GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Can Once Weekly Dulaglutide Lower Glycemic Hemoglobin Levels in Pediatric Patients?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes

Arslanian SA, Hannon T, Zeitler P, et al. Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes. *N Engl J Med*. 2022;387(5):433-443. doi:10.1056/NEJMoa2204601

KEY TAKEAWAY: Once a week injection of dulaglutide improves glycemic control for youths with type 2 diabetes without effect on BMI.

STUDY DESIGN: Double-blind, randomized controlled, phase three trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The pathophysiology of type 2 diabetes for youth-onset is like adult-onset, however, the insulin resistance and β-cell dysfunction are greater in youth than adults. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial found there is a high failure rate with metformin, the recommend first-line treatment for youth-onset type 2 diabetes. In addition, pharmacotherapeutic options for youth remains limited compared to adults. Two glucagon-like peptide-1 (GLP-1) receptor agonists have been approved for youth with type 2 diabetes, liraglutide and exenatide, however, both are inconvenient as one is daily injection with manual needle attachment and removal versus the other only has a single dose level that needs mixing. Thus, dulaglutide, a once weekly injection with multiple doses, has been approved for treatment in adults with type 2 diabetes, but not youth.

PATIENTS: Youths with type 2 diabetes mellitus

INTERVENTION: Dulaglutide

CONTROL: Placebo injection

PRIMARY OUTCOME: Glycated hemoglobin levels

Secondary Outcomes: Glycated hemoglobin <7.0%, fasting glucose, BMI

METHODS (BRIEF DESCRIPTION):

- Patients were randomly assigned in a 1:1:1 ratio after a four-week screening period to receive once weekly 0.75 mg dulaglutide, 1.5 mg dulaglutide (0.75 mg dose for the first four weeks to evaluate to adverse side effects, then increase to 1.5 mg), or placebo for 26 weeks based on glycated hemoglobin level and metformin and insulin use.
- During the open-label period for 26 weeks participants who were assigned dulaglutide continued to get their assigned dose while the placebo group received 0.75 mg dulaglutide.
- Safety was followed for four weeks. Fasting blood sugar and hypoglycemia symptoms were also measured.

INTERVENTION (# IN THE GROUP):

- 0.75 mg dulaglutide: 51
- 1.5 mg dulaglutide: 52

COMPARISON (# IN THE GROUP): 51

FOLLOW UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Dulaglutide reduced glycated hemoglobin more than placebo at 26 weeks (estimated treatment difference [ETD] –1.4%; 95% CI, –1.9 to –0.8).

Secondary Outcomes –

- Dulaglutide increased the likelihood patients would have glycated hemoglobin levels <7.0% compared to placebo (relative risk 3.5; 95% CI, 1.8–6.8).
- Dulaglutide decreased fasting blood glucose more than placebo at 26 weeks (ETD –36 mg/dL; 95% CI –54 to –19).
- Dulaglutide was not superior to placebo in decreasing BMI.

LIMITATIONS:

- Limited enrollment of participants outside of United States and Mexico.
- Was not able to use a higher dose of dulaglutide (3.0 mg and 4.5 mg) as it was not available when the trial was taking place.

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Improving Hospital Readmissions in Patients with Depression: Can We Do Better?

Reducing Readmission of Hospitalized Patients with Depressive Symptoms: A Randomized Trial

Mitchell SE, Reichert M, Howard JM, et al. Reducing Readmission of Hospitalized Patients with Depressive Symptoms: A Randomized Trial. *Ann Fam Med*. 2022;20(3):246-254. doi:10.1370/afm.2801

KEY TAKEAWAY: Weekly telephone counseling sessions improve readmissions up to 90 days post discharge but not hospital utilizations among patients with depression.
STUDY DESIGN: Multi-site randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Mental illness and its treatment play a significant role in the overall outcomes of patients, including their physical chronic illnesses. Research shows that healthcare utilization among patients with depression is higher than those without, regardless of the reason for their healthcare visit. There is currently no standardized process to address mental illness and its effects on hospital utilizations, so this study aims to determine if additional support to patients with mental illness decreases utilization rates.

