GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: To Deprescribe or Not to Deprescribe - Improving Outcomes for Folks with Frailty

To Deprescribe or Not to Deprescribe: Improving Outcomes for Folks with Frailty

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

A Systematic Review of the Evidence for Deprescribing Interventions Among Older People Living with Frailty

Ibrahim K, Cox NJ, Stevenson JM, Lim S, Fraser SDS, Roberts HC. A systematic review of the evidence for deprescribing interventions among older people living with frailty. *BMC Geriatr*. 2021;21(1):258. Published 2021 Apr 17. doi:10.1186/s12877-021-02208-8

KEY TAKEAWAY: Deprescribing is safe, feasible, and can have positive clinical impacts on elderly patients with frailty.

STUDY DESIGN: Systematic review of six interventional studies (2 RCTs, 2 pre- and post-comparison, 2 prospective international cohorts)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: The adverse effects of polypharmacy in the elderly are magnified in frail adults; however, there is a paucity of research examining the impact of deprescribing on frail adults. Primary care providers must carefully balance the benefits of medications in people with frailty with the risks of serious harm.

PATIENTS: Older adults with frailty

INTERVENTION: Deprescribing (reducing dose, stopping, or switching medication)

CONTROL: Any or no comparison

PRIMARY OUTCOME: Safety (adverse drug reactions, hospitalization, mortality)

Secondary Outcome: Clinical outcomes, medication-related outcomes, feasibility, acceptability, cost

METHODS (BRIEF DESCRIPTION):

- Six studies met the inclusion criteria of deprescribing as the only intervention or made up more than 50% of the total recommendations.
- Included patients had a median age of 65 (mean range 79 to 85) and were identified as frail using accepted frailty measures.
- A variety of deprescribing tools were used to guide interventions: STOPP criteria, STOPPFrail tool, Garfinkel algorithm, Beers criteria, guidelines for deprescribing anticholinergic and sedating medications
- Three studies involved pharmacist-led deprescribing.
- Three studies involved multidisciplinary team-led deprescribing.
- Frailty was measured using the Edmonton Frailty Scale.
- Adverse drug reactions were measured using the UKU Side Effect Rating Scale (UKU-SERS), a 48-item symptom rating scale including psychiatric, neurologic, autonomic, and other side effects.

INTERVENTION (# IN THE GROUP): 414

COMPARISON (# IN THE GROUP): 343

FOLLOW-UP PERIOD: Three months to three years

RESULTS:

Primary Outcome –

- Deprescribing reduced adverse drug reactions (n=46).
  - Three months: –2.8 (95% CI, –4 to –1.6)
  - Six months: –4.2 (95% CI, –5.7 to –2.8)
- Two studies showed no significant difference in unplanned hospital stays and mortality.

Secondary Outcome –

- Deprescribing led to decreased frailty at six months (n=46; mean difference –1.4; 95% CI, –2.2 to –0.48).
- Deprescribing did not affect falls, cognition, depression, or quality of life.
- Feasibility: Four studies revealed 72–91% of deprescribing interventions were able to be implemented.
- Acceptability: Two studies revealed 87% of participants were accepting of deprescribing interventions and satisfaction was high or very high among 89% of participants.
- Cost: Deprescribing resulted in monthly medication cost savings (n=65; mean difference $61.74; 95% CI, 8.9–114.5).

LIMITATIONS:

- None of the studies were completed in the U.S. or provided demographic or socioeconomic information about patients.
- Heterogeneity in settings (hospital, primary care, care home, community), frailty measures, and deprescribing.

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Does It Matter When I Take My Blood Pressure Medication?

