GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of January 30 - February 3, 2023

SPOTLIGHT: Now That My Mood is Better, Can I Stop My Antidepressant?

Now That My Mood is Better, Can I Stop My Antidepressant?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Managing Antidepressant Discontinuation: A Systematic Review

Maund E, Stuart B, Moore M, et al. Managing Antidepressant Discontinuation: A Systematic Review. *Ann Fam Med*. 2019;17(1):52-60. doi:10.1370/afm.2336.
doi: 10.1370/afm.2336.

KEY TAKEAWAY: Cognitive behavioral therapy (CBT) in combination with medication tapering can help patients discontinue antidepressants without increasing the risk of relapse/recurrence.

STUDY DESIGN: Systematic review with narrative synthesis and meta-analysis of seven RCTs, three single-arm studies, and two observational studies (N=5,203)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Physicians frequently prescribe antidepressants, but it is unknown how to effectively discontinue them when appropriate. This systematic review discusses the effectiveness of interventions to manage antidepressant discontinuation.

PATIENTS: Adults on antidepressant treatment

INTERVENTION: Discontinuing antidepressant

CONTROL: Usual care

PRIMARY OUTCOME: Depression relapse and recurrence, discontinuation syndrome

METHODS (BRIEF DESCRIPTION):

- Adults with depression or anxiety with depression were selected.
- Three studies included mean or median length of antidepressant use ranging from 9.2 months to 9.5 years.
- Inclusion criteria for length of remission/recovery ranged from eight weeks to six months.
- Interventions: Patient-specific letters to the primary care clinician with recommendations to discontinue antidepressants and tapering advice, CBT with tapering, MBCT with tapering, gradual discontinuation, one week of tapering
- Controls: Maintenance antidepressant treatment, rapid discontinuation, abrupt discontinuation, clinical management plus taper, and usual care

INTERVENTION (# IN THE GROUP): 5,203

COMPARISON (# IN THE GROUP): 1,013

FOLLOW UP PERIOD: Unavailable

RESULTS:

- CBT + taper reduced the risk of relapse or recurrence of depression compared to CM + taper at two years (risk ratio [RR] 0.43; 95% CI, 0.18–0.67).
- MBCT-TS did not reduce the risk of relapse or recurrence of depression compared to maintenance antidepressant (RR 0.90; 95% CI, 0.75–1.1).
- Gradual tapering in increments of 10 mg every 14 days reduced the risk of discontinuation syndrome compared to stopping medication suddenly (RR 0.14; 95% CI, 0.07–0.25).

LIMITATIONS:

- Research was conducted over several databases, unrestricted by date, language, publication status, and gray literature.

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Levaquin: Is Less Better?

Two-day versus seven-day course of levofloxacin in acute COPD exacerbation: a randomized controlled trial
Messous S, Trabelsi I, Bel Haj Ali K, et al. Two-day versus seven-day course of levofloxacin in acute COPD exacerbation: a randomized controlled trial. *Ther Adv Respir Dis*. 2022 Jan-Dec;16:17534666221099729. DOI: 10.1177/17534666221099729.

KEY TAKEAWAY: A two-day course of levofloxacin is non-inferior to a seven-day course in acute exacerbation of COPD.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Acute exacerbation of chronic obstructive pulmonary disease (COPD) is commonly treated with antibiotics and the use of antibiotics has been shown to reduce short-term mortality and reduce the recurrence of exacerbations. Systematic reviews have shown that shorter courses of antibiotics are non-inferior; the shortest duration studied was three days. This study investigates the efficacy of a short course of antibiotics, two-day levofloxacin compared to seven-day levofloxacin, along with other standard treatments.