PATIENTS: Hospitalized patients with depression
INTERVENTION: Re-engineered discharge for depression toolkit with pre-discharge support and telehealth visits with a counselor (RED-D)
CONTROL: Re-engineered discharge toolkit with pre-discharge support and a single follow-up phone call (RED)
PRIMARY OUTCOME: Hospital readmissions and total hospital utilizations
Secondary: Quality of life, enjoyment, satisfaction, depression, activation, and anxiety

METHODS (BRIEF DESCRIPTION):

- Patients admitted to two hospital sites in Massachusetts were recruited based on the following criteria:
  - Patient health questionnaire (PHQ-9) score of ten or more (score range 0–27, with higher scores indicating more severe depression)
  - Not admitted for altered mental status, end-of-life care, sickle cell crisis, or substance use
- Patients were randomly assigned to either RED-D or RED.
  - Both groups received the same pre-discharge support consisting of assistance with language barriers, follow-up care plans, medication overviews, and health education.
  - RED-D received 12 weekly telehealth sessions that were offered post hospital discharge with a licensed counselor for cognitive behavioral therapy, stress management, chronic disease symptom management, healthy lifestyle guidance, and scheduling assistance.
  - RED received a single phone call to confirm medications and follow-up appointments and to discuss further management of their health conditions.
- Primary Outcomes –
  - Readmission rates: Hospital readmissions in each group/total patients in each group
  - Hospital utilization rates: Emergency Department visits, hospital readmissions, and hospital observations in each group/total number of participants in each group
- Secondary Outcomes, assessed at enrollment, 30- and 90- days post discharge –
  - Quality of life, enjoyment, and satisfaction questionnaire short form (Q-LES-Q-SF, score range of 14–70, higher scores indicating more life satisfaction and enjoyment)
  - Patient activation measure -13 (PAM-13, score range of 0–100, higher scores indicating a more proactive outlook of one's health)
  - Generalized anxiety disorder-7 (GAD-7, score range of 0–21, higher scores indicating more severe anxiety)

INTERVENTION (# IN THE GROUP): 292
COMPARISON (# IN THE GROUP): 319

FOLLOW UP PERIOD: 30- and 90- days post hospital discharge.

RESULTS:
Primary Outcomes –

- Among patients receiving three or more RED-D sessions within 30 days post-discharge (n=104), RED-D significantly improved readmissions, but did not improve hospital utilizations, when compared with RED.
  - Readmissions (IRR 0.3; 95% CI, 0.1–0.8)
  - Hospital utilizations (IRR 0.8; 95% CI 0.5–1.3)
- Similarly, among patients receiving six or more RED-D

sessions (n=109) within 90 days post-discharge, RED-D significantly improved readmissions, but did not improve hospital utilizations, when compared with RED.
    - Readmissions (IRR 0.5; 95% CI, 0.3–0.9)
    - Hospital utilizations (IRR 0.8; 95% CI, 0.6–1.1)

Secondary Outcomes –

- Compared with RED, RED-D did not improve quality of life, enjoyment, satisfaction, depression, activation, and anxiety.

LIMITATIONS:

- Low study adherence in the RED-D might influence the internal validity of the study.
- Rates of unemployment, lack of education, and lower incomes among this study population might not be generalizable to other communities.
- Readmissions and hospital utilizations at other hospitals could not be accounted for in this study.

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Before the Fall: Implementing a Program to Prevent Falls in Long-Term Care Facilities

A Multidomain Decision Support Tool to Prevent Falls in Older People: The FinCH Cluster RCT

Logan PA, Horne JC, Allen F, et al. A multidomain decision support tool to prevent falls in older people: the FinCH cluster RCT. *Health Technol Assess*. 2022;26(9):1-136. doi:10.3310/CWIB0236

KEY TAKEAWAY: The Guide to Action for falls prevention in Care Homes (GtACH) program is a cost-effective multimodal staff intervention, decreasing fall rates by 43% in long-term elderly care facilities in the UK without decreasing resident quality of life or independence.
STUDY DESIGN: Multi-center, cluster, parallel RCT
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Resident falls in long-term care facilities lead to costly morbidity and mortality. Implementing effective staff protocols for fall risk prediction and prevention is key to decreasing the overall number of these events. The Guide to Action for fall prevention in Care Homes (GtACH) program is one such training and support tool currently being tested across adult UK care homes. The Fall prevention in Care Homes (FinCH) randomized control trial was performed to widen the program's implementation and evaluate clinical impact, cost-efficacy and potential barriers to widespread use.