Cardiovascular Outcomes in Adults with Hypertension with Evening Versus Morning Dosing of Usual Antihypertensives in the UK (TIME Study): A Prospective, Randomized, Open-Label, Blinded-Endpoint Clinical Trial

Mackenzie IS, Rogers A, Poulter NR, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): A prospective, randomised, open-label, blinded-endpoint clinical trial. *Lancet*. 2022;400(10361):1417-1425. doi:10.1016/S0140-6736(22)01786-X

KEY TAKEAWAY: There is no difference in cardiovascular outcomes between patients taking blood pressure (BP) medications in the evening compared to those taking them in the morning.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Cardiovascular events such as myocardial infarction (MI) and strokes are reduced by adequately controlling BP. BP exhibits a diurnal rhythm–lower BP at night followed by higher BP in the morning. Some studies claim taking BP medications in the evening is more effective at reducing cardiovascular events.

PATIENTS: Adults with hypertension

INTERVENTION: BP medication in the evening

CONTROL: BP medication in the morning

PRIMARY OUTCOME: Composite cardiovascular endpoint of the first event of vascular death, or hospitalization for non-fatal MI or non-fatal stroke

Secondary Outcome: Hospitalization for non-fatal MI, hospitalization for non-fatal stroke, hospitalization or death from congestive heart failure, vascular death, all-cause mortality, adherence, adverse events, hospitalization for glaucoma

METHODS (BRIEF DESCRIPTION):

- 21,104 UK adults were recruited if they were diagnosed with hypertension and taking at least one BP medication daily.
- The mean age was 65 years old, 57.5% were men, and 90.5% were White.
- Exclusion criteria: Those who regularly worked overnight shifts or those who took BP medication more than once daily.
- Patients were randomized in a 1:1 ratio via computer algorithm to take their medications either in the morning (6 am–10 am) or evening (8 pm–midnight).
- All screening, informed consent, randomization, and follow-up questionnaires (every 3 months) were performed via an online portal and email.
- Self-reported follow-up online questionnaires assessed if patients were adherent to medications at assigned times and if they had experienced any cardiovascular events, or side effects from medications (i.e., dizziness, GI symptoms, falls, or fractures) since completion of the last follow-up questionnaire.

INTERVENTION (# IN THE GROUP): 10,503

COMPARISON (# IN THE GROUP): 10,601

FOLLOW-UP PERIOD: Median 5.2 years

RESULTS:

Primary Outcome –

- Taking BP medications in the evening did not improve cardiovascular events compared to taking them in the morning (hazard ratio [HR] 0.95; 95% CI, 0.83–1.1).
  - Evening dosing: 0.69 events per 100 patient-years (95% CI, 0.62–0.76)
  - Morning dosing: 0.72 events per 100 patient-years (95% CI, 0.65–0.79)

Secondary Outcome –

- There were no significant differences in the secondary outcomes between morning and evening dosing.

LIMITATIONS:

- Patients were aware of their allocated medication dosing time which could bias their reporting.
- Patients' reporting of adverse events could be incomplete.
- The study had more participants withdraw from follow-up questionnaires from the evening group than the morning group which could underestimate study results.

- Self-reported data susceptible to recall bias and data entry errors.

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Are Vitamin D and Omega-3s the Answer to Medical Frailty?

Effect of Vitamin D3 and Omega-3 Fatty Acid Supplementation on Risk of Frailty: An Ancillary Study of a Randomized Clinical Trial

Orkaby AR, Dushkes R, Ward R, et al. Effect of Vitamin D3 and Omega-3 Fatty Acid Supplementation on Risk of Frailty: An Ancillary Study of a Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(9):e2231206. Published 2022 Sep 1. doi:10.1001/jamanetworkopen.2022.31206

KEY TAKEAWAY: Treating patients without cardiovascular disease or cancer with vitamin D3 or omega-3 fatty acid supplementation does not affect frailty progression or incidence.

STUDY DESIGN: Ancillary trial of a 2x2 factorial randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Frailty in the elderly has become a growing concern with the expansion of the demographic in all patient populations. The supplementation of vitamin D3 (VD3) and omega-3 fatty acids (O3FA) have been studied for their anti-inflammatory properties, as well as their use in curbing the hypothesized chronic inflammatory processes that may be the cause of frailty. Frailty is defined as a decrease in physiologic reserve in the setting of external stressors and has been associated with increased morbidity and mortality.

