GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 2 - Issue 1

What's in this week's issue?

Week of January 3 - 7, 2022

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Dementia and Depression: What Can Help?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Comparative Efficacy of Interventions for Reducing Symptoms of Depression in People with Dementia: Systematic Review and Network Meta-Analysis

Watt JA, Goodarzi Z, Veroniki AA, et al. Comparative efficacy of interventions for reducing symptoms of depression in people with dementia: systematic review and network meta-analysis. *BMJ*. 2021;372:n532. Published 2021 Mar 24. doi:10.1136/bmj.n532

KEY TAKEAWAY: Non-pharmaceutical interventions, such as exercise with social interaction and cognitive stimulation, are more effective in treating the symptoms of depression in patients with dementia than standard care.

STUDY DESIGN: Systematic review and meta- analysis of 256 randomized control trials (RCTs) (N=28,483)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Symptoms of depression commonly co-exist with dementia. With increasing evidence that anti-depressant use causes harm in this population, there is a need for non-drug interventions for management of depression symptoms in those with dementia.

PATIENTS: Patients with dementia and depression symptoms

INTERVENTION: Pharmaceutical or non-pharmaceutical therapy

CONTROL: Usual care or placebo

OUTCOME: Depression symptoms

METHODS (BRIEF DESCRIPTION):

- Study population included patients with dementia without history of major depressive disorder (MDD). Secondary analysis included patients with concurrent diagnoses of dementia and MDD.
- Interventions were separated into pharmaceutical and non-pharmaceutical.
  - Pharmaceutical approaches included antidepressants and anticholinesterases.
  - Non-pharmaceutical interventions were categorized into cognitive stimulation, environmental modification, touch therapy, occupational therapy, social interaction, exercise, psychotherapy, animal therapy, and reminiscence therapy.
- Usual care included access to appropriate healthcare (i.e., visits with healthcare providers) as well as social care (i.e., support for activities of daily living) based on the needs and preferences of the patient.
- Placebo was defined as an inert imitation of the control, such as a pill or sham intervention.
- Depression scale scores of varying types were standardized for statistical analysis and compared using paired meta-analysis.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD:

- <11 weeks: 43% of studies
- 11–20 weeks: 31% of studies
- 21–30 weeks: 11% of studies
- >30 weeks: 16% of studies

RESULTS:

- The following non-pharmaceutical interventions decreased depression symptoms more than standard care.
  - Cognitive stimulation (mean difference [MD] −2.9; 95% CI, −4.4 to −1.5)
  - Cognitive stimulation + a cholinesterase inhibitor (MD −11; 95% CI, −18 to −3.9)
  - Massage and touch therapy (MD −9.0; 95% CI, −12 to −5.9)
  - Multidisciplinary care (MD −2.0; 95% CI, −3.8 to −0.16)
  - Occupational therapy (MD −2.6; 95% CI, −4.7 to −0.40)
  - Exercise + social interaction + cognitive stimulation (MD −12; 95% CI, −19 to −5.4)
  - Reminiscence therapy (MD −2.3; 95% CI, −3.7 to −0.93)
- In patients with dementia and concurrent MDD, limited studies and significant heterogeneity of those studies precluded further evaluation of the efficacy of non-pharmacologic interventions.

LIMITATIONS:

- Most of the studies were based on Alzheimer's disease so results cannot be extrapolated to other forms of dementia.
- Since multiple measurement scales were used, it is difficult to compare treatment efficacy of treatment head-to-head.

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Efpeglenatide Improves Cardiovascular and Renal Outcomes in High-Risk Patients with Type II Diabetes

Cardiovascular and Renal Outcomes with Efpeglenatide in Type II Diabetes

Gerstein HC, Sattar N, Rosenstock J, et al. Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes. *N Engl J Med*. 2021; 385(10):896–907. doi:10.1056/NEJMoa2108269

KEY TAKEAWAY: In patients with type II diabetes and a history of cardiovascular or renal disease, Efpeglenatide reduced the risk of serious cardiovascular or renal events; however, diarrhea, constipation, nausea, vomiting, and bloating occurred more frequently in the treatment group.

STUDY DESIGN: Multicenter, randomized, double-blind, placebo-control trial (344 sites, 28 countries)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In the treatment of type II diabetes in patients with increased cardiovascular risk, the effect of an exendin-based GLP-1 receptor agonists, such as Efpeglenatide, on cardiovascular and renal outcomes is unknown.

