GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Are Lifestyle Interventions Superior to Standard Care in Reducing Mortality in Prediabetes or Type 2 Diabetes?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Long-Term Effect of Lifestyle Interventions on the Cardiovascular and All-Cause Mortality of Subjects with Prediabetes and Type 2 Diabetes: A Systematic Review and Meta-Analysis

Zucatti KP, Teixeira PP, Wayerbacher LF, et al. Long-term Effect of Lifestyle Interventions on the Cardiovascular and All-Cause Mortality of Subjects With Prediabetes and Type 2 Diabetes: A Systematic Review and Meta-analysis. *Diabetes Care*. 2022;45(11):2787-2795. doi:10.2337/dc22-0642

KEY TAKEAWAY: Lifestyle interventions are not superior to standard care in the reduction of cardiovascular and all-cause mortality in populations with prediabetes and type 2 diabetes mellitus.

STUDY DESIGN: Systematic review and meta-analysis of 11 randomized controlled trials (RCT) (N=27,571)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Type 2 diabetes is increasingly common with a large cost burden and public health concern. It has been shown that lifestyle interventions can significantly improve metabolic disease and are a cost-effective treatment and prevention of disease. However, there are conflicting findings on lifestyle interventions with a reduction in mortality, thus this review examines whether there has been a mortality reduction across multiple RCTs.

PATIENTS: Adults with diabetes

INTERVENTION: Lifestyle interventions

CONTROL: Usual care or standard advice

PRIMARY OUTCOME: Cardiovascular and all-cause mortality

METHODS (BRIEF DESCRIPTION):

- Patients with a diagnosis of prediabetes or type 2 diabetes were included in the study.
- Selected studies had randomized patients to at least 24 months of intensive lifestyle interventions (diet or fitness recommendation) vs control (standard care, which in some studies was less intensive diet and physical exercise as compared to the intervention).
- All-cause mortality rates and cardiovascular mortality rates were compared between the intervention and the control.

INTERVENTION (# IN THE GROUP):

- All-cause mortality: 8,782
- Cardiovascular mortality: 5,804

COMPARISON (# IN THE GROUP):

- All-cause mortality: 7,772
- Cardiovascular mortality: 5,213

FOLLOW-UP PERIOD: Variable, ranging 2–30 years (mean 9.8 years)

RESULTS:

Primary Outcome –

- Lifestyle interventions were not superior in reducing all-cause mortality compared to standard care (relative risk [RR] 0.93; 95% CI, 0.85–1.0).
- Lifestyle interventions were not superior in reducing cardiovascular mortality compared to standard care (RR 0.99; 95% CI, 0.79–1.2).

LIMITATIONS:

- The 11 combined trials had distinctly different interventions as some involved group education, some had dietician consultation, etc.
- Heterozygous interventions were grouped in the analysis.

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Shrooms for Sadness: A Mushuscript

Single Dose Psilocybin Treatment for Major Depression Disorder: A Randomized Clinical Trial

Raison CL, Sanacora G, Woolley J, et al. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial [published correction appears in JAMA. 2024 Jan 26]. *JAMA*. 2023;330(9):843-853. doi:10.1001/jama.2023.14530

KEY TAKEAWAY: Psilocybin with psychological support significantly reduces depressive symptoms and functional disability in adults with major depressive disorder (MDD) compared to niacin after six weeks, with a palatable safety profile.

STUDY DESIGN: Phase two randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Recent studies suggest psychedelic psilocybin brings a rapid antidepressant effect, lasting after the body clears the drug. However, questions remain, including the clinical utility of psilocybin for MDD beyond 2–3 weeks.

PATIENTS: Adults with MDD

INTERVENTION: Psilocybin

CONTROL: Niacin

PRIMARY OUTCOME: Depression symptoms on day 43

Secondary Outcome: Depression symptoms on day eight, sustained response and remission, disability score on day 43, safety

METHODS (BRIEF DESCRIPTION):