PATIENTS: UK care homes and their long-term residents with old age and/or dementia
INTERVENTION: GtACH program
CONTROL: Usual care
PRIMARY OUTCOME: Clinical Evaluation: rate of falls per 1,000 participating care home residents, starting 90 days post-study randomization (days 91-180)
Economic Evaluation: incremental cost per fall avoided, and incremental cost per quality-adjusted life-year

METHODS (BRIEF DESCRIPTION):

- Long-term care facilities (with or without nursing staff) with at least 10 elderly/dementia residents were identified across England. Residents within care facilities were eligible to participate if they were living in the facility long-term and not receiving end-of-life care.
- Care facilities were randomized 1:1 into either control or intervention arms, with the control arm continuing their regular fall prevention protocols. The intervention arm sites each received training in the GtACH program. Trainings happened within the first four weeks from randomization (days 0–28).
- The facility's adherence to the GtACH program was evaluated within the first 90 days by calculating the percent of all available staff who underwent the GtACH training.
- Data on fall events, medications taken, hospitalizations and deaths were collected. Questionnaires regarding quality of life were collected from residents directly or from staff that knew them well. Data was collected over four three-month periods from the date of study group randomization: 0–90 days, 91–180 days, 181–270 days, and 271–360 days.
- Economic analysis was conducted at the end of the study in a cost-utility format, using the quality-of-life questionnaire as the basis for calculating cost per quality of life-year.

INTERVENTION (# IN THE GROUP): 39 care homes, with 630 participating long-term residents
COMPARISON (# IN THE GROUP): 45 care homes, with 712 participating long-term residents

FOLLOW UP PERIOD: One year

RESULTS:
Primary Outcomes –

- Clinical Evaluation:
  - The GtACH arm had fewer falls at days 91–180 compared to the control arm (incidence rate ratio 0.57; 95% CI, 0.45–0.71; NNT=23).
- Economic Evaluation:
  - Incremental cost per fall avoided: £190.62
  - Incremental cost per quality-adjusted life-year: £4543.69

LIMITATIONS:

- Care home staff were unable to be blinded due to the nature of the intervention; however, potential impact on study is low as all care homes in the UK are mandated to report any fall events that occur.
- Data on the number of residents for whom the GtACH paper tool was utilized was not collected.
- Implementation may vary in cost and efficacy in other countries' health care systems

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How Over-Diagnosed is Breast Cancer in U.S. Patients Undergoing Biennial Breast Cancer Screening?

Estimation of Breast Cancer Overdiagnosis in a U.S. Breast Screening Cohort

Ryser MD, Lange J, Inoue LYT, et al. Estimation of Breast Cancer Overdiagnosis in a U.S. Breast Screening Cohort. Ann Intern Med. 2022;175(4):471-478. doi:10.7326/M21-3577

KEY TAKEAWAY: Among women 50–74 years old screened biennially for breast cancer, one in seven cases of screen-detected cancer is over diagnosed.

STUDY DESIGN: Cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Currently, the U.S. Preventive Services Task Force (USPSTF) identifies overdiagnosis (screen-detected breast cancer that would not have a clinical impact on the patient's life) as one of the principal potential harms related to mammography screening due to the possibility of cumulative effect of unnecessary and potentially deleterious treatments. Therefore, accurate information about overdiagnosis is crucial to support shared decision making, as per the recommendations of the USPSTF and the American Cancer Society.

PATIENTS: Women 50 to 74 years old

INTERVENTION: Mathematical model, a Bayesian learning algorithm combined with observed patterns of screen and interval cancer incidence to lead to the predicted rate cancer

CONTROL: Traditional breast cancer screening model

OUTCOME: Breast cancer overdiagnosis estimation

METHODS (BRIEF DESCRIPTION):

- Participants received one or more screening mammograms at a BCSC facility between 2000 and 2018.
- Overdiagnosis was estimated indirectly through Bayesian inference.
- Data from screening and interval cancer incidence were used to estimate the latency and fraction of indolent cancer.
- Using these estimates in conjunction with life tables on the death risks from non-breast cancer causes in a cohort of women undergoing regular mammography screening, to predict overdiagnosis of breast cancer.
- Used Uncertainty Interval: defined as credible interval around a posterior mean.
    - Determined to be analogous to classic 95% confidence interval around the point estimate.
- The inferred screening test sensitivity characterized the sensitivity of the full screening episode, including screening mammogram, diagnostic work-up, and biopsy referral.

INTERVENTION (# IN THE GROUP): 35,986

COMPARISON (# IN THE GROUP): 35,986

FOLLOW UP PERIOD: 18 months after the last screening examination in the data set

RESULTS:

Primary Outcomes –

- 15% of screen-detected cancer cases were estimated to be over diagnosed (95% Uncertainty Interval [UI], 9.4% to 27%).
- 6.1% of the over diagnosed cancer cases were due to detecting slowly progressing preclinical cancer (95% UI, 0.2% to 20%).
- 9.3% of over diagnosing cancer cases were due to detecting progressive clinical cancer in patients who would have died from some other cause prior to the clinical diagnosis (95% UI, 5.5% to 14%).
- 4.5% of preclinical cancer was estimated to be nonprogressive (95% UI, 0.1% to 15%).
- Screening episode sensitivity, 81% (95% UI, 73% to 89%)

LIMITATIONS:

- BCSC data is encounter based and cannot distinguish between patients who are lost to follow-up from those that did not complete their next screening examination.
- The cohort only included patients who had their first screening examination within the BCSC, excluding patients who had it done outside the consortium associated facilities, thus limiting representation of the population as a whole.

