GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 17

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of April 24 - 28, 2023

SPOTLIGHT: Opioid Versus Non-Opioid Pain Management After Surgical Discharge

- Fluticasone Furoate and Oxymetazoline Nasal Spray for Allergic Rhinitis
- How Efficacious is Semaglutide in Treating Adolescent Obesity?
- Get Moving to Decrease Your Risk of Sudden Cardiac Death?

Opioid Versus Non-Opioid Pain Management After Surgical Discharge

Opioid Versus Opioid-Free Analgesia After Surgical Discharge: A Systematic Review and Meta-Analysis of Randomised Trials

Fiore JF Jr, El-Kefraoui C, Chay MA, et al. Opioid versus opioid-free analgesia after surgical discharge: a systematic review and meta-analysis of randomised trials. *Lancet*. 2022;399(10343):2280-2293. doi:10.1016/S0140-6736(22)00582-7

KEY TAKEAWAY: In patients who underwent elective minor- and moderate-level surgeries, opioids at surgical discharge do not reduce pain compared to non-opioid pain analgesia.

STUDY DESIGN: Meta-analysis and systematic review of 47 randomized controlled trials (N=6,607)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The opioid epidemic from the overprescribing of opioids has resulted in the misuse of opioids, increases in dependence, and opioid-related overdoses. Opioid-related deaths have increased significantly over the last 10 years. In 2020, CDC reported almost 69,000 opioid-related deaths. Post-operative pain management can act as the first event leading to opioid dependence or opioid use disorders. There is a significant necessity to evaluate non-opioid pain management in the context of post-surgical discharge pain management.

PATIENTS: Patients who underwent elective minor and moderate surgeries

INTERVENTION: Multi-dosed opioid analgesia

CONTROL: Non-opioid analgesia (ibuprofen and/or Tylenol)

PRIMARY OUTCOME: Pain intensity on day one, post-operative vomiting

Secondary Outcome: Pain intensity at later time points, adverse events, dissatisfaction, healthcare reutilization

METHODS (BRIEF DESCRIPTION):

- Patients were 59% female and 41 % male with an average age range of 21–63 years old in North America (53%) and Europe (23%).
- Patients who underwent elective mild to moderate surgical procedures were at least 15 years old.
- Mild to moderate surgeries included dental, general surgery, OBGYN, otolaryngology, ophthalmology, orthopedic, and plastic surgeries.
- Each trial randomized patients into multi-dosed opioid pain management vs non-opioid pain management (Tylenol and/or ibuprofen).
- The standard pain metric was 0–10 intensity scale and was assessed post-operative on days 0, 1, 2, 3, 4–7, and 8–30 days.
- Adverse events (side effects) were also evaluated.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 30 days after surgical discharge

RESULTS:

Primary Outcome –

- Opioid management did not decrease pain intensity one-day post-surgical discharge (36 trials, n=3,848; weighted mean difference 0.01; 95% CI, –0.26 to 0.27).
- Opioid pain management was associated with an increased risk of vomiting (12 trials, n=2,789; RR 4.5; 95% CI, 1.9–11).

Secondary Outcome –

- Opioid pain management was not associated with decreased pain intensity on post-surgical discharge on days two through 30.
- Opioid pain management was associated with adverse events.
  - Nasua (RR 2.4; 95% CI, 1.6–3.6)
  - Constipation (RR 1.6; 95% CI, 1.04–2.6)
  - Dizziness (RR 2.2; 95% CI, 1.2–4.1)
  - Drowsiness (RR 1.6; 95% CI, 1.02–2.4)
- Opioid pain management was not associated with increased rates of healthcare utilization or dissatisfaction with pain regimen.

LIMITATIONS:

- There was no information regarding the number of patients in the intervention and comparison groups.
- There was limited focus on non-opioid medication side effects.
- This study did not include non-elective, major, or major-complex procedures.
- Trials did not report overdoses or post-operative diagnoses of opioid use disorder.

- Data was primary derived from low-quality trials with a high risk of bias.

Nicole Woodson-DeFauw, MD
University of Iowa Hospitals and Clinics
Iowa City, IA

Fluticasone Furoate and Oxymetazoline Nasal Spray for Allergic Rhinitis

Efficacy and Safety of Fluticasone Furoate and Oxymetazoline Nasal Spray: A Novel First Fixed-Dose Combination for the Management of Allergic Rhinitis with Nasal Congestion

Kumar RS, Jain MK, Kushwaha JS, et al. Efficacy and Safety of Fluticasone Furoate and Oxymetazoline Nasal Spray: A Novel First Fixed-Dose Combination for the Management of Allergic Rhinitis with Nasal Congestion. *J Asthma Allergy*. 2022; 15:783-792. Published 2022 Jun 10. doi:10.2147/JAA.S357288

KEY TAKEAWAY: Dual therapy consisting of Fluticasone Furoate, and Oxymetazoline Nasal Spray is superior and well tolerated compared to Fluticasone Furoate (placebo) nasal spray in the management of Allergic Rhinitis and nasal congestion.