- The study took place across 11 US sites from December 2019 to June 2022.
- Investigators recruited participants through a study-specific website, programs at study sites, advertisements, and national listservs.
- The mean age for patients was 41 years old with an even split between males and females, mostly White (89%), non-Hispanic (84%), and higher earners (40% made ≥ $100,000 per year).
- Inclusion criteria:
  - Medically healthy adults aged 21–65 years old
  - A current depressive episode of at least 60 days
  - Moderate-to-severe depression symptoms at screening and baseline, defined by the Montgomery-Asberg Depression Rating Scale (MADRS)
    - Scores of 28–60 with higher scores indicating more severe depression.
- Exclusion Criteria: Personal or first-degree family history of psychosis or mania, moderate or severe alcohol or substance use disorder, use of a psychedelic drug in the past five years or more than 10 lifetime uses, and suicidal behavior in the past 12 months.
- Eligible patients completed baseline assessments and were randomized 1:1 to receive:
  - A single dose of synthetic psilocybin 25 mg capsule
  - Niacin 100 mg identical capsule as an active placebo to aid in blinding with standardized psychological support from study facilitators
- Outcomes were blindly assessed over the telephone at baseline (within 7 days before dosing) and at two, eight, 15, 29, and 43 days after dosing.
- MADRS scores ranged from 0–60, higher scores indicate more severe depression.
  - An absolute change of six was clinically meaningful.
  - An absolute change of 12 was clinically substantial.
- Sustained response was defined as at least a 50% reduction in MADRS score at days eight, 15, 29, and 43 compared to baseline.
- Sustained remission was defined as an individual MADRS score ≤10 on days eight, 15, 29, and 43.
- Impaired functioning in responsibilities due to psychiatric symptoms was measured using the Sheehan Disability Scale (SDS).
  - SDS scores ranged from 0–30, higher scores indicate more impaired functioning
  - No minimally clinically important difference exists.
- Adverse events included active suicidal ideation, elevated blood pressure or heart rate requiring medication, drug overdose with suicidal intent, headache, nausea, and visual perceptual effects.
- Serious adverse events included those resulting in death, inpatient hospitalization, significant or persistent incapacity, or congenital birth defect/abnormality.

INTERVENTION (# IN THE GROUP): 51
COMPARISON (# IN THE GROUP): 53

FOLLOW-UP PERIOD: 43 days

RESULTS:

Primary Outcome –

- Psilocybin significantly reduced severe depression compared to niacin from baseline to day 43 (mean difference [MD] –12; 95% CI, –18 to –7.2).
  - This reduction was clinically substantial.

Secondary Outcome –

- Psilocybin significantly reduced severe depression compared to niacin from baseline to day eight (MD –12; 95% CI, –17 to –7.4).
  - This reduction was clinically substantial.
- More participants who received psilocybin had a sustained response to treatment compared with niacin (adjusted absolute difference 30; 95% CI, 14–47).
- Psilocybin significantly improved function impairment compared with niacin from baseline to day 43 (MD –2.3; 95% CI, 3.5–1.1).
- Psilocybin was associated with a higher rate of overall adverse events and severe adverse events compared to niacin:
  - At least one adverse event:
    - Psilocybin 44/50 (88%)
    - Niacin 33/54 (61%)
  - Severe adverse events:
    - Psilocybin 4/50 (8%)
    - Niacin 0/54 (0%)
  - All severe adverse events were known effects of psilocybin.
- There was no significant difference in MADRS-defined remission.
- The study resulted in no serious treatment-emergent adverse events from either group.

LIMITATIONS:

- Between-participant efficacy of psychological support from different facilitators across sites might have confounded results.
- Generalizability was limited due to a lack of diversity in participants.

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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.

Fluticasone for COVID Patients: A Breath of Fresh Air?

Inhaled Fluticasone Furoate for Outpatient Treatment of Covid-19

Boulware DR, Lindsell CJ, Stewart TG, et al. Inhaled Fluticasone Furoate for Outpatient Treatment of Covid-19. *N Engl J Med*. 2023;389(12):1085-1095. doi:10.1056/NEJMoa2209421

KEY TAKEAWAY: Inhaled fluticasone furoate is unlikely to affect symptom duration in non-hospitalized patients with COVID-19.

STUDY DESIGN: Decentralized, double-blind, randomized, placebo-controlled platform trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Inhaled corticosteroids are a potential therapeutic agent for patients with COVID-19 due to their targeted anti-inflammatory effect on the lungs. However, studies on their use in non-hospitalized patients with COVID-19 have been equivocal. Existing studies have been small, open-label, and/or predominated by young, healthy patients <35 years old.

