION):

- Participants were randomly assigned to 100 mg enteric-coated aspirin or placebo.
  - 16,703 Australians 70 years and older
  - 2,411 US African Americans and Hispanics 65 years and older
  - 19% had a previous history of cancer.
  - All were in good health and expected to live for at least 5 years.
- Detailed clinical records were obtained from treating practitioners and health-care institutions when evidence of a new or metastatic cancer was recorded or after a participant had died.
- Each participant could contribute more than one distinct cancer endpoint if the subtypes differed.
- Local recurrence of a previous cancer was not included.
- TNM staging and histological grading were collected if available.
- Blinded adjudicators confirmed all diagnoses when allocating cause of death.

INTERVENTION (# IN THE GROUP): 9,525

COMPARISON (# IN THE GROUP): 9,589

FOLLOW UP PERIOD: Median 4.7 years

RESULTS:

- Aspirin was not associated with an increased risk for new cancer (HR 1.0; 95% CI, 0.95–1.1).
- Aspirin was associated with an increased risk for:
  - New metastatic disease (HR 1.2; 95% CI, 1.0–1.4)
  - Stage 3 cancers at diagnosis (HR 2.1; 95% CI, 1.0–4.3)
  - Stage 4 cancers at diagnosis (HR 1.2; 95% CI, 1.0–1.5)
  - Deaths from solid tumors (4.4 to 5.9 cases/1000 person-years; HR 1.3; 95% CI, 1.1–1.6)

LIMITATIONS:

- The U.S. participants were minorities of a different age group.
- P-value for new metastatic disease risk was not included.

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Just Say Yes? Meta-Analysis Suggests E-Cigarettes May Have Benefit as Prescribed Therapy

E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis

Wang RJ, Bhadriraju S, Glantz SA. E-Cigarette Use and Adult Cigarette Smoking Cessation: A Meta-Analysis. *Am J Public Health*. 2021; 111(2):230–246. doi:10.2105/AJPH.2020.305999

KEY TAKEAWAY: E-cigarettes may increase smoking cessation rates as prescribed therapy but not as a consumer product.

STUDY DESIGN: Meta-analysis of observational trials and RCTs

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Smoking continues to be a major contributor towards early cardiovascular morbidity and death. E-cigarettes have been proposed as a possible therapy to increase rates of smoking cessation. Their use remains controversial, and their impact is unknown.

PATIENTS: Adult smokers seeking cessation
INTERVENTION: E-cigarettes
CONTROL: Standard therapy
OUTCOME: Smoking cessation

METHODS (BRIEF DESCRIPTION):

- PubMed, Web of Science Core Collection, and EMBASE databases searched for studies in peer-reviewed journals for adults exposed to e-cigarettes, with cessation as an outcome.
- Both observational and randomized controlled trials were included, with 55 observation studies and 9 RCTs included in the meta-analysis.
- Given wide variability in study design, the authors summarized findings to include motivation to quit, the intensity of e-cigarette use, and the effect of free e-cigarettes.

INTERVENTION (# IN THE GROUP): 2,708 participants from RCTs (# not available for observational studies)
COMPARISON (# IN THE GROUP): 2,726 participants from RCTs (# not available for observational studies)

FOLLOW UP PERIOD: Varied with at least 7 days and at least 30 days as the most common

RESULTS:

- E-cigarette use as a consumer product was not associated with smoking cessation (55 observational studies; OR 0.95; 95% CI, 0.77–1.2).
- Free e-cigarettes were associated with higher smoking cessation compared to conventional therapies (9 RCTs; RR 1.6; 95% CI, 1.2–2.1).

LIMITATIONS:

- Varying e-cigarette products
- Limited number of high-quality studies
- Heterogeneity in "motivation to quit"
- Publication bias

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