PATIENTS: Patients without cancer or cardiovascular disease

INTERVENTION: Vitamin D3 + omega-3 fatty acids

CONTROL: Placebo

PRIMARY OUTCOME: Frailty

Secondary Outcome: Rate and incidence of change in frailty

METHODS (BRIEF DESCRIPTION):

- Men ≥50 years old and women ≥55 years old (50.7% women, mean age 67.2 years) without cancer or cardiovascular disease with documented frailty (12.7 % frail).
- Patients were blinded and randomized into 4 groups in a 2 x 2 factorial fashion:
    - VD3+O3FA
    - VD3+placebo
    - O3FA+placebo
    - Placebo+placebo
- Vitamin D3 dosage: 2,000 U/day
- Marine omega-3 fatty acid dosage: 1 g/day
- Frailty was assessed using The Rockwood Frailty Index (FI), a tool used to estimate frailty on a scale of 1 (very fit) to 9 (terminally ill). Patients who score a 5 or higher are considered frail.

INTERVENTION (# IN THE GROUP):

- VD3+O3FA: 6,463

COMPARISON (# IN THE GROUP):

- VD3+placebo: 6,464
- O3FA+placebo: 6,470
- Placebo+placebo: 6,474

FOLLOW-UP PERIOD: Five years

RESULTS:

Primary Outcome –

- VD3 and/or O3FA did not decrease frailty over time.

Secondary Outcome –

- VD3 and/or O3FA did not affect the rate or incidence of change in frailty.
- Results did not change when factoring in age or sex.

LIMITATIONS:

- Frailty rates in the study population were lower than that of the general population of similar age (25%).
- The study excluded high-risk populations (institutionalized, cancer, cardiovascular disease, etc.).
- Single doses of each medication were studied but may not be optimal for frailty prevention.

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Comparing the Thiazide Siblings

Chlorthalidone vs. Hydrochlorothiazide for Hypertension–Cardiovascular Events

Ishani A, Cushman WC, Leatherman SM, et al. Chlorthalidone vs. hydrochlorothiazide for hypertension–cardiovascular events. New England Journal of Medicine. 2022;387:2401-2410.

KEY TAKEAWAY: Switching patients 65 years old and older with hypertension from hydrochlorothiazide (HCTZ) to chlorthalidone does not affect cardiovascular (CV) outcomes.

STUDY DESIGN: Pragmatic, comparative, open-label, randomized control trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding and limited generalizability)

BRIEF BACKGROUND INFORMATION: HCTZ and chlorthalidone are both thiazide diuretics prescribed to patients with HTN. Although studies observed chlorthalidone to be potentially superior to HCTZ in preventing CV outcomes, HCTZ is still prescribed more often. This large study seeks to compare these medications in affecting the incidence of non-fatal CV events while also elaborating on side effect differences.

PATIENTS: Patients with HTN who are taking HCTZ

INTERVENTION: Switch HCTZ to chlorthalidone

CONTROL: Continue HCTZ

PRIMARY OUTCOME: Composite of CV events

Secondary Outcome: Individual components of the composite primary outcome, adverse events

METHODS (BRIEF DESCRIPTION):

- Subjects were adults (77% white, 97% males) over 65 years old, in the VA system, and taking HCTZ 25 mg or 50 mg for HTN.
- Exclusion criteria: Patient refusal, taking combination pills that contained HCTZ with another medication
- Consent was obtained from physicians and their patients, then the electronic medical record (EMR) was utilized to manage the medication regimen depending on the patient's random assignment.
- The experimental group was switched to Chlorthalidone 12.5 mg or 25 mg depending on the dose of HCTZ they were on.
- The control group continued HCTZ as prescribed.
- The primary outcome tallied the initial occurrence of composite CV events.
- Secondary outcomes included subcategories of CV events (angina requiring PCI, stroke, heart failure hospitalization, and non-cancer deaths) and incidence of any adverse events.