PATIENTS: Adults with COPD exacerbation

INTERVENTION: Levofloxacin for two days

CONTROL: Levofloxacin for seven days

PRIMARY OUTCOME: Clinical cure

Secondary Outcome: Additional antibiotics, exacerbation-free interval, ICU admission, death

METHODS (BRIEF DESCRIPTION):

- Patients 45 years old and older from Finland with a diagnosis of acute exacerbation of COPD seen in the Emergency Department (ED).
    - Participants had at least ten packs per year of history and clinical diagnosis of mild-to-severe COPD (by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria) with acute worsening of respiratory symptoms requiring additional therapy.
    - Patients with hemodynamic instability (requiring vasopressor support), immediate need for endotracheal intubation, and pneumonia were excluded.
- The mean age was 67.7 years old, most of whom were male, with an average of 43.7 pack per year history, and a mean number of exacerbations of 2.3 in the past year.
- The intervention group received levofloxacin 500 mg daily by mouth for two days followed by a placebo for five days.
    - The comparison group received levofloxacin 500 mg daily by mouth for seven days.
    - All patients were treated in the emergency department for the initial 48 hours and received standard prednisone dosing along with usual care.
    - The decision to discharge, hospitalize or transfer to the intensive care unit (ICU) was made by the treating physician.
- The primary outcome was clinical cure rate defined as the resolution of acute exacerbation symptoms and no recurrence within 30 days.
- Follow-up was made at 1,3, 6, and 12 months after treatment.
- The secondary outcome was additional antibiotics, exacerbation-free interval, ICU admission, and death, measured at the time of discharge, one, three, six, and 12 months after treatment.

INTERVENTION (# IN THE GROUP): 155

COMPARISON (# IN THE GROUP): 155

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- A two–day regimen of levofloxacin was non-inferior to a seven-day regimen for clinical cure (odds ratio (OR) 1.3; 95% CI, 0.78–2.2).

Secondary Outcome –

- The rate of additional antibiotics was similar in the two-day group and seven-day group.
- The rate of ICU admission was similar in the two-day group and the seven-day group.
- Median exacerbation-free interval was similar in the two-day group and seven-day group.
- One-year death rate was similar in the two-day group and seven-day group.

LIMITATIONS:

- The study results are not generalizable to patients requiring mechanical ventilation or ICU admission.
- The results cannot be extrapolated to other antibiotics.
- In general, the overall role of antibiotics in COPD is under question.
- Few of the patients were female.

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Get Up and Go for Your Glomeruli

Effect of Structured, Moderate Exercise on Kidney Function Decline in Sedentary Older Adults: An Ancillary Analysis of the LIFE Study Randomized Clinical Trial

Shlipak MG, Sheshadri A, Hsu FC, et al. LIFE Investigators. Effect of Structured, Moderate Exercise on Kidney Function Decline in Sedentary Older Adults: An Ancillary Analysis of the LIFE Study Randomized Clinical Trial. *JAMA Intern Med*. 2022 Jun 1;182(6):650-659. DOI: 10.1001/jamainternmed.2022.1449.

KEY TAKEAWAY: Moderate exercise regimen may slow the decline of kidney function in older sedentary adults as compared to an aging health education course.

STUDY DESIGN: Ancillary analysis of a multisite, randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to ancillary analysis and disease-oriented outcome)

BRIEF BACKGROUND INFORMATION: Studies indicate that pharmacological treatment for hypertension and diabetes slows the progression of kidney function decline in older adults. The effect of greater physical activity has also been linked with slower declines in kidney function. This study investigates the effect of specific structured moderate exercise on kidney function decline in sedentary older adults with the goal to identify lifestyle interventions that may aid in preserving kidney function in this demographic group.

PATIENTS: Older community-dwelling sedentary adults

INTERVENTION: Structured physical activity

CONTROL: Health education classes

PRIMARY OUTCOME: Change in kidney function

Secondary Outcome: Step count associated rate of decline in kidney function

METHODS (BRIEF DESCRIPTION):

- Patients were 70–89 years old from 8 centers in the United States who met the criteria for a sedentary lifestyle.
- Other inclusion criteria were (1) Less than 20 minutes of daily physical activity, (2) the ability to complete a 400-meter walk test without an assistive device, and (3) the absence of cognitive impairment.
- Patients with unstable chronic disease, chronic kidney disease (CKD) requiring dialysis, and inability to participate in exercise regimen were excluded.
- The mean age was 79 years old with 66.7% women (800) and 33.3% male (399), and baseline estimated glomerular filtration rate (eGFR) by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin C (CysC) equation at 54 mL/min/1.73m^2.
- For 24 months, the treatment group received structured moderate exercise, including twice-weekly exercise sessions with the goal of 30 minutes walking, 10 minutes strength training, and 10 minutes balance training and home-based activities 3–4 times per week.
- Comparison group received health education classes with weekly workshops for 26 weeks followed by monthly workshops
- Decline in kidney function was measured via eGFR (CysC) at 12 and 24 months.
- Rapid kidney decline from baseline defined as the highest tertial of eGFR (CysC) over two years.
- Step count quartile by highest (>3,460 steps/d) and lowest (<1,567/d) measured by accelerometers.

