GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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Family Physicians Inquiries Network

What's in this week's issue?

Week of January 31 - February 4, 2022

SPOTLIGHT: Do No Harm - Topical NSAIDs Superior to Opioids for Acute Non-Low Back MSK Pain

Do No Harm: Topical NSAIDs Superior to Opioids for Acute Non-Low Back MSK Pain

Management of Acute Pain from Non-Low Back, Musculoskeletal Injuries: A Systematic Review and Network Meta-Analysis of Randomized Trials

Busse JW, Sadeghirad B, Oparin Y, et al. Management of Acute Pain from Non-Low Back, Musculoskeletal Injuries: A Systematic Review and Network Meta-analysis of Randomized Trials. *Ann Intern Med*. 2020;173(9):730-738. doi:10.7326/M19-3601

KEY TAKEAWAY: In acute non-low back musculoskeletal injuries, topical NSAIDS were among the most effective treatments for pain control and the most effective at improving physical function, whereas opioids led to the most harms.

STUDY DESIGN: Network meta-analysis of 207 RCTs (N=32,959)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Musculoskeletal injuries are extremely common and account for 4% of all ambulatory visits to U.S. physicians' offices. There is a wide variety of treatments for musculoskeletal injuries, with some having considerable side effects and unclear benefit.

PATIENTS: Adults 18 years old and older

INTERVENTION: Pharmacologic and non-pharmacologic interventions

CONTROL: Placebo

OUTCOME: Effectiveness (pain relief, physical function, treatment satisfaction) and harms (GI-related and neurologic adverse events)

METHODS (BRIEF DESCRIPTION):

- PRISMA network meta-analysis (NMA) of 207 RCTs using modified Cochrane Risk of Bias Tool.
- Included RCTs had at least 10 participants per group and compared commonly used pain relief therapies.
- Age: At least 18 years old (median of mean ages = 34 years)
- NMAs compared multiple interventions using both direct and indirect comparisons.
- GRADE criteria used to rate certainty of evidence.
- 10-cm visual analog scale (VAS) used to measure pain intensity and physical function, and direct comparisons were pooled using weighted mean difference (WMD).
- 1 cm on the 10-cm VAS was selected as the minimally important difference (MID).

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Pain relief compared ≤2 hours and 1–7 days; other outcomes were measured at six months

RESULTS:

- As compared to placebo, moderate-certainty evidence showed topical NSAIDs were:
  - Among the most effective treatments for pain control at ≤2 hours (28 trials, N=4,464; WMD –1.0 cm; 95% CI, –1.6 to –0.4) and pain control at 1–7 days (69 trials, N=10,829; WMD –1.1 cm; 95% CI, –1.4 to –0.8).
  - The most effective treatment at improving physical function (30 trials, N=3,549; WMD 1.7 cm; 95% CI, 1.2 to 2.2).
- Topical NSAIDs alone increased the likelihood of treatment satisfaction (17 trials, N=10,390; OR 5.2; 95% CI, 2.0-13; high-certainty).
- While transbuccal fentanyl was the most effective treatment for pain control ≤2 hours (28 trials, N=4,464; WMD –3.5 cm; 95% CI, –5.0 to –0.7; low-certainty), it was among the most harmful treatment with increased likelihood of adverse GI (45 trials, N=7,070; OR 59; 95% CI, 6.2–568) and neurologic (37 trials, N=6,245; OR 5.7; 95% CI, 1.2–28) events, with moderate certainty.
- Low-certainty evidence showed no difference between acetaminophen plus opioids as compared with NSAIDs for pain relief at 1 to 7 days; however, there was an increased likelihood of adverse GI (45 trials, N=7070; OR 5.6; 95% CI, 2.8 to 11) and neurologic (37 trials, N=6,245; OR 3.5; 95% CI, 1.9–6.5; high- to moderate-certainty) events with acetaminophen plus opioids as compared with placebo.

LIMITATIONS:

- Effects limited to acute (less than 4 weeks) non-low back musculoskeletal injuries.
- NMA is relatively new and statistically complex, hence the possibility of cofounding is high.
- 29% of the 207 studies reported industry funding.
- Exclusively English-only trials included.
- Limited head-to-head comparisons.

