GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 5 - 9, 2021

SPOTLIGHT: The Pocket Script - Treating Our Own Anxiety?

The Pocket Script: Treating Our Own Anxiety?

Delayed antibiotic prescription for children with respiratory infections: a randomized trial

Mas-Dalmau G, Villanueva López C, Gorrotxategi P, et al. Delayed Antibiotic Prescription for Children with Respiratory Infections: A Randomized Trial. *Pediatrics*. 2021; 147(3):e20201323

KEY TAKEAWAY: Children with uncomplicated respiratory tract infections (RTIs) who received delayed antibiotic prescription (DAP) had similar symptom duration and severity compared to immediate antibiotic prescription (IAP) or no antibiotic prescription (NAP); they also had fewer GI adverse effects and fewer antibiotics prescribed.

STUDY DESIGN: Multicenter randomized controlled non-blinded trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: RTIs result in a significant number of pediatric medical visits and uncomplicated RTIs have a high rate of inappropriately prescribed antibiotics. There is a growing body of evidence that DAP reduces antibiotic use with similar patient outcomes to IAP with less adverse effects of antibiotic usage. Therefore, it is useful to examine patient outcomes and parental satisfaction with DAP in the setting of uncomplicated RTIs in a pediatric population.

PATIENTS: Children 2 to 14 years old presenting with an acute uncomplicated RTI (acute otitis media, pharyngitis, acute bronchitis, rhinosinusitis)

INTERVENTION: Delayed antibiotic prescription (DAP)

CONTROL: Immediate antibiotic prescription (IAP) and no antibiotic prescription (NAP)

OUTCOMES: RTI symptom duration and severity

Secondary Outcomes: Antibiotic use, parental satisfaction, parental beliefs, additional primary care visits, complications

METHODS (BRIEF DESCRIPTION):

- Open-label multicenter randomized clinical trial comparing different antibiotic prescribing strategies
- Children seen at primary care clinic and diagnosed with uncomplicated RTI with questionable need for antibiotics
- DAP vs IAP vs NAP
- Delayed antibiotic prescription was defined as antibiotics given to parent and only filled if the child did not start to feel better after 4, 7, 15, or 20 days from symptom onset for acute otitis media, pharyngitis, rhinosinusitis, or acute bronchitis, respectively
- Patients randomly assigned by pathology to treatment group and given the same structured information regarding antibiotics and RTIs
- Antibiotic choice and duration determined by provider
- Symptom severity measured on a 7-point Likert scale (0=no symptoms, 6=worst possible). Duration was determined by symptom onset to disappearance.

INTERVENTION (# IN THE GROUP): DAP 146

COMPARISON (# IN THE GROUP): IAP 148; NAP 142

FOLLOW UP PERIOD: 30 days

RESULTS:

Primary Outcomes:

- Mean duration of symptoms was similar for all groups:
  - DAP 8.3 days vs IAP 8.3 days, *P*=.968
  - NAP 7.9 days vs IAP 8.3 days, *P*=.593
- Mean duration of severe symptoms was similar for all groups:
  - DAP 12.4 days vs IAP 10.1 days, *P*=.247
  - NAP 10.9 days vs IAP 10.1 days, *P*=.682

Secondary Outcomes:

- Antibiotic use was higher in IAP (n = 142 [96%]) vs. DAP (n = 37 [25.3%]) and NAP (n = 17 [12.0%]) (*P*<.001)
- Gastrointestinal adverse effects were higher in IAP 8.8% vs. DAP 0.7% (*P*=.064) and NAP 2.8% (*P*=.04).
  - No difference in complications, additional visits to primary care, and parental satisfaction.

LIMITATIONS:

- Open label design
- Outcomes reported by children
- Inferred results for acute bronchitis and rhinosinusitis as large majority had acute otitis media or pharyngitis
- Parental motivation to avoid antibiotic use

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the U.S. Air Force Medical Corps, the Air Force at large, or the Department of Defense.

Is Cryoablation Finding its Way to the Front of the Line for Atrial Fibrillation Treatment?