INTERVENTION (# IN THE GROUP): 596

COMPARISON (# IN THE GROUP): 603

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- Moderate exercise regimen slowed decline of kidney function in older sedentary adults to a greater degree than educational classes at 24 months (adjusted mean difference 0.96 mL/min/1.73 m^2; 95% CI, 0.02-1.91, positive value revealing slower decline).

Secondary Outcome –

- Highest quartile step counts associated with a slower decline in kidney function in older sedentary adults as compared to those with the lowest quartile step counts (odds ratio [OR] 0.62; 95% CI, 0.44-0.87).

LIMITATIONS:

- This was a secondary analysis, an ancillary study to an existing trial.
- Minimally applicable to other populations outside of nonmobile elders.
- Study participants were not blinded.

- The change in eGFR may have questionably meaningful clinical effects.
- Cystatin C lab is not readily available at many health care centers.

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Does Liraglutide Reduce Visceral Adipose Tissue in Overweight and Obese Adults?

Effects of Liraglutide on Visceral and Ectopic Fat in Adults with Overweight and Obesity at High Cardiovascular Risk: A Randomised, Double-Blind, Placebo-Controlled, Clinical Trial

Neeland IJ, Marso SP, Ayers CR, et al. Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial. *Lancet Diabetes Endocrinol*. 2021;9(9):595-605. doi:10.1016/S2213-8587(21)00179-0

KEY TAKEAWAY: Liraglutide, in addition to specific dietary and exercise lifestyle changes, reduces visceral adipose tissue (VAT) in non-diabetic overweight or obese patients with cardiovascular risk factors by an average of 11% when compared to placebo.

STUDY DESIGN: Randomized, double-blind, controlled trial, phase four, single-center trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high dropout rate)

BRIEF BACKGROUND INFORMATION: GLP-1 medication use has increased in the clinical setting given their benefit in decreasing glucose levels, delaying gastric emptying, appetite suppression, and weight loss. Liraglutide has shown benefits to patients with cardiovascular disease, but the mechanism is unclear. This study attempts to determine the effects of liraglutide on VAT.

PATIENTS: Non-diabetic adults

INTERVENTION: Liraglutide

CONTROL: Placebo

PRIMARY OUTCOME: Visceral adipose tissue

Secondary Outcome: Other types of adipose tissue, circulating blood markers of cardiometabolic risk

METHODS (BRIEF DESCRIPTION):

- Non-diabetic adults ≥35 years old who have a BMI ≥ 30 or BMI greater than 27 and metabolic syndrome.
- Eligible participants who completed a two-week trial run of a 500 kcal/day decrease diet and a minimum of 150 minutes per week of moderate-intensity activities were then randomized.
- Patients were blinded and randomized to one of the following treatments:
    - Liraglutide 3 mg or placebo subcutaneous injection daily for 36 weeks.
- After completing a two-week trial, participants were required to continue following the recommended diet and physical activity.
- Participants underwent a body fat distribution MRI and had plasma biomarkers assessed at the beginning and end of the study.
- The circulating cardiac biomarkers that were analyzed included fasting blood glucose, fasting insulin, HOMA-IR, C- reactive protein, triglyceride, HDL-C ratio, and NT-proBNP.
- In addition, participants had their weight, BMI, waist circumference, and total body fat compared at the beginning and end of the study.
- The visceral adipose tissue percentage was compared between the initial and final MRI.
- Initial and final biomarkers of cardiometabolic risk were compared.

INTERVENTION (# IN THE GROUP): 73

COMPARISON (# IN THE GROUP): 55

FOLLOW-UP PERIOD: 36 weeks

RESULTS:

Primary Outcome –

- Liraglutide significantly reduces VAT percentage compared to placebo (–12% vs –1.6%, respectively; –11%; 95% CI, –7.0 to –15).

