GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Is It Worth Implementing Vestibular Rehabilitation to Improve Balance and Gait in Patients After Stroke?

Is It Worth Implementing Vestibular Rehabilitation to Improve Balance and Gait in Patients After Stroke?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Vestibular Rehabilitation Therapy on Balance and Gait in Patients After Stroke: A Systematic Review and Meta-Analysis

Meng L, Liang Q, Yuan J, et al. Vestibular rehabilitation therapy on balance and gait in patients after stroke: a systematic review and meta-analysis. BMC Med. 2023;21(1):322. Published 2023 Aug 25. doi:10.1186/s12916-023-03029-9

KEY TAKEAWAY: There may be a positive benefit to using vestibular rehabilitation therapy (VRT) for improving balance and gait in patients after a stroke occurring within six months.

STUDY DESIGN: Systemic review and meta-analysis of 15 randomized controlled trials (N=769)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Patients with varying degrees of stroke can develop significant balance and gait impairment. Most patients undergo usual rehabilitation alone, however, the addition of vestibular rehabilitation therapy may be beneficial in restoring gait and balance function if implemented within six months of onset. Previous systematic reviews did not include meta-analysis and had low certainty of evidence.

PATIENTS: Individuals diagnosed with stroke with verified impaired balance and gait

INTERVENTION: VRT and usual rehabilitation (UR)

CONTROL: UR treatment only

PRIMARY OUTCOME: Improved balance and gait

METHODS (BRIEF DESCRIPTION):

- The 15 randomized controlled trials were selected if the patient had verified impaired balance and gait due to a stroke.
- Verified computerized databases and expert reviewers performed study selection and data extraction.
- VRT included at least one of the following training techniques; eye-head movement, head movement, vestibular stimulation, specific exercises to enhance vestibular function, or gaze stability exercises.
- Patients were grouped into VRT and UR vs UR alone
- Balance was assessed using different scales such as the Postural Assessment Scale, Activities-specific Balance Confidence, and Berg Balance Scale (BBS), a 14-item scale that ranges from 0–56 and is based on what balance-based task the patient can execute.
- Gait was assessed by using timed up and go (TUG), 10 m walking test, dynamic gait index, functional gait assessment, and gait parameters.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- VRT with UR improved balance compared to UR alone (standard mean difference [SMD] 0.59; 95% CI, 0.40–0.78).
- Four weeks of VRT with UR improved balance more than less than four weeks of VRT with UR (SMD 0.64%; 95% CI, 0.40–0.89).
- Less than four weeks of VRT with UR improved gait more than UR alone (mean difference [MD] –4.7; 95% CI, –7.2 to –2.3).
- VRT with UR improved step length on the affected side more than UR alone (MD 2.3; 95% CI, 1.1–3.5).

LIMITATIONS:

- Lack of allocation blinding in the trials introduced bias
- The effectiveness of VRT in patients with a duration of onset of stroke beyond six months could not be assessed because there's a lack of data synthesis for gait and balance measures.
- One of the authors for a potentially eligible trial could not be reached for raw data

Joshua Wheatley, MD
Ocean Medical Center FMRP
Brick, NJ

Does OMT Decrease Dizziness?

Impact of Osteopathic Manipulative Techniques on the Management of Dizziness Caused by Neuro-Otologic Disorders: Systematic Review and Meta-Analysis

Rehman Y, Kirsch J, Wang MY, et al. Impact of osteopathic manipulative techniques on the management of dizziness caused by neuro-otologic disorders: systematic review and meta-analysis. *J Osteopath Med.* 2022;123(2):91-101. Published 2022 Oct 12. doi:10.1515/jom-2022-0119

KEY TAKEAWAY: Osteopathic manipulative techniques (OMT) moderately reduce disability associated with dizziness, dizziness frequency, and dizziness severity.

STUDY DESIGN: Systemic review and meta-analysis of 11 randomized control studies and one observational study (N=367)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to lack of dizziness standardization between studies)

BRIEF BACKGROUND INFORMATION: OMT has been used to treat neuro-otologic disorders that cause dizziness. This is the first study that compares OMT as a treatment to other comparative interventions. This is important because in the U.S. there is a cost of loss of productivity in the workforce of an estimated $23 billion annually due to dizziness.