PATIENTS: Adults with type II diabetes

INTERVENTION: Efpeglenatide

CONTROL: Placebo

OUTCOME: Incidence of major adverse cardiovascular events (MACE)

Secondary Outcomes: Composite renal outcome, death, adverse events

METHODS (BRIEF DESCRIPTION):

- Included patients had with type II diabetes, HbA1c greater than 7%, a history of cardiovascular disease (defined as coronary artery disease, stroke, and peripheral arterial disease) or ≥50 years old with a history of kidney disease and at least one additional cardiovascular risk factor.
  - 67% were male and the mean age was 65 years old.
  - 90% had cardiovascular disease, 32% had eGFR <60 ml/min, and 22% had cardiovascular disease and low eGFR.
- Patients randomized to weekly Efpeglenatide 4 mg, Efpeglenatide 6 mg, or placebo subcutaneous injections.
  - No changes were made to the use of glucose lowering drugs for the first 12 weeks, after which any such drug except for a GLP-1 receptor agonist or a DPP 4 inhibitor could be added.
- MACEs included nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or undetermined causes, coronary revascularization, or hospitalization for unstable angina.
- Renal outcomes included incident macroalbuminuria, increased urine albumin to creatinine ratio from baseline, sustained decrease in EGFR, renal replacement therapy for greater than 90 days, kidney transplantation, sustained EGFR of <15 m/L min.

INTERVENTION (# IN THE GROUP): 2,717

COMPARISON (# IN THE GROUP): 1,359

FOLLOW UP PERIOD: Median of 1.8 years

RESULTS:

Primary Outcome –

- Efpeglenatide decreased the incidence of MACE compared to placebo (7.0% vs 9.2%, respectively; hazard ratio [HR] 0.73; 95% CI, 0.58–0.92; number needed to treat [NNT]=46).

Secondary Outcomes –

- Efpeglenatide decreased the incidence of composite renal outcomes compared to placebo (13% vs 18%, respectively; HR 0.68; 95% CI, 0.57–0.79; NNT=19).
- Efpeglenatide decreased the incidence of MACE or death from noncardiovascular causes compared to placebo (7.9% vs 11%, respectively; HR 0.73; 95% CI, 0.59–0.91; NNT=39).
- Efpeglenatide increased the incidence of gastrointestinal events compared to placebo (3.3% vs 1.8%, respectively; P<.009; NNT=67).

LIMITATIONS:

- The participants were followed for a short period of time.
- The incidence of the primary outcome was lower in the number of participants than originally estimated (314 vs 330).
- The study only chose patients with high risk factors limiting generalizability.

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Be True to Your Heart and Substitute Your Salt

Effect of Salt Substitution on Cardiovascular Events and Death

Neal B, Wu Y, Feng X, et al. Effect of Salt Substitution on Cardiovascular Events and Death. *N Engl J Med*. 2021 Sep 16; 385(12):1067–1077.

KEY TAKEAWAY: Salt substitution compared to usual salt consumption protects against stroke, major cardiovascular events, and death.

STUDY DESIGN: Multisite, single blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Previous studies indicate increased dietary sodium consumption results in elevated blood pressure and an increased risk of cardiovascular events and death. Studies have shown salt substitution is beneficial for blood pressure. Previous studies have not assessed salt substitution's effect on serious outcomes such as stroke, acute coronary syndrome, and death.

PATIENTS: Adults with hypertension and/or a history of stroke

INTERVENTION: Salt substitution

CONTROL: Regular salt intake

OUTCOME: Stroke

Secondary Outcomes: Major adverse cardiovascular events and death from any cause

METHODS (BRIEF DESCRIPTION):

- Patients were adults from 600 rural villages in China with a history of stroke or were ≥60 years old with poorly controlled blood pressure.
  - The mean age was 65 years old.
  - Participants with poorly controlled blood pressure had systolic blood pressure ≥140 mmHg + blood pressure medication or ≥160 mmHg if not on medication.
  - Patients were excluded if their life expectancy was <6 months, ate most meals outside of their home, or had a contraindication to salt substitution.
- The treatment group received salt substitution (75% sodium chloride/25% potassium chloride). Average consumption was 20 g per person per day.
- The comparison group was instructed to use regular salt intake in their diet.
- Stroke was defined as a focal neurologic deficit that resulted in death or lasted for >24 and was measured via a patient completed questionnaire.
- Documentation on stroke, major cardiovascular events, and death from medical facility were reviewed by an adjudication committee every six months.

INTERVENTION (# IN THE GROUP): 10,504

COMPARISON (# IN THE GROUP): 10,491

FOLLOW UP PERIOD: Five years

RESULTS:

Primary Outcome –

- Salt substitution prevented stroke compared to regular salt use (29 vs 34 events per 1,000 person years; rate ratio (RR) 0.86; 95% CI, 0.77–0.96).

