GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Automated vs Traditional Office Blood Pressure Readings - Which to Use in the Primary Care Office

Automated vs Traditional Office Blood Pressure Readings: Which to Use in the Primary Care Office

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Comparing Automated Office Blood Pressure Readings with Other Methods of Blood Pressure Measurement for Identifying Patients with Possible Hypertension

Roerecke M, Kaczorowski J, Myers MG. Comparing Automated Office Blood Pressure Readings with Other Methods of Blood Pressure Measurement for Identifying Patients With Possible Hypertension: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2019; 179(3):351–362. doi:10.1001/jamainternmed.2018.6551

KEY TAKEAWAY: Automated office blood pressure (AOBP) measurements used in primary care settings nullify white coat hypertension and are equivalent to awake ambulatory blood pressure (BP) measurements, the current benchmark for predicting cardiovascular disease.

STUDY DESIGN: Systematic review and meta-analysis

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Hypertension increases the risk of multiple diseases, including coronary artery disease, stroke, and kidney disease among others. Therefore, an accurate measurement of blood pressure is critical to providing optimal in-office preventative care. Previously, in-office blood pressure measurement was thought to be mildly affected by "white coat hypertension." Multiple recent studies have shown that the white coat effect was underestimated. Studies have found that AOBP is more accurate than routine office BP measurement. No systematic review has previously been completed on this topic.

PATIENTS: Multinational adults in physician's office and research settings

INTERVENTION: Automated office blood pressure measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP)

CONTROL: Awake ambulatory BP (ABP), routine office BP measurements, and research BP measurements

OUTCOME: Systolic and diastolic blood pressure

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria:
  - Unattended and fully automated AOBP assessments were performed.
  - A sample of at least 30 patients
  - Mean differences were reported between AOBP and other BP measurements, including awake ambulatory blood pressure, office blood pressure, and research blood pressure.
  - Maximum time between BP readings of 1 month
  - Studies that used an interval between AOBP measurements of 2 minutes or less and had 3 readings or more of AOBP.
- A total of 31 studies were included in the systematic review, the majority of which were cross-sectional.
- Sample sizes ranged from 50 to 2,145 adults with a mean age of 55.9 years.
- In half of included studies patients had a mean SBP on AOBP of greater than 130 mmHg.
- Most studies were from Canada, but other high-income countries were also included.

INTERVENTION (# IN THE GROUP): 9,279

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: Less than one month

RESULTS:

- Routine office BP measurements were higher than AOBP (SBP mean difference 14.5 mmHg; 95% CI, 11.8–17.2).
- AOBP was statistically equivalent to ABP (mean difference 0.3 mmHg; 95% CI, –1.1 to 1.7).
- Research BP measurements were higher than AOBP (SBP mean difference 7.0 mmHg; 95% CI, 4.9–9.1).

LIMITATIONS:

- 2 of the 31 included studies declared partial support from a manufacturer.

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The Interest in Apathy: Can Methylphenidate Help in Alzheimer's Disease?

Methylphenidate for Apathy in Community-Dwelling Older Veterans with Mild Alzheimer's Disease: A Double-Blind, Randomized, Placebo-Controlled Trial

Padala PR, Padala KP, Lensing SY, et al. Methylphenidate for Apathy in Community-Dwelling Older Veterans with Mild Alzheimer's Disease: A Double-Blind, Randomized, Placebo-Controlled Trial. *Am J Psychiatry*. 2018; 175(2): 159–168.

KEY TAKEAWAY: At doses of 10 mg twice daily, methylphenidate significantly improved apathy in men with Alzheimer's disease at 3 months; however, it did not significantly improve activities of daily living.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Apathy associated with Alzheimer's disease can lead to functional impairment and higher mortality when untreated. The safety and efficacy of stimulant use in this population is based on limited data.

PATIENTS: Veterans with Alzheimer's disease and apathy

INTERVENTION: Oral methylphenidate up to 10 mg twice daily

CONTROL: Placebo

OUTCOME: Apathy

Secondary Outcomes: Measures of cognition, function, severity, caregiver burden, and depression

