GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of December 25 - 29, 2023

SPOTLIGHT: Can Icosapent Ethyl Reduce Risk of Cardiovascular Events Associated with Smoking?

- Shedding Meds with a Patient-Centered Deprescribing Intervention
- Is It Hot in Here or Is It Just Menopause?
- Multiple Interventions may be Beneficial for Mothers Experiencing Perinatal Bereavement

Can Icosapent Ethyl Reduce Risk of Cardiovascular Events Associated with Smoking?

Potential Effects of Icosapent Ethyl on Cardiovascular Outcomes in Cigarette Smokers: REDUCE-IT Smoking

Miller M, Bhatt DL, Steg PG, et al. Potential effects of icosapent ethyl on cardiovascular outcomes in cigarette smokers: REDUCE-IT smoking. *Eur Heart J Cardiovasc Pharmacother.* 2023;9(2):129-137. doi:10.1093/ehjcvp/pvac045

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KEY TAKEAWAY: Twice daily icosapent ethyl (IPE) in cigarette smokers reduces the risk of cardiovascular events to the same level as nonsmokers.

STUDY DESIGN: Post-hoc analysis of the REDUCE-IT trial, a randomized, multinational, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Cigarette smoking is a well-known risk factor for cardiovascular disease morbidity and mortality. The risk of adverse cardiovascular outcomes is further multiplied in patients with hypertriglyceridemia. Currently, the standard management for the reduction of triglycerides, and therefore cardiovascular risk in these patients, are statins. Icosapent ethyl is a type of omega-3 fatty acid that has been shown to reduce cardiovascular events in high-risk patients with hypertriglyceridemia.

PATIENTS: Smokers with elevated triglycerides and cardiovascular risk

INTERVENTION: Icosapent ethyl

CONTROL: Placebo

PRIMARY OUTCOME: Cumulative incidence of cardiovascular events

Secondary Outcome: Risk of adverse events

METHODS (BRIEF DESCRIPTION):

- The study was performed in 11 countries from Westernized (71%), Eastern Europe (27%), and Asian Pacific (2%) geographic areas.
- Patients were predominantly male (71%) with a median age of 64 years old, median BMI of 30.8, and 92% identifying as White, 2% Black, and 4% Asian.
- Inclusion Criteria: Adults who were current and former smokers with elevated triglycerides (fasting TG level 135–499) and cardiovascular risk (>45 yo with cardiovascular disease or >50 yo with diabetes and at least one additional risk factor) with LDL-C levels 41–100 were included.
- Patients were blinded and randomized to one of the following treatments: 2 g icosapent ethyl oral twice daily or a matching placebo.
- A composite of the incidence of cardiovascular death, nonfatal MI or stroke, coronary revascularization, or hospitalization for unstable angina was measured as the primary outcome.
- The number of patients and type of adverse events experienced including atrial fibrillation and serious bleeding events were recorded for both treatment groups.

INTERVENTION (# IN THE GROUP): 2,485

- 628 current smokers
- 1,857 former smokers

COMPARISON (# IN THE GROUP): 2,428

- 613 current smokers
- 1,815 former smokers

FOLLOW-UP PERIOD: Median 4.9 years

RESULTS:

Primary Outcome –

- Icosapent ethyl reduced the incidence of total cardiovascular events in current/former smokers (rate ratio [RR] 0.71; 95% CI, 0.61–0.82).
- Current/former smokers treated with icosapent ethyl had a reduced risk of:
  - Cardiovascular death or nonfatal MI (relative risk reduction [RRR] 23%; *P*=.002)
  - Fatal or non-fatal MI (RRR 30%; *P*=.0004)
  - Urgent or emergent revascularization (RRR 26%; *P*=.004)
  - Composite of total mortality, non-fatal MI, and non-fatal stroke (RRR 19%; *P*=.004)
- Current (23.8%) and former (23.0%) smokers treated with icosapent ethyl had a similar cumulative incidence rate of cardiovascular events compared to placebo-treated never-smokers (25.7%; *P*≤.05).

Secondary Outcome –

- Current/former smokers who received IPE were more likely to be hospitalized for atrial fibrillation/flutter than those receiving a placebo (3.3% vs. 2.2%, respectively; log-rank *P*=.01).

    - However, results were not statistically significant for current smokers alone (2.7% vs. 1.5%, respectively; log-rank *P*=.12).
- Current/former smokers who received IPE were more likely to experience adverse bleeding events than those receiving a placebo (13.4% vs. 11.4%, respectively; Fisher's exact *P*=.03).
    - However, results were not statistically significant for current smokers alone (10.7% vs. 9.8%, respectively; Fisher's exact *P*=.64).

LIMITATIONS:

- This study is a post-hoc analysis of data from REDUCE-IT so the intervention and control groups were not pre-specified subgroups for which the experiment was designed. As such, the groups were not balanced at baseline, and other therapies may influence outcomes. One such noted difference is that current smokers assigned to icosapent ethyl had lower LDL-C levels than placebo (median, 76 vs. 80 mg/dL, respectively; *P*=.02).
- Smoking status was self-reported.
- Only 6% of the study population was non-White.
- REDUCE-IT was sponsored by Amarin Pharma, Inc so sponsorship bias cannot be excluded.