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Key Lifestyle Modifications That Aid in the Prevention of Gout

Estimation of Primary Prevention of Gout in Men Through Modification of Obesity and Other Key Lifestyle Factors

McCormick N, Rai SK, Lu N, Yokose C, Curhan GC, Choi HK. Estimation of Primary Prevention of Gout in Men Through Modification of Obesity and Other Key Lifestyle Factors. *JAMA Netw Open*. 2020;3(11):e2027421. Published 2020 Nov 2. doi:10.1001/jamanetworkopen.2020.27421

KEY TAKEAWAY: Addressing lifestyle risk factors such as excess adiposity, alcohol use, unhealthy diet and diuretic use prevents gout among male health care professionals. However, the male health care professionals with obesity do not benefit from lifestyle modifications unless weight loss is first addressed.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Painful gouty arthropathy is an increasingly more common condition affecting men in Western countries. Obesity, unhealthy diet, alcohol, and diuretic use have been implicated as lifestyle modifiable risk factors for gout. This study investigates the extent to which modification of these risk factors can prevent gout.

PATIENTS: Male healthcare professionals with no prior history of gout

INTERVENTION: Gout risk factors

CONTROL: No gout risk factors

PRIMRY OUTCOME: Incidence of gout

METHODS (BRIEF DESCRIPTION):

- 44,654 male dentists, pharmacists, optometrists, podiatrists, and veterinarians (mean age 54.0 years old) with no prior history of gout completed a questionnaire about their medical history, diet, medications, and lifestyle choices every two years from 1986 through 2012.
- Men were then categorized as low risk or non-low risk for gout, based on the following definitions of low risk:
  - Normal weight (BMI<25)
  - No alcohol use
  - The highest quintile of adherence to the dietary approaches to stop hypertension (DASH) diet, based on responses on the validated food frequency questionnaire (FFQ)
  - No diuretic use
- The incidence of gout in various risk groups was then tracked during the 26 years of follow-up.
- Statistical analysis:
  - Cox hazard regression models were performed to obtain the relative risk (RR).
  - Population attributable risk (PAR) was calculated to estimate the percentage of preventable incident gout cases if a risk factor had been modified to low risk.
  - Risks were also calculated based on BMI stratification.
    - BMI <23 (lower end of normal weight/underweight)
    - BMI 23.0–24.9 (higher end of normal weight)
    - BMI 25.0–29.9 (overweight)
    - BMI 30 or greater (obese)

INTERVENTION (# IN THE GROUP): 4,850

COMPARISON (# IN THE GROUP): 2,110

FOLLOW UP PERIOD: 26 years

RESULTS:

- Outcomes compared to men who are underweight or at the lower end of normal weight, higher end of normal weight and overweight/obesity significantly increase incident gout:
  - For men with the higher end of normal weight (RR 1.3; 95% CI, 1.1–1.6)
  - For overweight men (RR 1.9; 95% CI, 1.6-2.2)
  - For obese men (RR 2.6; 95% CI, 2.2–3.2)
- For men with normal weight or underweight, incident gout cases could be prevented by the modifiable risk factors.
  - No alcohol use (PAR 43%; 95% CI, 32–54%) meaning that 43% of incident gout cases could be prevented by having normal weight or underweight and no alcohol use.
  - No alcohol use, and highest quintile of DASH diet adherence (PAR 69%; 95% CI, 47–82%).
  - No alcohol use, highest quintile of DASH diet adherence, and no diuretics (PAR 77%; 95% CI, 56–88%).
- For overweight men, 60% of incident gout cases could have been prevented if they adhered to a DASH diet, no alcohol use and no diuretic use (PAR 60%; 95% CI, 33–75%).

- For obese men, PAR was not significant even with modifying the risk factors, suggesting that obese men would not benefit from lifestyle modifications unless weight loss was first addressed (PAR 5%; 95% CI, 0–47%).

LIMITATIONS:

- Exact dates of gout diagnosis were unavailable.
- Data showing variation in the dates from initial gout diagnosis to maintaining a diagnosis of gout for the remainder of the study was unavailable.
- The external validity to the general population was limited considering the sample was restricted to male health care professionals who were predominantly white (91%).

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