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Community-dwelling patients with established Alzheimer's disease who scored ≥18 on the Mini-Mental State Examination (MMSE), >40 on the Apathy Evaluation Scale-Clinician (AES-C), and must have a caregiver at Veteran's Affairs Medical Center
- Randomly assigned to methylphenidate 5 mg twice daily (2 weeks) titrated to 10 mg twice daily thereafter or matching placebo.
- AES-C and secondary measures assessed at baseline and follow-up at 4, 8, and 12 weeks.
  - Apathy: A change of 3.3 points on the AES-C is generally considered a clinically meaningful improvement (scores 18-72).
  - Cognition: 3MS scored 30-100 (higher scores=better cognition)
  - Function: Instrumental activities of daily living scale with scores 0 to 23 (high scores=better function)
  - Caregiver Burden: Zarit Burden Scale consists of 24 questions, with each question ranging 0 to 4 (higher scores=more burden)
  - Depression: Cornell Scale for Depression in Dementia ranging from 0 to 38 (higher scores=worse depression)

INTERVENTION (# IN THE GROUP): 30

COMPARISON (# IN THE GROUP): 29

FOLLOW UP PERIOD: 12 weeks

RESULTS:

Primary Outcome:

- Methylphenidate significantly improved apathy at all three time points compared to placebo (between group difference):
  - 4 weeks: –5.2; 95% CI, –9.0 to –1.5.
  - 8 weeks: –7.2; 95% CI, –10.9 to –3.5.
  - 12 weeks: –9.9; 95% CI, –13.6 to –6.2

Secondary Outcomes:

- Between Group Differences at 12 weeks:
  - Improved cognition (6.1; 95% CI, 2.7–9.6)
  - Improved function (2.3; 95% CI, 0.7–3.9)
  - Less caregiver burden (–5.8; 95% CI, –10 to –1.4)
  - Less depression (–2.5; 95% CI, –4.2 to –0.8)
- Significant increase in systolic blood pressure in the methylphenidate group at 12 weeks (MD 18 mmHg; 95% CI 7.9–29).
- No difference in patient-reported adverse events.

LIMITATIONS:

- All participants were men.
- Single-site with small sample size
- Some secondary outcome measures statistically, but not clinically significant.

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Vitamin E and Thiazolidinediones for the Treatment of NASH in the Diabetic Patient

Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients with Type 2 Diabetes: A Randomized Controlled Trial

Bril F, Biernacki DM, Kalavalapalli S, et al. Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients with Type 2 Diabetes: A Randomized Controlled Trial. *Diabetes Care*. 2019; 42(8):1481–1488. doi:10.2337/dc19-0167

KEY TAKEAWAY: The combination of pioglitazone and vitamin E for treatment of NASH in the diabetic patient is superior to placebo or vitamin E alone based on improved histology.

STUDY DESIGN: Randomized, double blinded placebo controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Lifestyle modification is the mainstay of treatment for patients with nonalcoholic fatty liver disease (NAFLD). There are several compounds (vitamin E, pentoxifylline, pioglitazone, and liraglutide), while not FDA approved for the treatment of NAFLD, have shown benefit in RCTs which exclude patents with diabetes. This proof of concept study aims to investigate the effectiveness of vitamin E alone or in combination with pioglitazone in the treatment of NASH in the diabetic patient.

PATIENTS: Adults with type II diabetes (T2DM) and biopsy proven NASH

INTERVENTION: Vitamin E 400 IU po b.i.d. + placebo; Vitamin E 400 IU po b.i.d. + pioglitazone

CONTROL: Placebo only

OUTCOME: Decrease of ≥2 in NAFLD activity score (NAS) specifically in two separate histological categories and without an increase in fibroids

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from endocrine and hepatology clinics at VA medical centers and randomized into 3 groups.
- 105 patients (primarily male)
- Exclusion criteria: Type 1 diabetes, liver disease of other etiology, 3-fold increase in LFT from normal range, taking medications that worsen NASH or already taking thiazolidinediones, GLP-1 agonists, or SGLT2 inhibitors.
- Patients were asked to keep diet and lifestyle unchanged, and then were educated on diet and exercise interventions.
- Participants were randomized into 1 of 3 groups:
  - Group 1: Vitamin E 400 IU po b.i.d and placebo
  - Group 2: Vitamin E 400 IU po b.i.d. and pioglitazone (started at 30mg po daily and increased to 45mg po daily after 2 months)
  - Group 3: Control group received placebo for both medications.
- Repeat laboratory studies and repeat liver biopsies were performed after 18 months of treatment and evaluated by two separate pathologists who were blinded to patient, treatment group, and prior biopsy results.
- NAS score was calculated by scoring degree of steatosis, lobular inflammation, and ballooning. NAS score was used to evaluate response to treatment or progression on NASH.

INTERVENTION (# IN THE GROUP):

- Vitamin E + Placebo: 36
- Vitamin E + Pioglitazone: 37

COMPARISON (# IN THE GROUP): 32

FOLLOW UP PERIOD: Follow up visits monthly for 4 months and then once every two months for duration of study, total of 18 months.