PATIENTS: Adults with dizziness

INTERVENTION: OMT

CONTROL: Sham manipulation or standard of care treatment

PRIMARY OUTCOME: Disability associated with dizziness, dizziness severity, dizziness frequency, risk of fall, improved quality of life (QOL), return to work (RTW)

METHODS (BRIEF DESCRIPTION):

- Adult patients >18 years old experiencing dizziness from neuro-otologic disorders
- OMT interventions included:
  - Four studies on multiple OMT techniques
  - Four studies on articular OMT
  - Two studies on high-velocity, low-amplitude (HVLA) techniques
  - One study on osteopathic cranial manipulation
  - One study on progressive inhibition of neuromuscular structures
- OMT analogue techniques in six studies
- Comparison interventions included:
  - Five studies used sham treatment
  - Three studies used control treatment
  - Two studies used pharmacologic agents
  - One study used counseling
  - One study had four arms
    - OMT vs vestibular rehabilitation
    - OMT with vestibular rehabilitation
    - No intervention
- Disability associated with dizziness was scored using the Dizziness Handicap Inventory score. Scores range from 0–100, with a higher score indicating more severe disability.
- Dizziness severity was based on a converted scale from 0–10.
- Dizziness frequency was based on a converted scale from 0–5.
- The risk of fall was evaluated in three studies.
- Quality of life was evaluated with a physical component summary (PCS) and mental component summary (MCS) using a 36-item short-form health survey.
- No study incorporated return to work.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable

RESULTS:

Primary Outcome –

- Articular OMT techniques were associated with decreased disability compared to sham treatment:
  - Associated with dizziness (mean difference [MD] –11; 95% CI, −16 to –5.9)
  - Dizziness severity (MD −1.6; 95% CI,−2.4 to −0.7)
  - Dizziness frequency (MD −0.6; 95% CI, −1.1 to −0.2)

LIMITATIONS:

- None of the studies met all risk of bias criteria.
- Small sample sizes
- High dropout rates
- Studies lacked power.
- Not all studies accounted for missing data.
- Each study did not define dizziness in the same way.
- The same technique was not used in each study.

- Some studies also used medicine.
- Different scales for different studies
- Unable to directly compare with common interventions

Lisa Kassenoff, DO
Ocean Medical Center FMRP
Brick, NJ

Gout Wars: Allopurinol vs Febuxostat - A Critical Review

Comparative Effectiveness of Allopurinol and Febuxostat in Gout Management

O'Dell JR, Brophy MT, Pillinger MH, et al. Comparative Effectiveness of Allopurinol and Febuxostat in Gout Management [published correction appears in NEJM Evid. 2022 Jul;1(7):EVIDx2200150] [published correction appears in NEJM Evid. 2022 Aug;1(8):EVIDx2200180]. *NEJM Evid*. 2022;1(3):10.1056/evidoa2100028. doi:10.1056/evidoa2100028

KEY TAKEAWAY: Both allopurinol and febuxostat are similarly effective in managing gout, with allopurinol showing noninferiority to febuxostat in controlling flares and achieving target serum urate levels.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: This study investigates the comparative effectiveness of allopurinol and febuxostat in managing gout, a common inflammatory arthritis caused by elevated uric acid levels. Both medications are widely used to lower uric acid levels, but their relative efficacy and safety profiles in gout management have not been extensively studied. This trial aims to fill the gap by comparing the ability of allopurinol and febuxostat to control flares and achieve target serum urate levels in patients with gout and hyperuricemia, including those with stage three chronic kidney disease (CKD).

PATIENTS: Patients with gout and hyperuricemia

INTERVENTION: Allopurinol treatment titrated to a target serum urate level

CONTROL: Febuxostat treatment titrated to a target serum urate level

PRIMARY OUTCOME: Proportion of patients experiencing one or more gout flares during phase three of the trial

Secondary Outcome: Efficacy in patients with chronic kidney disease, the proportion achieving the predefined serum urate goal at the end of phase two, serious adverse events

METHODS (BRIEF DESCRIPTION):

- The study population consisted of adults previously diagnosed with gout and hyperuricemia (>6.8 mg/dl). The mean age of participants was 62 years old, predominantly male (98%) and White (68%). Of the included participants, at least 33% of participants had stage three chronic kidney disease.
- Comorbidities were similar in both study groups and consisted of hypertension, CKD, diabetes, and cardiovascular disease.
- The mean disease duration was 10 years with tophi present in 16%.
- The treatment protocol consisted of three phases: Urate-lowering therapy titration (weeks 0–24), maintenance (weeks 25–48), and observation (weeks 49–72).
- Participants were initiated on allopurinol or febuxostat at daily doses of 100 mg and 40 mg, respectively.
- Therapies titrated until achieving serum urate levels below 6.0 mg/dl (or below 5.0 mg/dl if tophi were present) or reaching maximum doses of 800 mg for allopurinol and 120 mg for febuxostat.
- Anti-inflammatory prophylaxis with colchicine, nonsteroidal anti-inflammatory drugs, or glucocorticoids was administered during phases one and two.
- Treatment dose adjustments are permitted until week 33 to achieve the serum urate goal.
- In phase three, no study drug dose adjustments were allowed, and prophylactic anti-inflammatory treatments were discontinued, though they could be restarted in case of a gout flare.
- The proportion of participants experiencing one or more gout flares during phase three was measured as the primary outcome.
    - Definition of gout flare (3 of 4):
        - Warm joint(s)
        - Swollen joint(s)
        - Pain (≥3) at rest on a scale of 0–10
        - Self-identified gout flare
    - Or reported use of standard anti-inflammatory medications
    - Collected via patient diaries, questionnaires, and/or phone visits every six weeks.
- The secondary outcome was measured as:

