GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 24 - 28, 2023

SPOTLIGHT: A Drop a Day Keeps the Glasses Away

- ASA for Pre-eclampsia Prophylaxis: Discontinuation of Tx at 24-28 Weeks' Gestation
- Varenicline Increases Smoking Cessation Rates Among African American Daily Smokers
- The Swelling Problem: Diuretic Prescribing Cascade for Gabapentinoid-Induced Edema

A Drop a Day Keeps the Glasses Away

Effect of Low-Concentration Atropine Eyedrops vs Placebo on Myopia Incidence in Children

Yam JC, Zhang XJ, Zhang Y, et al. Effect of Low-Concentration Atropine Eyedrops vs Placebo on Myopia Incidence in Children: The LAMP2 Randomized Clinical Trial. *JAMA*. 2023;329(6):472–481.

KEY TAKEAWAY: Atropine eye drops (0.05% concentration) applied every night can significantly reduce the incidence of myopia and fast myopic shift in children.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Delaying myopia onset can decrease the severity of disease and lead to lifelong improvements in vision. Low-concentration atropine eyedrops have been shown to reduce myopia progression and are a widespread practice in Asia. Previous retrospective studies have suggested that low-concentration atropine may also be helpful in delaying myopia onset. This study aimed to assess the efficacy and safety of low-concentration atropine in delaying myopia onset in children.

PATIENTS: Children aged 4 to 9 years old

INTERVENTION: Atropine eye drops

CONTROL: 0.9% sodium chloride eye drops

PRIMARY OUTCOME: Incidence of myopia and development of fast myopic shift

Secondary Outcome: Changes in spherical equivalent and axial length, time to myopia onset, changes in accommodation amplitude, pupil diameters, visual acuity, and adverse events

METHODS (BRIEF DESCRIPTION):

- The study was conducted at the Chinese University of Hong Kong from July 11, 2017 to June 4, 2022.
- Participants were included in the study if they were children, 4 to 9 years, without myopia, and had at least one parent with myopia. Participants were excluded if they had any ocular disease, had previously used atropine, were using orthokeratology lenses or other optical methods for myopia management, were allergic to atropine, had any systemic disease or developmental abnormalities.
- Participants were randomized to receive 0.05% atropine, 0.01% atropine, or placebo every night in both eyes for two years.
- A baseline eye exam was obtained at the initial visit.
- Participants were scheduled for follow-up visits at two weeks, four, eight, 12, 16, 20, and 24 months after the initial visit. Repeat eye exams were obtained at the subsequent visits.
- Questionnaires evaluating outdoor time and other activities were obtained at the initial visit, and at the 12 and 24-month follow-up.
- Each participant's family was also required to keep a diary to assess medication adherence.
    - A 75% adherence rate (mean use of 5.25 days per week) was considered good adherence. Only participants with good adherence were included in the study.

INTERVENTION (# IN THE GROUP):

- 0.05% atropine: 160
- 0.01% atropine: 159

COMPARISON (# IN THE GROUP): 155

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- 0.05% atropine reduced myopia incidence at two years when compared with placebo (25% difference; 95% CI, 12%–36%).
- 0.05% atropine reduced the percentage of participants with fast myopic shift at two years when compared with placebo (29% difference; 95% CI, 17%–41%).
- 0.05% atropine significantly reduced myopia incidence at two years when compared with 0.01% atropine (18% difference; 95% CI, 5.2%–29%).
- 0.05% atropine reduced the percentage of participants with fast myopic shift at two years when compared with placebo (20% difference; 95% CI, 8.0%–32%).
- There was no significant difference between the 0.01% atropine group and placebo in myopia incidence or percentage of participants with fast myopic shift.

Secondary Outcome –

- 0.05% atropine reduces changes in spherical equivalent and axial length when compared to 0.01% atropine and placebo. This result is not seen when 0.01% atropine is compared to placebo.
- The time to myopia onset was longer in the 0.05% atropine group when compared to the 0.01% atropine group and placebo. There was no difference in time to myopia onset between the 0.01% atropine group and placebo.
- At two years, there was improved accommodation amplitude and increased pupil size in the 0.05% atropine group when compared to the 0.01% atropine group and placebo. There was no difference in accommodation amplitude or pupil size between the 0.01% atropine group and placebo.
- There was no difference between the groups in visual acuity.
- The most common side effect was photophobia.

LIMITATIONS:

- There was potential unmasking due to atropine-induced mydriasis and cycloplegia.
- All participants in the study were Chinese, limiting generalizability to other populations, especially individuals with different iris pigmentation.
- This was a single-center study with a small sample size.
- There was a high participant dropout rate, which could potentially affect the statistical power.
- There was potential for parental recall bias since adherence information was self-reported.