INTERVENTION (# IN THE GROUP): 6,756

COMPARISON (# IN THE GROUP): 6,767

FOLLOW-UP PERIOD: Three years

RESULTS:

Primary Outcome –

- There was no significant difference in CV events between the two groups (HR 1.0; 95% CI, 0.9–1.2).

Secondary Outcome –

- There was no significant difference in the occurrence of each of the CV outcomes between the two groups.
- Patients on chlorthalidone had a greater risk for hypokalemia than patients who continued on HCTZ (HR 1.4; 95% CI, 1.2–1.6).

LIMITATIONS:

- Since this was an open-label study, blinding was not possible.
- Total number of CV events was likely underreported as the authors stopped the trial after a pre-determined limit of such events.
- Since patients were on HCTZ in this open-label study, those who were switched to chlorthalidone were more likely to request HCTZ back.
- The results of the study may not be applicable to higher doses of medication.
- The generalizability is limited as White males were overrepresented.

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Do Intra-Articular Injections Worsen Osteoarthritis?

Do Glucocorticoid Injections Increase the Risk of Knee Osteoarthritis Progression Over 5 Years?

Latourte A, Rat AC, Omorou A, et al. Do Glucocorticoid Injections Increase the Risk of Knee Osteoarthritis Progression Over 5 Years? *Arthritis Rheumatol*. 2022;74(8):1343-1351. doi:10.1002/art.42118

KEY TAKEAWAY: Intra-articular glucocorticoid and hyaluronic acid injections do not increase the five-year risk of total knee replacement in patients with symptomatic knee osteoarthritis.

STUDY DESIGN: Multicenter cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Intra-glucocorticoid injections are effective for short-term pain relief for symptomatic knee osteoarthritis (OA). Long-term consequences of repeat intra-glucocorticoid injections remain uncertain, with some evidence suggesting decreased cartilage volume and joint space and worsening radiographic findings. The purpose of this study is to clarify the effect of intra-glucocorticoid injections on knee OA progression.

PATIENTS: Patients with symptomatic knee OA 40–75 years old

INTERVENTION: Intra-articular (IA) glucocorticoid injections or intra-articular hyaluronic acid (IAHA) injections

CONTROL: No treatment

PRIMARY OUTCOME: Total knee replacement

Secondary Outcome: Radiographic worsening

METHODS (BRIEF DESCRIPTION):

- Patient data were derived from the Knee and Hip Osteoarthritis Long-Term Assessment Cohort in France.
- Patients were included if they had symptomatic knee OA based on the American College of Rheumatology criteria and radiographic evidence of Kellgren/Lawrence (K/L) grade ≥2.
- Annual self-reported questionnaires collected sociodemographic information, number of IA glucocorticoid or IAHA injections, knee-related pain score using a visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, and knee replacement surgery.
- The cohort obtained knee radiographs at years zero, three, and five. They were read and given a K/L grade by two independent readers.
- The primary outcome was the five-year incidence of total knee replacement.
- The secondary outcome was radiographic worsening based on K/L grade.

INTERVENTION (# IN THE GROUP): 150

- IA Glucocorticoid: 51
- IAHA: 99

COMPARISON (# IN THE GROUP): 414

FOLLOW-UP PERIOD: Five years

RESULTS:

Primary Outcome –

- IA glucocorticoid injections did not affect the five-year risk of total knee replacement compared to untreated knees (hazard ratio [HR] 0.92; 95% CI, 0.20–4.1).
- IAHA injections did not affect the five-year risk of total knee replacement compared to untreated knees (HR 0.81; 95% CI, 0.14–4.6).

Secondary Outcome –

- IA glucocorticoid injections did not cause radiographic worsening compared to untreated knees (HR 1.3; 95% CI, 0.64–2.8).
- IAHA injections did not cause radiographic worsening compared to untreated knees (HR 1.4; 95% CI, 0.85–2.2).