Cryoablation or drug therapy for initial treatment of atrial fibrillation

Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N Engl J Med*. 2021; 384(4):305–315.

KEY TAKEAWAY: At 1 year, tachyarrhythmias recurred at much lower rates in adults with symptomatic, paroxysmal atrial fibrillation treated with catheter cryoballoon ablation rather than with antiarrhythmic drug therapy.

STUDY DESIGN: Multicenter randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current guidelines recommend antiarrhythmic drug therapy as initial treatment for maintaining sinus rhythm in symptomatic patients with atrial fibrillation. Catheter ablation has been demonstrated to be better at maintaining sinus rhythm and improving quality of life for patients who have failed initial drug therapy. Evidence is lacking on the efficacy of cryoablation as initial therapy vs drug therapy.

PATIENTS: Adults with symptomatic, paroxysmal, untreated atrial fibrillation

INTERVENTION: Cryothermy balloon catheter ablation

CONTROL: Antiarrhythmic drug therapy

OUTCOME: Recurrence of any atrial tachyarrhythmia

Secondary Outcomes: Recurrence of symptomatic atrial tachyarrhythmia, atrial fibrillation burden, quality of life, and serious adverse events

METHODS (BRIEF DESCRIPTION):

- Multicenter RCT at 18 sites in Canada.
- Adult patients (age >18) with symptomatic, paroxysmal, untreated atrial fibrillation detected on EKG within 24 months randomized to receive either cryothermy balloon catheter ablation or antiarrhythmic drug therapy (flecainide, propafenone, sotalol, dronedarone, and amiodarone).
  - Specific drugs and dosages determined by treating provider.
- Excluded if daily use of antiarrhythmic drugs (Class I or III). Patients received an implantable cardiac monitoring device before initiating therapy.
- Telephone follow-up at 7 days and visits at 3, 6, and 12 months.
- Outcomes assessed by intention to treat and power analysis conducted. No correction of significance for multiplicity. Crossover permitted after independent review by treating provider.
- Trial funded by Canadian government with unrestricted grants from industry.

INTERVENTION (# IN THE GROUP): 154

COMPARISON (# IN THE GROUP): 149

FOLLOW UP PERIOD: 1 year

RESULTS:

Primary Outcome:

- Atrial tachyarrhythmias recurred (after a 90-day blanking period) in 66 of 154 patients assigned to ablation (43%) and 101 of 149 assigned to antiarrhythmic drugs (68%) (Hazard Ratio [HR] 0.48; 95% CI, 0.35–0.66; NNT 4)

Secondary Outcomes (ablation vs drugs):

- Lesser recurrence of symptomatic atrial tachyarrhythmia (11% vs 26%; HR 0.39; 95% CI, 0.22–0.68)
- Greater quality of life with no symptoms at 12 months (86% vs 73%; RR 1.2; 95% CI, 1.1–1.3)
- Less serious adverse events (3.2% vs 4.0%; RR 0.39; 95% CI, 0.22–0.68)

LIMITATIONS:

- Cardiovascular outcomes, such as strokes, not examined.
- Study involved use of a single ablation technology, when others exist.
- Trial limited to 12-months follow-up.
- Screening logs not maintained; number initially screened not available.

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Osteopathic Manual Treatment Improves Pain and Quality of Life in Chronic Pain Patients

Osteopathic manual treatment for pain severity, functional improvement, and return to work in patients with chronic pain: a meta-analysis

Rehman Y, Ferguson H, Bozek A, et al. Osteopathic Manual Treatment for pain severity, functional improvement, and return to work in patients with chronic pain: a systematic review and meta-analysis. *Journal of the American Osteopathic Association*. 2020; 120(12):888–906.

KEY TAKEAWAY: There is moderate quality evidence that osteopathic manual therapy (OMTh) is effective in reducing pain while improving quality of life (QOL) in patients with chronic non-cancer pain (CNCP).