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ASA for Pre-eclampsia Prophylaxis: Discontinuation of Tx at 24–28 Weeks' Gestation

Aspirin Discontinuation at 24 to 28 Weeks' Gestation in Pregnancies at High Risk of Preterm Preeclampsia: A Randomized Clinical Trial

Mendoza M, Bonacina E, Garcia-Manau P, et al. Aspirin Discontinuation at 24 to 28 Weeks' Gestation in Pregnancies at High Risk of Preterm Preeclampsia: A Randomized Clinical Trial. *JAMA*. 2023;329(7):542-550. doi:10.1001/jama.2023.0691

KEY TAKEAWAY: ASA discontinuation at 24–28 weeks' gestation is non-inferior to the continuation of prophylaxis until 36 weeks for preterm preeclampsia prevention in pregnant individuals at high risk of pre-eclampsia with normal sFlt-1:PIGF ratio.

STUDY DESIGN: Multicenter, randomized noninferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Aspirin prophylaxis reduces the incidence of preterm preeclampsia in pregnant women at high risk, but also poses the risk of peripartum bleeding. Few studies have looked at the appropriate time course of aspirin administration to maximize benefits and minimize risks.

PATIENTS: Pregnant individuals at high risk of pre-eclampsia on first-trimester screening with a normal sFlt-1:PIGF ratio between 24–28 weeks' gestation

INTERVENTION: Aspirin discontinuation at 24–48 weeks' gestation

CONTROL: Aspirin continuation until 36 weeks of gestation

PRIMARY OUTCOME: Delivery due to preeclampsia before 37 weeks' gestation

Secondary Outcome: Preeclampsia before 34 weeks' gestation, preeclampsia at or after 37 weeks' gestation, and adverse pregnancy outcomes

METHODS (BRIEF DESCRIPTION):

- The trial was conducted in 9 maternity hospitals in Spain.
  - Participants were pregnant individuals 18 years of age or older with singleton pregnancies of gestational age 24–28 weeks.
  - Participants were high-risk for pre-eclampsia based on first-trimester screening and with a normal sFlt-1:PIGF ratio defined as 38 or less between 24–38 weeks' gestation.
- Race and ethnicity were self-reported.
  - More than 92% of participants were White
  - 3.5% Black
  - 0.40% East Asian
  - 2.2% South Asian
  - 1.9% multiracial/multiethnic
- Participants were randomly assigned 1:1 to the control or the intervention group.
- ASA dose of 150 mg daily was used for prophylaxis starting at 16 weeks and 6 days or earlier.
- Stata Statistical Software was used for randomization sequence and statistical analysis.
- For a noninferiority margin of 1.9%, there was a required sample size of 540 pregnant persons in each group.

INTERVENTION (# IN THE GROUP): 473

COMPARISON (# IN THE GROUP): 463

FOLLOW-UP PERIOD: Delivery

RESULTS:

Primary Outcome –

- Discontinuation of ASA PPX at 24–28 weeks' gestation was non-inferior compared to control for the primary outcome of preeclampsia before 37 weeks.
  - 1.5% in the intervention group vs 1.7% in the control group; absolute difference –0.25%; 95% CI, –1.9% to 1.4%
- There were no significant differences between groups for adverse outcomes with delivery before 37 weeks', 34 weeks', or at or above 37 weeks' gestation.

LIMITATIONS:

- The open-label design is a potential source of bias.
- The study is not adequately powered to assess the effect of aspirin discontinuation in rarer pregnancy complications.
- The study lacks the racial and ethnic diversity needed to generalize results.

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Varenicline Increases Smoking Cessation Rates Among African American Daily Smokers

Effect of Varenicline Added to Counseling on Smoking Cessation Among African American Daily Smokers

Cox LS, Nollen NL, Mayo MS, et al. Effect of Varenicline Added to Counseling on Smoking Cessation Among African American Daily Smokers: The Kick It at Swope IV Randomized Clinical Trial. *JAMA*. 2022;327(22):2201-2209. doi: 10.1001/jama.2022.8274

KEY TAKEAWAY: Varenicline plus counseling results in greater smoking cessation at 26 weeks versus counseling alone among self-identified African American and Black smokers.

STUDY DESIGN: Double-blind, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: African Americans have some of the highest rates of tobacco-attributable morbidity and mortality in the US. This study demonstrates that there is an effective method to help avoid the morbidity and mortality of tobacco use through cessation.

PATIENTS: African American adults who smoke daily

INTERVENTION: Counseling plus 12 weeks of Varenicline

CONTROL: Counseling plus 12 weeks of placebo

PRIMARY OUTCOME: Biomarkers of tobacco use at week 26 post-intervention

Secondary Outcome: Abstinence at the end of week 12

METHODS (BRIEF DESCRIPTION):

- Self-identifying African American or Black adults who smoke daily were invited to participate. The participants resided in the Kansas City, Missouri metropolitan area.
- Patients with an allergy to Varenicline or use of cessation products in the past month, and patients with serious psychiatric illness were excluded.
- Participants were randomized to take Varenicline or placebo, and medication and allocation were blinded to patients and staff.
- Participants took 0.5 mg once daily for three days, followed by 0.5 mg twice daily for four days, and finally one mg twice daily for the remaining 11 weeks of Varenicline which is the current dosage recommendation.
- Participants completed self-assessments during the study including National Cancer Institute's Common Toxicity Criteria for Adverse Events for reporting adverse events of medication.
- Medication adherence was defined as greater than or equal to 80% self–reported compliance (i.e., taking medication 8 out of the last 10 days).
- On day 0, the patient's blood cotinine levels (a predominant metabolite of nicotine) were collected.
- Abstinence was defined throughout the study as self-report, and salivary cotinine levels less than or equal to 15 ng/mL which were checked at weeks four, 12, 16, and 26.
- Every participant took part in six sessions of cognitive behavioral counseling, the frequency of which was at weeks 0, one, four, eight, 12, and 16. The content was standardized and followed tobacco treatment guidelines.