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Shedding Meds with a Patient-Centered Deprescribing Intervention

Deprescribing Medications Among Older Adults from End of Hospitalization Through Postacute Care: A Shed-MEDS Randomized Clinical Trial

Vasilevskis EE, Shah AS, Hollingsworth EK, et al. Deprescribing Medications Among Older Adults from End of Hospitalization Through Postacute Care: A Shed-MEDS Randomized Clinical Trial. *JAMA Intern Med.* 2023;183(3):223-231. doi:10.1001/jamainternmed.2022.6545

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KEY TAKEAWAY: Shed-MEDS reduces the total number of medications at post-acute care (PAC) facility discharge and 90 days after PAC facility discharge.

STUDY DESIGN: Randomized, single-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Polypharmacy is common among older adults with multiple comorbidities. Patient-centered deprescribing may be an effective intervention in reducing polypharmacy and associated adverse effects. Few studies have examined deprescribing that begins in the hospital setting and continues in a PAC facility.

PATIENTS: Hospitalized adults discharged to a PAC facility

INTERVENTION: Shed-MEDS intervention

CONTROL: Usual care at the hospital and PAC facility

PRIMARY OUTCOME: Total medication count at hospital discharge, PAC facility discharge, and 90 days after PAC facility discharge

Secondary Outcome: Total number of Potentially Inappropriate Medications (PIM) at each time point, the Drug Burden Index (DBI), adverse events

METHODS (BRIEF DESCRIPTION):

- Participants were hospitalized adults ≥50 years old with ≥5 prehospital medications who were discharged to a PAC facility.
- Patients were assigned to Shed-MEDS intervention or usual care in a blinded randomized fashion.
- The Shed-MEDS intervention consisted of a hospital intervention phase and a PAC intervention phase, which included a medication review led by a pharmacist or nurse practitioner, deprescribing recommendations approved by the patient or surrogate, and continuation of active deprescribing initiated in the hospital throughout the PAC facility stay.
- The intervention began at the time of hospital enrollment and ended at discharge from the PAC facility.
- Total medication count, PIMs, and the DBI were recorded at hospital discharge, PAC facility discharge, and 90 days after PAC facility discharge.
- Medications included prescribed and over-the-counter drugs whether scheduled or PRN.
- A PIM was defined as a medication on the Beers Criteria, the STOPP (Screening Tool of Older Persons' Prescriptions) Criteria, and the RASP (Rationalization of Home Medication by an Adjusted STOPP in Older Patients) List.
- The DBI is a validated measure of sedative and anticholinergic burden.

INTERVENTION (# IN THE GROUP): 142

COMPARISON (# IN THE GROUP): 142

FOLLOW-UP PERIOD: 90 days after discharge from PAC facility

RESULTS:

Primary Outcome –

- Shed-MEDS reduced medications compared to usual care.
  - At PAC facility discharge: 14% fewer medications (mean ratio 0.86; 99% CI, 0.80–0.93)
  - 30 days after PAC facility discharge: 15% fewer medications (mean ratio 0.85; 99% CI, 0.78–0.92)

Secondary Outcome –

- Shed-MEDS reduced PIMs and DBI compared to usual care.
  - At PAC facility discharge: 14% fewer PIMs (mean ratio 0.86; 99% CI, 0.79–0.93) and lower DBI (mean difference –0.59; 99% CI, –0.85 to –0.34)
  - 90 days after PAC facility discharge: 12% fewer PIMS (mean ratio 0.88; 99% CI, 0.80–0.97) and lower DBI (mean difference –0.34; 98% CI, –0.63 to – 0.07)
- Shed-MEDS showed a trend toward fewer overall adverse events, but this was not statistically significant.

LIMITATIONS:

- Clinical research staff conducting the intervention and hospital clinicians taking care of both intervention and control groups were not blinded.
- The small sample size reduces statistical power and the observed magnitude of effect.
- Potential for selection/Berkson bias given intervention and control group patients were selected from hospitals.
- Despite randomization and blinding of patients, enrolled patients may have been more willing to deprescribe.
- Limited generalizability of results as the study was limited to a single academic hospital and geographic area.

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Is It Hot in Here or Is It Just Menopause?

Efficacy of Continuous Transdermal Nitroglycerin for Treating Hot Flashes by Inducing Nitrate Cross-Tolerance in Perimenopausal and Postmenopausal Women: A Randomized Clinical Trial

Huang AJ, Cummings SR, Ganz P, et al. Efficacy of Continuous Transdermal Nitroglycerin for Treating Hot Flashes by Inducing Nitrate Cross-tolerance in Perimenopausal and Postmenopausal Women: A Randomized Clinical Trial. *JAMA Intern Med.* 2023;183(8):776-783. doi:10.1001/jamainternmed.2023.1977

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KEY TAKEAWAY: Continuous transdermal nitroglycerin did not improve hot flashes for perimenopausal and postmenopausal women who were experiencing greater than seven hot flashes a day when compared to the placebo patches.