STUDY DESIGN: Meta-analysis of 16 low quality RCTs

LEVEL OF EVIDENCE: STEP 2 (downgraded due to low quality of included studies)

BRIEF BACKGROUND INFORMATION: Osteopathic manipulative treatment (OMT) and OMTh are treatment modalities gaining favor for patients with CNCP, yet previous reviews have been low quality.

PATIENTS: Adults with CNCP

INTERVENTION: OMTh as active or combination therapy (with exercise or gabapentin)

CONTROL: Other forms of therapy

OUTCOME: Pain severity, QOL, disability, or return to work

METHODS (BRIEF DESCRIPTION):

- Intervention: OMTh, OMTh with exercise, OMTh with gabapentin
- Comparators: exercise, sham OMT/light touch, range of motion (ROM), laser therapy, stretching, chemonucleolysis, hot or cold packs, transcutaneous electrical nerve stimulation, physiotherapy, or gabapentin
- Inclusion criteria for studies: >18 years old, reported outcomes used previously validated tools, at least two techniques were employed (OMTh and comparison as listed above, usual care could not be the control)
- Exclusion Criteria: cancer related pain, pregnancy, headaches, gynecologic pain, irritable bowel syndrome, visceral pain, crossover trials
- 16 studies met inclusion criteria reporting the following outcomes:
  - Pain severity (13 pooled studies)
  - Disability (8 pooled studies)
  - Quality of life (2 pooled studies)
  - Return to work (2 studies)

INTERVENTION (# IN THE GROUP): 591

COMPARISON (# IN THE GROUP): 564

FOLLOW UP PERIOD: 7 to 365 days

RESULTS:

The OMTh group experienced significant improvements compared to active controls in the following areas:

- Reduction in pain (13 trials, N=996; standardized mean difference (SMD) –0.37; 95% CI, –0.58 to –0.17)
- Reduction in disability (8 trials, N=742; SMD –0.28; 95% CI, –0.46 to –0.10)
- Improved quality of life (2 trials, N=120; SMD 0.67; 95% CI, 0.29 to 1.1)

The OMTh group experienced a sooner return to work than active controls at 4 weeks, but there was no difference at 12 weeks (2 trials, N=521; no numerical results reported)

LIMITATIONS:

- High risk of bias due to inability to blind patients or practitioners.
- Small sample sizes in the RCTs with high dropout rates.
- OMTh performed by non-physicians.

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Can Low Dose Aspirin Prevent Preterm Delivery?

Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy: a randomized multi-country placebo controlled trial

Hoffman MK, Goudar SS, Kodkany BS, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial [published correction appears in Lancet. 2020 Mar 21;395(10228):e53]. *Lancet*. 2020; 395(10220):285- 293. doi:10.1016/S0140-6736(19)32973-3

KEY TAKEAWAY: Low dose ASA initiated in singleton, nulliparous women between 6.0–13.6 weeks gestational age (GA) resulted in lower rates of preterm delivery.
STUDY DESIGN: Randomized multi-country double masked trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Studies and current practice encourage ASA for preventing pre-eclampsia and some meta-analyses have shown that ASA might also help prevent preterm delivery. Preterm birth is a common cause of neonatal mortality, more so in areas with poor socioeconomic status.

PATIENTS: Nulliparous women in Democratic Republic of Congo, Guatemala, India, Kenya, Pakistan, and Zambia with a singleton pregnancy
INTERVENTION: 81 mg ASA, daily until 36 weeks of GA
CONTROL: Placebo
OUTCOMES: Preterm birth (before 37 weeks GA)
Maternal Outcomes: late abortion, maternal mortality through 42 weeks GA, vaginal bleeding, antepartum or postpartum hemorrhage, gestational hypertension
Fetal Outcomes: Small for gestation age, birth weight <1,500g and <2,500g, perinatal mortality, early preterm birth, spontaneous abortion, stillbirth, fetal loss, medical termination of pregnancy

METHODS (BRIEF DESCRIPTION):