LIMITATIONS:

- K/L grade is not as precise compared to MRI when assessing cartilage volume and joint space width
- Small sample size and underpowered study
- Data collected via questionnaires can have recall bias.
- Limited generalizability – data is French population with knee OA treated in a primary care setting.
- No data on dosage or type of glucocorticoid used or type of hyaluronic acid used.

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To Operate or Not in Asymptomatic Severe Carotid Stenosis?

Incidence of Ischemic Stroke in Patients with Asymptomatic Severe Carotid Stenosis without Surgical Intervention

Chang RW, Tucker LY, Rothenberg KA, et al. Incidence of Ischemic Stroke in Patients with Asymptomatic Severe Carotid Stenosis without Surgical Intervention. *JAMA*. 2022;327(20):1974-1982. doi:10.1001/jama.2022.4835

KEY TAKEAWAY: In asymptomatic severe (70-90%) carotid stenosis, the estimated ipsilateral carotid acute ischemic stroke risk is 4.7% over a five-year period without surgical intervention compared to the previously observed risk of 10% with medical management.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to unreliable and missing data)

BRIEF BACKGROUND INFORMATION: The current management of asymptomatic patients was informed by the deferred group of ACST-1 trial (1993-2003), which showed an observed 10% risk of non-perioperative stroke at 5 years and optimal treatment has involved surgical intervention. However, a 2009 meta-analysis showed a persistent decline in stroke risk amongst these asymptomatic patients. Data on outcomes of modern medical treatment for asymptomatic carotid disease is sparse and no study has ascertained the absolute incremental benefit of surgical intervention to prevent stroke in asymptomatic patients.

PATIENTS: Asymptomatic adults with severe carotid stenosis

INTERVENTION: Surgical operative treatment

CONTROL: Non-surgical treatment

PRIMARY OUTCOME: Ipsilateral carotid acute ischemic stroke

METHODS (BRIEF DESCRIPTION):

- A manual chart review included 3,737 adult patients (4,230 arteries) with asymptomatic severe (70–90%) carotid stenosis diagnosed via imaging between 2008 and 2012.
- Exclusion criteria: No prior intervention or ipsilateral neurologic event in the past six month, non-atherosclerotic carotid lesion
- Primary outcome events, documentation, and imaging were manually reviewed by vascular surgeons or neurologists to confirm the occurrence of acute stroke.
- Secondary outcomes were obtained via clinical notes, laboratory values, and pharmacy refill histories.

INTERVENTION (# IN THE GROUP): 1,423 patients (1,691 arteries)

COMPARISON (# IN THE GROUP): 2,314 patients (2,539 arteries)

FOLLOW-UP PERIOD: Through death, disenrollment, or ipsilateral carotid intervention

RESULTS:

Primary Outcome –

- The unadjusted annual rate of ipsilateral carotid acute ischemic stroke was 0.9% (95% CI, 0.7–1.2%) with a Kaplan-Meier analysis estimate over five years of 4.7% (95% CI, 3.9–5.7%) in the non-intervention group.
- Independent variables associated with ipsilateral stroke:
  - For every 10-year increase in age, there was an associated increase in the risk of ipsilateral stroke (adjusted HR 1.3; 95% CI, 1.02–1.5).
  - Baseline high-grade lesion increased the risk for ipsilateral stroke (adjusted HR 1.7; 95% CI, 1.1–2.8).
  - History of non-ipsilateral stroke increased the risk for ipsilateral stroke (adjusted HR 2.8; 95% CI, 1.6–4.8).
  - Statin use reduced the risk of ipsilateral stroke (adjusted HR 0.38; 95% CI, 0.21–0.72).

LIMITATIONS:

- Possible selection bias.
- Treatment decisions and resource utilization could not be accounted for.
- No practical method to assess new image data used, quality assurance of vascular lab, or information regarding plaque characteristics.
- Aspirin use by participants was not assessed or tracked.
- Unreliable TIA diagnosis code in EHR, thus the effect on cohort composition and outcome was not fully assessed.
- The cohort was composed of only insured patients.

- Missing data were replaced with median values.
- Some cases were conservatively assigned ipsilateral when laterality was in doubt.

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