Secondary Outcomes –

- Salt substitution prevented major cardiovascular events compared to regular salt use (49 vs 56 events per 1,000 person years; RR 0.87; 95% CI, 0.80–0.94).
- Salt substitution prevented all-cause mortality compared to regular salt use (39 vs 45 events per 1,000 person years; RR 0.88; 95% CI, 0.82–0.95).

LIMITATIONS:

- Only one type of salt substitute was used.
- Participants instructed to continue with their "usual sodium intake," which differs between diets of different countries and cultures.
- Risk of bias with unblinded population (though results reviewed by blinded adjudication committee).

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Atrial Fibrillation in Athletes? Goldilocks and the Heart

Risk of Atrial Fibrillation in Athletes: A Systematic Review and Meta-Analysis

Newman W, Parry-Williams G, Wiles J, et al. Risk of atrial fibrillation in athletes: a systematic review and meta-analysis. *Br J Sports Med*. 2021; 55(21):1233–1238. doi:10.1136/bjsports-2021-103994

KEY TAKEAWAY: Athletes appear to have a higher risk of atrial fibrillation than non-athletes.

STUDY DESIGN: Meta-analysis

LEVEL OF EVIDENCE: STEP 3 (downgraded due to intervention done in non-randomized controlled cohorts)

BRIEF BACKGROUND INFORMATION: There is abundant awareness of how a sedentary lifestyle can increase cardiovascular and atrial fibrillation risk, however there is yet evolving data on how exercise can alter atrial fibrillation risk. Based on observational studies, the prevalence of atrial fibrillation in athletes who participate in high-intensity aerobics appears to be higher than the general population. Further delineation of risk categories based on type, duration, and intensity of exercise as well as length of participation are still under investigation.

PATIENTS: Individuals 18 years or older

INTERVENTION: Regular exercise training

CONTROL: Leisure-time physical activity

OUTCOME: Atrial fibrillation risk by activity status

Secondary Outcomes: Atrial fibrillation risk by age and by cardiovascular disease (CVD) risk factors

METHODS (BRIEF DESCRIPTION):

- Online databases were searched for articles published before 2 December 2020 describing atrial fibrillation or atrial flutter in athletes.
- Studies were only retained if they were case-control or cohort studies that reported numbers of atrial fibrillation cases in both adult athletes and non-athlete controls with data that could be used for OR and CI calculations (13 studies: 6 Case-control and 7 Cohort; N=70,478).
- The athletes must have performed at least two years of regular exercise training prior to screening and must have been participating in cycling, running, swimming, Nordic skiing, orienteering, rowing, or mixed sports during the screening.
- The control groups included individuals without any particular training regimen or competition schedule and were involved in only leisure time physical activity.
- Both the control and athlete populations included participants with hypertension and diabetes, but other common conditions known to elevate risk for atrial fibrillation were excluded.
- In each study, raw data was extracted regarding reported cases of atrial fibrillation in both athlete and non-athlete groups as well as data on additional variables of interest such as presence of diabetes, hypertension, cigarette smoking, BMI, mode of exercise, hyperlipidemia, age, and sport type. These data were used to create odds ratios (OR) with 95% CIs.

INTERVENTION (# IN THE GROUP): 6,186

COMPARISON (# IN THE GROUP): 63,662

FOLLOW UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Athletes were at higher risk for atrial fibrillation than non-athletes (13 trials, N=70,478; OR 2.5; 95% CI, 1.7–3.5).

Secondary Outcomes –

- Athletes with CVD risk factors (type II diabetes or hypertension) were at no significantly increased risk for atrial fibrillation compared to non-athletes with CVD risk factors (5 trials, N=69,164; OR 1.5; 95% CI, 0.9–2.5).
- Athletes without CVD risk factors were at a higher risk for atrial fibrillation that non-athletes without CVD risk factors (5 trials, N=69,164; OR 3.7; 95% CI, 2.3–5.9).
- Athletes less than 55 years old were at higher risk for atrial fibrillation than athletes more than 55 years old (13 trials, N=70,478; OR 1.8; 95% CI, 2.1–6.3).

LIMITATIONS:

- Inability to control for confounders due to study types.
- Significant heterogeneity among the studies included especially given that both cohort and case-control studies were included.

- Publication bias as studies with data supporting the null hypothesis are less likely to be published.
- Lastly, only two studies provided data on volume or average duration of exercise which makes it difficult to compare true differences in overall exercise burden.

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