PATIENTS: Non-hospitalized adults with mild-to-moderate COVID-19

INTERVENTION: Inhaled fluticasone furoate

CONTROL: Placebo

PRIMARY OUTCOME: Time to symptom resolution

Secondary Outcome: Death, hospitalizations, urgent care/emergency department visits, number of days unwell, COVID-19 clinical progression

METHODS (BRIEF DESCRIPTION):

- Adults >30 years old with confirmed positive PCR or antigen test for SARS-CoV-2 infection within 10 days of screening and at least two symptoms of COVID-19 for up to seven days prior to enrollment.
  - Patients with allergies/contraindications to the trial drug, use of the trial drug within 14 days before enrollment, or current hospitalization were excluded from the study.
- Patients were blinded and randomized to one of the following treatments:
  - Fluticasone furoate 200 µg daily for 14 days (dry powder in foil blister strip)
  - Placebo
    - Matched inhaled placebo in foil blister strip daily for 14 days
    - Oral placebo for 14 days
- The time from intervention initiation to symptom resolution was defined as the third of three consecutive asymptomatic days.
- Patients completed assessments and reported safety events daily through day 14.
- On days 15–28, patients continued to report if they had symptoms until they had three consecutive asymptomatic days.
- Secondary outcomes were measured at 28 days.
- Outcomes were analyzed via Bayesian proportional hazards or proportional odds models.

INTERVENTION (# IN THE GROUP): 656

COMPARISON (# IN THE GROUP):

- Matched placebo: 350
- Concurrent placebo: 271

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- There was no significant difference in time to recovery between the fluticasone furoate and placebo groups (hazard ratio [HR] 1.0, 95% credible interval 0.91–1.1).

Secondary Outcome –

- There were no significant differences in deaths, hospitalizations, urgent care/emergency department visits, number of days unwell, and COVID-19 clinical progression between the fluticasone furoate and placebo groups.

LIMITATIONS:

- Few clinical events occurred, which limited the study's power to identify effects on clinical outcomes.
- As the study was remote, patients received drug/placebo a median of six days following symptom onset, which is longer than the recommended target of <5 days to start antiviral therapy.
- The study employed different administration methods for placebo groups (inhaled vs oral), with the resultant possible heterogeneity of placebo groups.

- The study group was predominantly White (80%), <50 years old (61%), and had a BMI <30 kg/m2 (61%), which underrepresents minority, older, and obese populations.
- Participants were allowed to use standard-care therapies for COVID-19, which limited standardization.

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Achieving Weight Loss in a Racially Diverse Population: Adding Time or Cutting Calories?

Time-Restricted Eating Without Calorie Counting for Weight Loss in a Racially Diverse Population: A Randomized Controlled Trial

Lin S, Cienfuegos S, Ezpeleta M, et al. Time-Restricted Eating Without Calorie Counting for Weight Loss in a Racially Diverse Population: A Randomized Controlled Trial. *Ann Intern Med.* 2023;176(7):885-895. doi:10.7326/M23-0052

KEY TAKEAWAY: Time-restricted eating (TRE) results in greater weight loss than no intervention. Calorie restriction (CR) resulted in greater weight loss than no intervention. Neither TRE nor CR were more effective than the other.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to not blinded and small sample size)

BRIEF BACKGROUND INFORMATION: Calorie restriction is a well-known method for weight loss. However, tracking calories is often tedious and taxing for some patients. Time-restricted eating is relatively new, but few studies have analyzed its effectiveness.

PATIENTS: Racially diverse adults with obesity

INTERVENTION: TRE and CR

CONTROL: No diet intervention

PRIMARY OUTCOME: Absolute weight loss

Secondary Outcome: Changes in blood pressure, heart rate, total cholesterol, HbA1c level at 12 months

METHODS (BRIEF DESCRIPTION):

- Participants were adults 18–65 years old (mean 44 years) with a BMI of 30–50 kg/m^2 (mean 37).
- The study consisted of Black (33%), Hispanic (46%), and Asian (6%) participants.
- Participants were excluded if they had a history of diabetes mellitus, use of weight loss medications, irregular menstrual cycle, were nightshift workers, pregnant, or current smokers.
- Patients were randomized 1:1:1 to one of the following groups of daily eating habits.
  - TRE: Eating only between noon and 8:00 p.m. without calorie counting
  - CR: 25% energy restriction
  - Control: Eating over a period of ≥10 hours
- All participants were directed not to change their physical activity levels during the trial.
- Participants in the TRE and CR groups received dietary counseling from trained registered dietitians.
- Body weight, blood pressure, heart rate, total cholesterol levels, and HbA1c were measured at six and 12 months.

INTERVENTION (# IN THE GROUP):

- TRE: 30
- CR: 30

COMPARISON (# IN THE GROUP): 30

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- TRE resulted in greater absolute weight loss than the control (mean difference [MD] –4.6 kg; 95% CI, –7.4 to –1.9 kg).
- CR resulted in greater absolute weight loss than the control (MD –5.4 kg; 95% CI, –9.1 to –1.7 kg).
- There was no statistically significant difference between the TRE and CR groups after 12 months (MD –0.81 kg; 95% CI, –3.1 to 4.7 kg).