STUDY DESIGN: Randomized, double-blinded, placebo-controlled clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Menopausal women are concerned about using long-term systemic estrogen therapy due to potential adverse events. Non-hormonal options could avoid these risks. Nitric oxide is involved in hot flash vasodilation, suggesting it might benefit women with vasomotor symptoms.

PATIENTS: Perimenopausal and postmenopausal women reporting hot flashes

INTERVENTION: Uninterrupted daily use of transdermal NTG

CONTROL: Identical placebo patches

PRIMARY OUTCOME: Decrease in frequency or severity of hot flashes

Secondary Outcome: Number of daily severe/moderate hot flashes, quality of life, hot flash interference in daily activities

METHODS (BRIEF DESCRIPTION):

- Perimenopausal or postmenopausal women 40–62 years old who reported seven or more hot flashes per day were included.
- Patients were randomized 1:1 to receive either uninterrupted daily use of transdermal nitroglycerin or an identical placebo patch.
- Perimenopausal was defined as amenorrhea for 60 days in the last year.
- Postmenopausal was defined as amenorrhea for 12 months, a history of bilateral oophorectomy, or follicle-stimulating hormone level >20 mU/mL.
- Primary outcome was measured as a change in the frequency of hot flashes recorded in a seven day diary at five and 12 weeks.
- Secondary outcomes included the average number of daily moderate to severe hot flashes and changes in scores on the hot flash-related daily interference and the menopause-specific quality of life questionnaire.

INTERVENTION (# IN THE GROUP): 70

COMPARISON (# IN THE GROUP): 71

FOLLOW-UP PERIOD: Five and 12 weeks

RESULTS:

Primary Outcome –

- There was no significant change in the number of hot flashes with continuous NTG compared to the placebo.
  - Five weeks (mean change [MC] −0.9; 95% CI, −2.1 to 0.3)
  - 12 weeks (MC −0.1; 95% CI, −1.2 to 1.4)

Secondary Outcome –

- There was no significant overall change between the two groups in:
  - Average number of moderate to severe hot flashes per day (MC −0.8; 95% CI, −1.9 to 0.2)
  - Quality of life (MC −0.2; 95% CI, −0.9 to 0.5)
  - Hot flash-related daily interference scale score (MC 0.4; 95% CI, −6.2 to 7.1)

LIMITATIONS:

- The patient population was women who had seven or more hot flashes a day.
- It was based only in northern California in one academic center; therefore, the study may not be generalizable to the general patient population.
- The study results were only measured at five and 12 weeks.
- The study measured participants' symptom diaries.

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Multiple Interventions may be Beneficial for Mothers Experiencing Perinatal Bereavement

Nursing Interventions to Facilitate the Grieving Process After Perinatal Death: A Systematic Review

Fernández-Férez A, Ventura-Miranda MI, Camacho-Ávila M, et al. Nursing Interventions to Facilitate the Grieving Process after Perinatal Death: A Systematic Review. *Int J Environ Res Public Health*. 2021;18(11):5587. Published 2021 May 24. doi:10.3390/ijerph18115587

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KEY TAKEAWAY: Multiple interventions are available that can potentially help grieving mothers after experiencing perinatal death.

STUDY DESIGN: Systematic review of two randomized control trials and two quasi-experimental studies (N=401)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of numerical and statistical results)

BRIEF BACKGROUND INFORMATION: Parents who experience perinatal death are at greater risk for mood disorders, PTSD, eating disorders, sleep disorders, isolation, and loss of faith. Interventions that could cultivate long-lasting biopsychosocial benefits while also providing much-needed relief for this population are needed.

PATIENTS: Women experiencing perinatal death

INTERVENTION: Cognitive counseling, grief counseling family support, and nursing support programs

CONTROL: No intervention

PRIMARY OUTCOME: Severity of depression, grief, and family dysfunction after perinatal loss

METHODS (BRIEF DESCRIPTION):

- Two randomized control trials and two quasi-experimental studies were selected after a comprehensive search of English and Spanish language studies published in the last five years.
- Participants were women ≥18 years old with a gestational age of at least 20 weeks and had experienced a stillbirth or fetal death.
- Studies were excluded if women were less than 14 weeks pregnant or did not describe specific interventions used.
- Perinatal loss was defined as death of a baby that occurs between the 22nd week of pregnancy and seven days after birth.
- Interventions consisted of the Roy adaption model, family support programs, cognitive behavioral therapy, and grief counseling.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable (2–6 week follow up interviews post-intervention)

RESULTS:

Primary Outcome –

- All interventions improved the level of anxiety, post-traumatic stress, depression, and the symptoms of grief if they were performed both before perinatal loss and after it occurred.
- Results in the interventional group were significant.
- Both coping and anxiety reduction were improved using interventions before perinatal death.
- Depression and sleep were improved by interventions used after perinatal loss.

LIMITATIONS:

- Interventions focused primarily on mothers while fathers experience similar symptoms.
- Further studies are needed to assess the efficacy of similar interventions on this population and how this could affect study outcomes.
- No objective statistical outcomes were provided.
- Multiple heterogeneous interventions were studied.

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