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Monoclonal Antibodies: Effective Treatment in Adolescents and Adults at High Risk for Severe COVID-19

Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19

Dougan M, Nirula A, Azid M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N Engl J Med.* 2021; 385(15):1382–1392

KEY TAKEAWAY: Bamlanivimab plus Etesevimab reduces the incidence of COVID-19 related hospitalization and death among high-risk patients with mild or moderate COVID-19 infection in the ambulatory setting.

STUDY DESIGN: Randomized, double blind, placebo-controlled, single dose trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: COVID-19 symptoms can progress to hospitalization or death, especially in patients with underlying medical conditions. The FDA granted emergency use authorization for two monoclonal antibodies, Bamlanivimab plus Etesevimab, administered together to treat COVID-19. These antibodies target the surface spike glycoprotein of SARS-CoV-2, providing immediate passive immunity that can potentially limit disease progression and complications.

PATIENTS: High risk adolescents and adults with mild or moderate COVID-19

INTERVENTION: Single IV infusion of Bamlanivimab and Etesevimab

CONTROL: Single IV infusion of placebo

OUTCOME: COVID-19 related hospitalization; death from any cause

Secondary Outcomes: SARS-CoV-2 viral load at day 7, time to patient-reported resolution of symptoms, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients who tested positive for SARS-CoV-2 by direct antigen or PCR testing and presented in an ambulatory setting with mild or moderate COVID-19 symptoms (defined according to FDA guidance; fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, and dyspnea with excretion) within three days were enrolled in the study.
- Adolescent patients were between 12 and 17 years old and had at least one high risk factor (BMI >85th percentile, sickle cell, heart disease, neurodevelopmental disorder, chronic respiratory disease, diabetes, immunocompromised condition).
- Adult patients were 18 years old or older with at least one high risk factor (BMI >35, over 65 years old, chronic kidney disease, immunosuppressive disease; over 55 years old with cardiovascular disease, hypertension, or chronic respiratory disease).
- Patients randomly received a single IV infusion with either a combination of 2,800 mg Bamlanivimab and 2,800 mg Etesevimab or placebo over a one-hour period.
- Patients were scheduled for visits or contacted by investigators for 29 days following the infusion.
- The following outcomes were recorded: COVID-19 related hospitalization (acute care for >24 hours), death from any cause, SARS-CoV viral load from day 0 to day 7, patient-reported resolution of symptoms, and safety.

INTERVENTION (# IN THE GROUP): 518

COMPARISON (# IN THE GROUP): 517

FOLLOW UP PERIOD: 29 days

RESULTS:

Primary Outcomes –

- Monoclonal antibody treatment reduced COVID-19 related hospitalizations compared to placebo (2.1% vs 7.0%, respectively; absolute risk difference –4.8%; 95% CI, –7.4 to –2.3).
- No deaths occurred in the monoclonal antibody group compared to 10 deaths in the placebo group.

Secondary Outcomes –

- Monoclonal antibody treatment reduced persistently high viral load compared to placebo (9.8% vs 30%; difference –20; 95% CI, –24 to –15).
- The monoclonal antibody group had 8 days to symptom resolution (95% CI, 7–8) and the placebo group had 9 days to symptom resolution (95% CI, 8–10).
- 1.4% of the monoclonal antibody group had adverse events (nausea, rash, dizziness, diarrhea, hypertension) compared to 1.0% of the placebo group.

LIMITATIONS:

- Only 13% of the patients enrolled in the study identified as non-white.
- Viral variants were not accounted for in this study.

- Patient hospitalizations may have been influenced by demographic differences and differences in health care utilization.
- Treatment relies on a health care system that currently faces stretched resources.
- Correlating results globally is difficult as the study was only conducted in the U.S.