- Patients: nulliparous women with a singleton fetus confirmed by ultrasound
- Inclusion Criteria: Blood pressure <140/90, Hgb ≥7 g/dl, ultrasound confirming a singleton pregnancy, fetal heartbeat, and no anomalies
- Exclusion Criteria: nulliparous women with a singleton fetus confirmed by ultrasound, meeting inclusion criteria above who have taken low dose aspirin for 7 days during this pregnancy, multiple gestations seen, allergy to aspirin, having a diagnosis for which low dose aspirin is indicated, having more than 2 first trimester losses
- Location: Democratic Republic of Congo, Guatemala, India, Kenya, Pakistan, Zambia
- Type of Study: Randomized, double masked; consent was obtained; both patients and medical personnel obtaining consent were blinded

INTERVENTION (# IN THE GROUP): 5,990 with 5,787 in the Modified Intent-to-Treat population
COMPARISON (# IN THE GROUP): 5,771

FOLLOW UP PERIOD: Up to 42 weeks GA

RESULTS:
Primary Outcome:

- Preterm birth occurred 12% in the aspirin group compared to 13% in the placebo group (RR 0.89; 95% CI, 0.81–0.98; risk difference –0.02; 95% CI, –0.03 to –0.01, NNT=67)

Secondary Outcomes:

- Statistical significance was only seen in two secondary outcomes:
- Early preterm hypertensive disorders occurred 0.1% in the aspirin group compared to 0.4% in the placebo group (RR 0.38; 95% CI, 0.17–0.85)
- Early preterm delivery occurred 3.3% in the aspirin group compared to 4.0% in the placebo group (RR 0.75; 95% CI, 0.61–0.93)

LIMITATIONS:

- The study was done with low dose 81 mg of aspirin. The optimal dosage of aspirin needed to reduce preterm delivery would need further investigation.
- The study was done in developing countries and should be repeated in developed countries in order to apply these results to women in the U.S.
- The study was limited to nulliparous, singleton pregnancies.
- Optimal timing of initiation of aspirin is unknown.

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Are Naltrexone and Bupropion the Response to Methamphetamine Use Disorder in the United States?

Bupropion and naltrexone in methamphetamine use disorder

Trivedi MH, Walker R, Ling W, et al. Bupropion and Naltrexone in Methamphetamine Use Disorder. *N Engl J Med*. 2021; 384(2):140–153. doi:10.1056/NEJMoa2020214

KEY TAKEAWAY: Adults with moderate to severe methamphetamine use disorder treated with naltrexone-bupropion had a higher number of methamphetamine-negative urine tests at the end of 12 weeks than adults who received placebo.

STUDY DESIGN: Multisite, double blind, two-stage, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Methamphetamine use disorder is prevalent in the United States and is the main cause of overdose deaths. There are not pharmacological treatments approved for treatment of methamphetamine use disorder.

PATIENTS: Adults 18 to 65 years old with moderate or severe methamphetamine use disorder

INTERVENTION: Combination of extended-release naltrexone IM and extended-release bupropion

CONTROL: Placebo injection and bupropion tablets

OUTCOME: Urine methamphetamine tests

METHODS (BRIEF DESCRIPTION):

- Adults between 18 and 65 years of age with diagnosis of moderate to severe methamphetamine use disorder who answered recruitment efforts at different locations.
- Pre-screening phone call
- Visit to different centers for randomization
- Urine tests collected twice a week.
- Urine tested for 10 drugs with point-of-care test.
- Given combination of two medications: Extended-release naltrexone 380 mg vial given IM. Dose given the day of randomization and in the third week of each stage. Extended-release bupropion 150 mg tablets, with increase in dose to 450 mg daily over 3 days.
- Two randomizations to enrich the sample in the second stage with participants who were unlikely to have a response to placebo.
- Two stages of 6 weeks each
- Total of 12 weeks: Randomizations at week 1 and week 6
- Analysis: Weighted average of responses in the two stages

INTERVENTION (# IN THE GROUP): 109 in first stage, 114 in second stage

COMPARISON (# IN THE GROUP): 294 in first stage, 111 in second stage

FOLLOW UP PERIOD: Two stages of 6 weeks each

RESULTS:

Primary Outcome:

- There was a higher weighted average of at least 3 methamphetamine negative tests in the naltrexone-bupropion group vs placebo group obtained at the end of stage 1 or end of stage 2 (14% vs 2.5%; *P*<.001).