STUDY DESIGN: Prospective, randomized, double-blind, comparative clinical study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Intranasal steroids are recommended as the first line of treatment for allergic rhinitis (AR), according to current guidelines. However, in patients with moderate to severe AR, this is frequently insufficient to provide control. Additionally, it takes a few days to reach its peak effectiveness. An adrenomimetic known as oxymetazoline (intranasal decongestant) has been demonstrated to significantly reduce nasal blockage with the onset of action in minutes.

PATIENTS: Adults with moderate to severe seasonal allergic rhinitis

INTERVENTION: Fluticasone Furoate and Oxymetazoline Nasal Spray (fixed-dose combination)

CONTROL: Fluticasone Furoate (placebo) nasal spray

PRIMARY OUTCOME: Nighttime AR sensitivity

Secondary Outcome: Daytime AR sensitivity, nasal congestion, complete relief of nasal congestion, nasal symptoms (congestion, sneezing, itching, rhinorrhea), ocular symptoms (itching, tearing, redness)

METHODS (BRIEF DESCRIPTION):

- Participants were recruited from six tertiary care centers in India from December 2020 to March 2021.
- Participants' age ranged from 18 to 65 years old (median 34) and 62% were male and 38% were female.
- Participants with seasonal allergic rhinitis that worsened during the study season with a Total Nasal Symptom Score (TNSS) ≥6, a Nasal Congestion Score ≥2, and adequate literacy to complete the diary card were included in the study.
- Patients were blinded and randomly assigned to receive either Fluticasone Furoate and Oxymetazoline Nasal Spray (27.5/50 mcg) or placebo nasal spray (27.5 mcg).
- Patients were instructed to take two sprays of the study drug in each nostril nightly for 28 days.
- Using the Total Nasal Symptom Score, patients assessed the severity of their AR in their diary cards. (TNSS) twice daily.
- The TNSS scale ranges from 0 to 3, with 0 denoting no symptoms and 3 denoting severe symptoms that interfere with more than two everyday tasks or cause insomnia for most of the night.
- Total Ocular Symptom Score (TOSS), calculated by adding the scores of the three ocular symptoms ranges from 0 to 9, with 0 denoting no symptoms and 9 denoting severe symptoms.

INTERVENTION (# IN THE GROUP): 123

COMPARISON (# IN THE GROUP): 127

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- Fixed-dose combination (FDC) resulted in more patients achieving allergic rhinitis symptom improvement, per nighttime TNSS, compared to placebo at 28 days (–7.0 vs –6.4, respectively; *P*<.01).

Secondary Outcome –

- FDC resulted in clinically greater symptom improvement (per daytime TNSS) compared to placebo (*P*<.05).
  - Day 3: –2.7 vs –1.7
  - Day 7: –3.3 vs –2.8
  - Day 14: –4.6 vs –3.9
- FDC reduced nighttime nasal congestion compared to placebo (*P*<.01).

- Day 3: –1.6 vs –0.7
- Day 7: –1.9 vs –1.2
- Day 14: –2.2 vs –1.7
- Day 28: –2.4 vs –2.1

- FDC reduced daytime nasal congestion compared to placebo (*P*<.01).
  - Day 3: –1.3 vs –0.7
  - Day 7: –1.4 vs –0.8
  - Day 14: –1.6 vs –1.2
  - Day 28: –1.9 vs –1.6
- FDC was more likely to lead to clinically significant complete relief of nasal congestion throughout the day compared to placebo (*P*<.05).
  - Day 3: 9.8% vs 1.6%
  - Day 7: 20%vs 4.7%
  - Day 14: 29%vs 7.9%
  - Day 28: 45% vs 27%
- FDC resulted in a clinically greater reduction in nighttime allergic rhinitis symptoms (congestion, sneezing, itching, and rhinorrhea compared to placebo (*P*<.05).
  - Day 3: –4.3 vs –3.4
  - Day 7: –5.8 vs –5.1
  - Day 14: –8.2 vs –7.3
  - Day 28: –10 vs –9.2
- There was no difference in the reduction of night or daytime ocular symptoms (itching, tearing, or redness) in either group.

LIMITATIONS:

- The study had a small sample size.
- The study was funded by Cadila Healthcare Limited India which manufactures Oxymetazoline.

Omosefe Ogbeifun, MD, MPH
Cahaba – UAB Family Medicine Residency Program
Birmingham, AL

How Efficacious is Semaglutide in Treating Adolescent Obesity?

Once-Weekly Semaglutide in Adolescents with Obesity
Weghuber D, Barrett T, Barrientos-Pérez M, et al. Once-Weekly Semaglutide in Adolescents with Obesity. *N Engl J Med*. 2022;387(24):2245-2257. doi:10.1056/NEJMoa2208601

KEY TAKEAWAY: Once weekly semaglutide plus lifestyle intervention in adolescents with obesity causes greater weight loss than lifestyle intervention alone.