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Better Late Than Never… Beginning to Exercise Later in Life Can Still Be Beneficial

It Is Never Too Late to Start: Adherence to Physical Activity Recommendations for 11–22 Years and Risk of All-Cause and Cardiovascular Disease Mortality. The HUNT Study

Moholdt T, Skarpsno ES, Moe B, Nilsen TIL. It is never too late to start: adherence to physical activity recommendations for 11-22 years and risk of all-cause and cardiovascular disease mortality. The HUNT Study [published online ahead of print, 2020 Sep 28]. *Br J Sports Med*. 2020; bjsports-2020-102350. doi:10.1136/bjsports-2020-102350

KEY TAKEAWAY: Individuals who are consistently physically inactive have a much higher risk of cardiovascular and all-cause mortality compared to those who met physical activity guidelines throughout their lifetime.

STUDY DESIGN: Prospective population-based cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: It has been shown that leisure time physical activity has an inverse and dose-dependent relationship with all-cause mortality and cardiovascular morality. However, much of this data has come from single time point measurements and there is not much data on levels of physical activity over time. This study aimed to look at how physical activity levels over 11–22 years affect all-cause and cardiovascular mortality.

PATIENTS: Adults 20 years old or older

INTERVENTION: Inconsistent physical activity

CONTROL: Maintenance of recommended physical activity levels throughout sampling period

OUTCOME: All-cause mortality

Secondary Outcome: Cardiovascular mortality

METHODS (BRIEF DESCRIPTION):

- Longitudinal, population-based health questionnaire in Norway from three time points: 1994-86, 1995-97, and 2006-08.
- Divided groups into four samples by participation years:
  - Sample 1: 1984-86 and 1995-97
  - Sample 2: 1984-86 and 2006-08
  - Sample 3: 1995-97 and 2006-08
  - Sample 4: all three time points
- Used national cause of death registry to cross reference participants to get mortality data.
- Recommended physical activity was defined as a minimum of moderate-intensity aerobic activity for 30 minutes five days a week or vigorous-intensity aerobic activity for 20 minutes three days a week.
- Participants were identified based on levels of physical activity:
  - Inactive
  - Below the recommended level
  - At or above the recommended level
- Participants were also assessed for other comorbidities via measuring their BMI, blood pressure, diabetes history, cardiovascular disease, family history, occupational physical activity, smoking status, and dietary habits.
- Performed analysis to compute hazard ratios (HRs) of all-cause and cardiovascular mortality.

INTERVENTION (# IN THE GROUP):

- Sample 1: 32,811
- Sample 2: 22,058
- Sample 3: 31,948
- Sample 4: 19,349

COMPARISON (# IN THE GROUP):

- Sample 1: 55,683
- Sample 2: 20,251
- Sample 3: 45,211
- Sample 4: 11,436

FOLLOW UP PERIOD: 11 to 22 years

RESULTS:

Primary Outcome –

- Sustained physical inactivity was associated with 56 to 65% greater all-cause mortality compared to those who met the recommended levels of physical activity.
  - Sample 1: 2,170 vs 422 (HR 1.6; 95% CI, 1.4–1.7)
  - Sample 2: 343 vs 144 (HR 1.6; 95% CI, 1.3–2.0)
  - Sample 3: 347 vs 204 (HR 1.7; 95% CI, 1.4–2.0)
  - Sample 4: 572 vs 72 (HR 1.6; 95% CI, 1.2–2.0)

Secondary Outcome –

- Sustained physical inactivity was associated with 58 to 94% greater cardiovascular mortality compared to those who met the recommended levels of physical activity.
  - Sample 1: 907 vs 144 (HR 1.9; 95% CI, 1.6–2.3)
  - Sample 2: 115 vs 46 (HR 1.7; 95% CI, 1.2–2.5)
  - Sample 3: 106 vs 61 (HR 1.6; 95% CI, 1.1–2.2)
  - Sample 4: 184 vs 22 (HR 1.7; 95% CI, 1.1–2.7)

LIMITATIONS:

- Questionnaire-based study
- Classification of PA levels could be difficult with varying questions in each survey.
- Unclear if previous health issues contributed to lack of physical activity.
- Unsure of previous exercise history other than at specified time points.

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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 Air Force Medical Department, the Air Force at large, or the Department of Defense.