Secondary Outcome –

- Liraglutide significantly reduced fasting blood glucose compared to placebo (–5.6% vs 0.83%, respectively; –6.5%; 95% CI, –2.1 to –11).
- Liraglutide significantly reduced C-reactive protein compared to placebo (–20% vs 19%, respectively; –39%; 95% CI, –17 to –60).
- Liraglutide provided no significant reduction in fasting insulin, triglyceride, HDL-C ratio, or NT-proBNP.

LIMITATIONS:

- There was a lack of a standardized method for measuring the liver fat on MRI which may cause difficulty to compare in other studies.
- One-third of participants did not complete the study and follow-up imaging assessment. Dropout rates may have been due to difficulty with compliance

with lifestyle regimen or due to little or no weight loss in the placebo group which may have altered the results.

- Ninety-two percent of participants in the study were female which may not be representative of the overall US population.

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Oral Nirmatrelvir/Ritonavir Combination Therapy for High-Risk, Non-Hospitalized Adults with COVID-19? Something to Consider

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med*. 2022;386(15):1397-1408. doi:10.1056/NEJMoa2118542

KEY TAKEAWAY: Nirmatrelvir with ritonavir decreases the overall progression and severity of COVID-19 in adults with risk factors for severe COVID-19 infection and who are unvaccinated.

STUDY DESIGN: Double-blinded, multicenter, multinational, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current non-hospital-based therapies for preventing severe COVID-19 infection in adults include monoclonal antibodies and Malnupiravir. The combination of oral nirmatrelvir and ritonavir is less cumbersome than IV therapies in the outpatient setting and may be more effective than current therapies.

PATIENTS: Adults with COVID-19 and at high risk for severe disease due to comorbidities

INTERVENTION: Oral nirmatrelvir + ritonavir

CONTROL: Placebo

PRIMARY OUTCOME: COVID-19-related hospitalization or death, viral load, safety

Secondary Outcome: Viral load, hospitalizations, and death from any cause

METHODS (BRIEF DESCRIPTION):

- Unvaccinated, symptomatic, non-hospitalized adults with comorbidities that placed them at high risk for progression to severe COVID-19 disease.
  - Average age in years: 45 in the intervention group and 47 in the comparison group
  - Male: 51% in the intervention group and 52% in the comparison group
  - White: 71% in the intervention group and 72% in the placebo group
- The intervention group received nirmatrelvir with ritonavir, every 12 hours for a total of five days.
- The intervention group received an oral placebo every 12 hours for five days.
- All patients were followed for a total of 28 days.
- COVID-19-related hospitalizations or deaths were measured using a Kaplan-Meier method, a z-test with standard error estimation calculated with Greenwood's formula.
- Viral loads were compared using a change from baseline to day 5 using a logarithmic scale along with the ANCOVA model to account for covariance.
- Adverse events were tracked via incidence in each trial group.

INTERVENTION (# IN THE GROUP): 1,053

COMPARISON (# IN THE GROUP): 1,049

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- Nirmatrelvir with ritonavir decreased the risk for COVID-19-related hospitalizations and deaths compared to placebo (Mean difference –6.3%; 95% CI, –9.0 to –3.6).
- Nirmatrelvir with ritonavir reduced viral load at day five of treatment by a factor of 10 when compared with placebo (adjusted mean of 0.87 ±0.11 $\log_{10}$ copies per mL; 95% CI, –1.1 to –0.66).
- Safety profiles were similar between the groups.

Secondary Outcome –

- Nirmatrelvir with ritonavir reduced the risk of COVID-19-related hospitalizations by 88% when compared to placebo when therapy was initiated five days after symptom onset (95% CI, −7.2 to −4.0).
- Nirmatrelvir with ritonavir reduced viral load at day five when therapy was initiated five days after symptom onset (adjusted mean of 0.70 ±0.085 $\log_{10}$ copies per mL; 95% CI, –0.86 to –0.53).

LIMITATIONS:

- The trial was limited to unvaccinated individuals. It is not rare for someone who has been vaccinated against COVID-19 to become infected with the SARS-CoV-2 virus. It would be useful to be able to extrapolate these results to individuals who have been vaccinated.
- There was no breakdown of participant age included with the demographic data, only an average participant age.

- Study was “supported” by Pfizer, a large multinational corporation with a vested interest in the results of this study.

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