STUDY DESIGN: Randomized, multinational, parallel-group, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Currently, the standard management for childhood obesity is lifestyle modification, which often fails to achieve a substantial reduction in BMI. The only FDA-approved Glucagon-like peptide-1 (GLP-1) receptor agonist for use in adolescents is the daily injection of liraglutide. Semaglutide is a once-weekly injection that has been shown to promote long-term weight loss in adults which could prove useful in treating adolescents with obesity.

PATIENTS: Adolescents with obesity

INTERVENTION: Once weekly semaglutide injection plus lifestyle intervention

CONTROL: Placebo plus lifestyle intervention

PRIMARY OUTCOME: Percent change in BMI

Secondary Outcome: Weight loss

METHODS (BRIEF DESCRIPTION):

- Participants were adolescents (defined as 12 to <18 years old) whose BMI were in the 95th percentile or greater, or whose BMI were greater than or equal to the 85th percentile with one or more weight-related comorbidity.
- Eligible participants had to have failed a dietary weight loss effort in the past.
- All participants completed a 12-week run-in phase of lifestyle interventions before randomly being assigned in a 2:1 ratio to receive the study drug, once-weekly subcutaneous semaglutide 2.4 mg (titrated up from 0.25 mg over a period of 16 weeks), or placebo, for 68 weeks.
- All participants received counseling on physical activity and nutrition throughout the trial.
- The primary outcome was a percent change in BMI from week 0 to 68.
- The main secondary outcome was weight loss of at least 5% at the end of week 68.

INTERVENTION (# IN THE GROUP): 134

COMPARISON (# IN THE GROUP): 67

FOLLOW-UP PERIOD: 68 weeks

RESULTS:

Primary Outcome –

- Semaglutide injections significantly reduced BMI compared to placebo (–17% estimated difference; 95% CI, –20% to –13%).

Secondary Outcome –

- Semaglutide injections were significantly more successful in achieving at least 5% weight loss compared with the placebo group (estimated OR 14; 95% CI, 6.3–31).

LIMITATIONS:

- Patients were mostly white (78%) and female (63%), results may vary across other racial groups that traditionally have a higher prevalence of obesity such as Black or Hispanic individuals.
- The treatment group was only monitored for 7 additional weeks after the last dose of semaglutide at 68 weeks (75 weeks total), so long-term durability could not be assessed.
- The study was industry-funded, so sponsorship bias cannot be definitively excluded.

Loren Swanson, DO
Abrazo Family Medicine Residency Program
Phoenix, AZ

Get Moving to Decrease Your Risk of Sudden Cardiac Death

Physical Activity and the Risk of Sudden Cardiac Death: A Systematic Review and Meta-Analysis of Prospective Studies

Aune D, Schlesinger S, Hamer M, Norat T, Riboli E. Physical activity and the risk of sudden cardiac death: a systematic review and meta-analysis of prospective studies. *BMC Cardiovasc Disord*. 2020;20(1):318. Published 2020 Jul 6. doi:10.1186/s12872-020-01531-z

KEY TAKEAWAY: Increased levels of physical activity compared to low levels may reduce the risk of sudden cardiac death among the general adult population.

STUDY DESIGN: Systematic review and meta-analysis of 13 prospective cohort and nested case-control studies (N= 136,298)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to design of included studies)

BRIEF BACKGROUND INFORMATION: Most people know that exercise is "good for you." But often, we fail to quantify, or even qualify, what this truly means. This study is important in demonstrating the risk reduction of exercise on sudden cardiac death and offers some statistical evidence to support this over a very large cohort of people.

PATIENTS: Adult men and women

INTERVENTION: Increased physical activity

CONTROL: Limited physical activity

PRIMARY OUTCOME: Sudden cardiac death

Secondary Outcome: Dose-response relationship based off the level of exercise

METHODS (BRIEF DESCRIPTION):

- Adult men and women of the general population were included in the study.
- Individuals participated in varying levels of physical activity.
- The studies included had differing stratifications for treatment and non-treatment arms, but, in general, there was a high physical activity group vs a low physical activity group, with varying levels of activity across the studies.
- Relative risk reduction of sudden cardiac death was the primary measurement outcome by measuring rates of sudden cardiac death in treatment vs non-treatment arms.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied from six to 26 years

RESULTS:

Primary Outcome –

- Higher levels of exercise decreased the risk for sudden cardiac death (relative risk 0.52; 95% CI, 0.45–0.60; I^2=0%).

Secondary Outcome –

- The study exhibited a dose-response relationship. In other words, per 20 MET (metabolic equivalent)-hrs/week, there was a quantifiable decrease in the risk of sudden cardiac death (relative risk 0.68; 95% CI, 0.55-0.86; I^2=44%).
- There was not a significant difference in risk reduction beyond 20–25 MET-hrs/week.

LIMITATIONS:

- Though most of the studies controlled for confounders, there are inherent confounders when assessing people who exercise vs those who do not (i.e. lower prevalence of smoking, eating habits, etc.).
- The systematic review did not assess the specific types of exercise that was used as "physical activity" across the studies.
- Physical activity was self-reported in many of the studies, so errors in reporting or self-reporting bias could have occurred.

Daniel Brake, MD
Cahaba – UAB Family Medicine Residency
Birmingham, AL