INTERVENTION (# IN THE GROUP): 300

COMPARISON (# IN THE GROUP): 200

FOLLOW-UP PERIOD: 26 weeks

RESULTS:

Primary Outcome –

- Varenicline plus counseling significantly increased abstinence rates versus placebo plus counseling at week 26 (15.7% vs. 6.5%, respectively; difference 9.2%; 95% CI, 3.8%–15%).
    - All of the participants that were counted in the abstinence group had saliva cotinine levels less than or equal to 15 ng/mL.

Secondary Outcome –

- Varenicline plus counseling significantly increased abstinence rates at week 12 post-intervention compared to placebo plus counseling (18.7% vs 7.0%, respectively; difference 11.7%; 95% CI, 6.0%–18%).

LIMITATIONS:

- Single-center intervention may limit generalizability.
- There was insufficient power to assess differences between subsets of light and heavy smokers, which does not help us understand if Varenicline is more or less effective based on how many cigarettes a person smokes per day.
- This study was restricted to those without major psychiatric conditions which limits the study as

there are many patients who have psychiatric conditions and also consume cigarettes.

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The Swelling Problem: Diuretic Prescribing Cascade for Gabapentinoid-Induced Edema

Evidence of a Gabapentinoid and Diuretic Prescribing Cascade among Older Adults with Lower Back Pain

Read SH, Giannakeas V, Pop P, et al. Evidence of a gabapentinoid and diuretic prescribing cascade among older adults with lower back pain. *J Am Geriatr Soc*. 2021;69(10):2842-2850. doi:10.1111/jgs.17312

KEY TAKEAWAY: Among older adults, gabapentinoid use in the setting of low back pain was associated with increased subsequent diuretic use.

STUDY DESIGN: Population-based, retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Gabapentinoids (such as pregabalin and gabapentin) are often prescribed off-label to treat low back pain. In 2018 gabapentin was the sixth most commonly prescribed medication in the United States; its use has increased 3-fold between 2002 and 2015. Between 2 and 16% of patients using gabapentinoids may experience peripheral edema, leading to a prescription cascade including diuretics.

PATIENTS: Older adults with low back pain

INTERVENTION: Gabapentinoid prescription

CONTROL: No gabapentinoid prescription

PRIMARY OUTCOME: Diuretic prescription within 90

Secondary Outcome: Diuretic prescription at 180 days

METHODS (BRIEF DESCRIPTION):

- Study was a retrospective cohort study using administrative health data from Ontario, Canada.
- The observation period was from April 2011 to March 2019.
- Eligible participants included adults between the ages of 66-110 with a recent diagnosis with low back pain (including lumbar strain, lumbago, coccydynia, or sciatica) but no prior history of low back pain in the preceding year.
- Exclusion criteria included epilepsy, prescription NSAID use, end-stage renal disease, heart failure, and hepatic failure.
- Both the gabapentinoid and non-gabapentinoid groups had a mean age of 74 years, were 59% (gabapentinoid) vs 55% (non-gabapentinoid) female, and utilized 7-8 distinct medications in the year prior.
- Participants were classified between those who were dispensed a gabapentinoid within one week of diagnosis and those who were not.
- The incidence of subsequent diuretic prescription was calculated for both groups at 90 and 180 days.
- Researchers further examined a gabapentinoid dose-response effect comparing low, maintenance, or high gabapentinoid dosages against non-gabapentinoid users.

INTERVENTION (# IN THE GROUP): 7,867

COMPARISON (# IN THE GROUP): 252,477

FOLLOW-UP PERIOD: 180 days

RESULTS:

Primary Outcome –

- Gabapentinoid users at any dose had an increased risk of being prescribed diuretics within 90 days of treatment (adjusted hazard ratio (aHR) of 1.4; 95% CI, 1.2–1.7) as compared to those without a prescription.

Secondary Outcome –

- Gabapentinoid users at any dose had an increased risk of being prescribed diuretics within 180 days of treatment (aHR 1.3; 95% CI, 1.1–1.4).
- Older adults prescribed a high-dose gabapentinoids had a significantly higher risk of diuretic use within 180 days (aHR 2.3; 95% CI, 1.2–4.7) as compared to those without a gabapentinoid prescription.

LIMITATIONS:

- Although patients with common indications for diuretic prescription were excluded, subsequent diuretic prescriptions may have had indications outside of gabapentinoid-induced edema.
- NSAIDs are known to cause edema; prescription NSAID use was included in the exclusion criteria, but over-the-counter NSAID use was not.

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