RESULTS:

- Vitamin E + pioglitazone led to a greater improvement in NAFLD activity score compared to placebo (54% vs 19% respectively, *P*=.003).
- Vitamin E + pioglitazone led to greater resolution of NASH compared to placebo (43% vs 12% respectively, *P*=.005).
- Vitamin E alone led to greater resolution of NASH compared to placebo (33% vs 12% respectively, *P*=.04).
- Vitamin E alone improved Average Stenosis Scores compared to placebo.
- Vitamin E + pioglitazone improved average stenosis, inflammation, and ballooning.
- Neither treatment group improved mean fibrosis scores, but there was an overall downtrend over 18 months in both groups.

- There were no significant reported side effects in vitamin E alone or placebo. In the vitamin E + pioglitazone group the most common side effects were weight gain, edema, and hypoglycemia.

LIMITATIONS:

- Lack of patient diversity (88% male, 72% Caucasian)
- Small sample size (N=105)
- No confidence intervals included in publication.
- The role of pioglitazone alone was not assessed in this study. Therefore, it is difficult to deduce whether the addition of vitamin E to pioglitazone is effective.

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Age of Ultrasound: Can Supplemental Imaging Save the Day for Patients with Increased Breast Density?

Performance of Screening Ultrasonography as an Adjunct to Screening Mammography in Women across the Spectrum of Breast Cancer Risk

Lee JM, Arao RF, Sprague BL, et al. Performance of Screening Ultrasonography as an Adjunct to Screening Mammography in Women across the Spectrum of Breast Cancer Risk. *JAMA Intern Med*. 2019; 179(5):658–667. doi:10.1001/jamainternmed.2018.8372

KEY TAKEAWAY: Women who received screening ultrasound in addition to mammography had a significantly higher short-interval follow up and biopsy recommendation rate, but there was no significant increase in the rate of cancer detection or interval cancer detection compared to screening mammography alone.
STUDY DESIGN: Observational cohort study
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Over 40% of women undergoing breast cancer screening have dense breasts, which may decrease the sensitivity of mammography, thus they often undergo supplemental ultrasound. Prior studies evaluating the efficacy of screening ultrasounds focused on higher risk women with additional breast cancer risks besides breast density.

PATIENTS: Women undergoing breast cancer screening
INTERVENTION: Screening mammography with supplemental ultrasound
CONTROL: Screening mammography alone
OUTCOME: Cancer detection rate, biopsy recommendation rate, false-positive biopsy, sensitivity

METHODS (BRIEF DESCRIPTION):

- Patients either had screening mammography with or without same-day supplemental ultrasound at breast imaging facilities in 1 of 2 Breast Cancer Screening Consortium (BCSC) Registries.
- Exclusion criteria included personal history of breast cancer, unilateral imaging, or self-reported symptoms (besides pain).
- Screening exams from two BCSC Registries during a 13-year period were abstracted and reviewed for indication.
- Reviewed pathology databases, state tumor registries, and regional data for breast cancer diagnoses and tumor type during 13-year period.
- Patients completed questionnaires to provide demographic information and calculate BCSC 5-year risk score.
- Mammography plus ultrasound exams were matched to mammography alone across demographics to create similar groups using propensity score matching.
- Performance measures were calculated and compared between the two groups.

INTERVENTION (# IN THE GROUP): 6,081 supplemental ultrasound exams in 3,386 women
COMPARISON (# IN THE GROUP): 30,062 screening mammograms alone in 15,176 women

FOLLOW UP PERIOD: 12 months or until the next screening examination (whichever occurred earlier)

RESULTS:

- Cancer detection rates per 1,000 screens were similar between supplemental ultrasound and mammography alone.
  - 5.4 in ultrasound group vs 5.5 in mammogram alone (RR 1.1; 95% CI, 0.76–1.7)
- The supplemental ultrasound group had higher rates of biopsy with ultimately benign pathology.
  - 52 per 1,000 in ultrasound group vs 22 per 1,000 in mammogram alone (RR 2.2; 95% CI 1.9–2.6)
- Supplemental ultrasound group had increased sensitivity but the difference was not statistically significant.
  - 79 for ultrasound group vs 74 for mammogram alone (RR 1.1; 95% CI 0.97–1.3)

LIMITATIONS:

- Only 13% of ultrasound reports were abstracted from one registry and authors assumed the rest of the ultrasounds had screening indication.
- There was no standardization of procedure at breast imaging facility, introducing a degree of human error.

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