Secondary Outcome –

- After 12 months there was no significant difference in heart rate, blood pressure, HbA1c, or total cholesterol levels.

LIMITATIONS:

- The study was small and was not blinded.
- Patients with diabetes and cardiovascular disease were not included.
- Energy expenditure was not measured.

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Should Personalized Decision Tools be Considered in Primary Care?

Effect of Individualized Preventative Care Recommendations vs Usual Care on Patient Interest and Use of Recommendations: A Pilot Randomized Clinical Trial

Taksler GB, Hu B, DeGrandis F Jr, et al. Effect of Individualized Preventive Care Recommendations vs Usual Care on Patient Interest and Use of Recommendations: A Pilot Randomized Clinical Trial. *JAMA Netw Open.* 2021;4(11):e2131455. Published 2021 Nov 1. doi:10.1001/jamanetworkopen.2021.31455

KEY TAKEAWAY: Patients provided with a personalized decision tool of preventative health recommendations found it helpful and wanted an updated form in the future.

STUDY DESIGN: Non-blinded randomized clinical trial (RCT)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and unblinded design)

BRIEF BACKGROUND INFORMATION: Previous research highlighted the potential of disease prevention to add over two million healthy life-years across the country. The US Preventive Services Task Force (USPSTF) recommends 25 different preventive services for middle-aged adults. In 2015, only a small proportion of adults 35 years old or older received all recommended preventative services. There is little published on the most effective ways to provide these 25 preventive services to patients in ways that increase adherence.

PATIENTS: Adults 45–70 years old

INTERVENTION: Individualized preventive care recommendations + usual care

CONTROL: Usual care

PRIMARY OUTCOME: Patient interest in individualized preventive care recommendations

Secondary Outcome: Shared decision-making (SDM), decisional comfort, readiness to change, preventive services within one year.

METHODS (BRIEF DESCRIPTION):

- Eligible patients were adults with two or more active risk factors including a BMI >25, smoking, blood pressure 140/80 or greater, HbA1c of 9% or above, 10-year ASCVD risk of 7.5% or above, alcohol misuse, depression, history of sexually transmitted infection, and is overdue for colorectal, cervical, breast, or lung cancer screening.
- The study was completed in two phases: development phase and RCT phase.
- In the development phase, a patient-physician advisory panel and a group of graphic designers provided input to develop a graphical representation that could highlight the most important aspects of individual preventative health services.
- Feedback was collected from primary care patients during regular visits.
- Once a handout design was settled on, they transitioned to a non-blinded RCT.
- Patients in the intervention group received a personalized preventative handout in addition to usual care.
    - Nurses identified eligible patients, calculated individualized recommendations, and provided intervention patients with a one-page handout.
- Patients in the control group received only counseling on preventative health services.
- Randomization was conducted using block sequences.
- Both control and intervention group patients were invited to complete a post-visit survey in exchange for a $25 gift card, and intervention patients received hard copies of recommendations.
- The primary outcome included patient interest in individualized recommendations.
- Secondary outcomes were assessed through survey responses and included measures of shared decision-making, decisional comfort, readiness to change, and preventive services received.

INTERVENTION (# IN THE GROUP): 39 (31 assessed)

COMPARISON (# IN THE GROUP): 39 (30 assessed)

FOLLOW-UP PERIOD: One year

RESULTS:

Primary Outcome –

- The intervention group reported a median rating of 9 of 10 (IQR, 8–10) for "Overall, how helpful did you find the written material (handouts)?"

- The intervention group reported a median rating of 10 of 10 (8-10), for "In the future, would you like to see updated written materials (handouts)?"

Secondary Outcome –

- The intervention group reported greater use of SDM than the control (SDM-Q-9 score of 79 vs 74; *P*=.50).
- The intervention group and control group reported similar levels of decisional comfort (56% vs 58%; *P*=.81).
- More patients in the intervention group expressed readiness to change over the next month compared with the control groups for the top three ranked recommendations (85% vs 71%; *P*=.25).
- Fewer intervention patients rated their health as excellent or very good compared with controls (13% vs 34%; *P*=.01).

LIMITATIONS:

- Small sample size limits validity.
- Randomization was not stratified by site resulting in higher education among individuals in the intervention group.
- Intervention group individualized plans focused on increasing length of life rather than quality.
- No survey was provided to the usual care group to assess if there was a difference in primary outcome between the intervention and control groups.
- The study incorporated an individualized care model preventative handout alongside standard care procedures. To further refine the evaluation, an additional trial group solely receiving the individualized care handout without concurrent standard care could offer a more isolated assessment of the handout.

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