Secondary Outcomes:

- Methamphetamine Cravings: There was a lower weighted difference of –9.7 points on a scale of 0 to 100 in the naltrexone-bupropion group vs the placebo group (95% CI, –14 to –5.6).
- Depressive Symptoms: There was a lower weighted difference in PHQ-9 scores of –1.1 points on a scale of 0 to 27 in the naltrexone-bupropion group vs the placebo group (95% CI, –1.9 to –0.2).
- Nausea: Nausea was significantly higher in the naltrexone-bupropion group in both stage 1 (38% vs 15%; *P*<.001) and stage 2 (28% vs 7.2%; *P*<.001).

LIMITATIONS:

- Low number of participants
- Lower number of women
- The use of the medication was obtained through personal report and not objective observation
- Difficult trial design (sequential parallel comparison design)

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Are We "Bean-g" Healthier with Beans & Legumes in a Type 2 Diabetic Diet?

Effect of legumes as part of a low glycemic index diet on glycemic control and cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial

Jenkins DJ, Kendall CW, Augustin LS, et al. Effect of legumes as part of a low glycemic index diet on glycemic control and cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med*. 2012; 172(21):1653–1660. doi:10.1001/2013.jamainternmed.70

KEY TAKEAWAY: Incorporation of at least one cup of legumes per day in a low glycemic index diet may lead to improvement in glycemic control and decreased risk of cardiovascular death.

STUDY DESIGN: Randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Consideration of incorporating more legumes into a Western diabetic diet or encouraging continued use in a bean eating community diet could provide a glycemic, blood pressure, and cardiovascular advantage for these patients.

PATIENTS: Patients with type 2 diabetes on a stable dose of oral antihyperglycemic agents

INTERVENTION: Legume low glycemic index diet

CONTROL: High wheat fiber diet

OUTCOMES: Change in A1c, total cholesterol, body weight, blood pressure, cardiovascular death risk

METHODS (BRIEF DESCRIPTION):

- Patients with type 2 diabetes with A1c values of 6.5–8.5% on oral antihyperglycemic agents were selected.
- Half were randomized to a legume low-glycemic index diet and the other half to a high wheat fiber diet for 3 months.
- Nutritionists provided instructions for what foods could be used in each group's diet with a focus on at least one cup of legumes in the legume low-glycemic index diet.
- At the end of 3 months, A1c, lipid levels, weight, blood pressures and heart rate were re-measured and CHD risk calculated.

INTERVENTION (# IN THE GROUP): 67 with 60 included in primary analysis

COMPARISON (# IN THE GROUP): 67 with 61 included in primary analysis

FOLLOW UP PERIOD: 3 months

RESULTS:

A legume low glycemic index diet compared to a high wheat fiber diet resulted in a decrease in:

- A1c (–0.5% vs –0.3%; *P*<.001)
- Body weight (–2.7 kg vs –2.0kg; *P*<.001)
- Total cholesterol (–8.0 mg/dL vs –2.0 mg/dL; *P*=.005)
- Systolic BP (mean difference [MD] –4.5 mmHg; 95% CI, –7 to –2.1)
- Diastolic BP (MD –3.1 mmHg; 95% CI, –5.0 to –1.6)
- Calculated absolute CHD risk score (MD –0.8%; 95% CI, –1.4 to –0.3)
- The relative CHD risk was not significant (*P*=.27)

LIMITATIONS:

- The composition of foods can vary greatly and food quantity may be difficult to control and quantify.
- Data dependent on accuracy of patient's self-reporting. Consider possible accidental under or over reporting of values.
- Patients were not blinded to their treatment. Consider bias.

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