- Efficacy in patients with CKD was assessed based on serum urate levels, flare frequency, and side-effect profiles.
- The proportion achieving target serum urate levels was determined during phase two of the trial.
- Serious adverse events were monitored throughout the trial, including acute kidney injury as per KDIGO criteria (50% increase in serum creatinine or increase of 0.3 mg/dl from baseline in a 48-hour period).

INTERVENTION (# IN THE GROUP): 468 (367 completed)
COMPARISON (# IN THE GROUP): 472 (373 completed)

FOLLOW-UP PERIOD: 72 weeks

RESULTS:

Primary Outcome –

- Allopurinol decreased gout flares compared to febuxostat (37% vs 44%, respectively; p<.001)

Secondary Outcome –

- No significant difference was observed between allopurinol and febuxostat groups in terms of serum urate levels and flare frequency.
- 80% of participants achieved the predefined serum urate goal by the end of phase two, with no significant difference between treatment groups.
- No significant difference detected in the occurrence of serious adverse events between the allopurinol and febuxostat groups.

LIMITATIONS:

- The study primarily enrolled older White men, potentially limiting generalizability to more diverse populations, including women and individuals of other racial or ethnic backgrounds.
- Some gout flare information was obtained via phone visits, possibly introducing subjectivity in evaluating joint warmth or swelling, and reliance on patient-reported symptoms may have led to variability in flare assessment.
- The use of patient-reported "gout flare" and pain scales to define gout flares introduces variability in reporting, potentially affecting the accuracy of flare assessment.
- With a study duration limited to 72 weeks, longer-term outcomes beyond this period were not evaluated, potentially impacting the assessment of sustained efficacy and safety of the interventions.
- The trial experienced interruptions due to changes in febuxostat dosages mandated by FDA warnings, leading to adjustments in the maximum allowable daily dose from 120 mg to 80 mg, which may have affected treatment consistency.
- Disruptions caused by the COVID-19 pandemic, particularly in the later stages of in-person data collection, could have influenced participant adherence, data quality, and study outcomes despite efforts to mitigate these interruptions.

Matthew Spence, MD
Cahaba Medical Care FMR
Birmingham, AL

Inhalers as Dual Maintenance and Reliever Therapy: More Applications Than Asthma?

Budesonide/Formoterol Maintenance and Reliever Therapy Versus Fluticasone/Salmeterol Fixed-Dose Treatment in Patients with COPD

Muiser S, Imkamp K, Seigers D, et al. Budesonide/formoterol maintenance and reliever therapy versus fluticasone/salmeterol fixed-dose treatment in patients with COPD. *Thorax*. 2023;78(5):451-458. doi:10.1136/thorax-2022-219620

KEY TAKEAWAY: In patients with moderate to severe chronic obstructive pulmonary disease (COPD), budesonide/formoterol used as maintenance and reliever therapy (MART) might be similarly effective and safe as fluticasone/salmeterol fixed-dose therapy, at a considerably lower daily dosage of inhaled corticoidsteroids (ICS).

STUDY DESIGN: Open-label, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The mainstay of COPD treatment is the use of long-acting beta-2-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and ICS. Symptom-driven MART is a frequently used treatment strategy in asthma, having been shown to reduce the number of severe asthma exacerbations when compared with the same or higher dose of a fixed combination ICS/LABA plus as-needed short-acting beta-2-agonists (SABA). Improvements in lung function and symptoms have been observed with MART. No studies have investigated the efficacy and safety of ICS/formoterol MART in patients with COPD.

PATIENTS: Patients with a clinical diagnosis of COPD

INTERVENTION: Budesonide/formoterol used as MART

CONTROL: Fixed-dose fluticasone/salmeterol combination (FSC)

PRIMARY OUTCOME: Moderate to severe COPD exacerbations

Secondary Outcome: Average daily ICS exposure, as-needed medication use, improvement in pulmonary function test (PFT)

METHODS (BRIEF DESCRIPTION):

- COPD patients 40–80 years old with a postbronchodilator FEV1 <80% predicted, smoking history of ≥10 pack-years, and a history of at least one COPD exacerbation in the last two years were included in the study.
- Patients with a history of asthma were excluded.
- Patients were randomized to one of the following treatments:
  - Budesonide/formoterol (200/6 ug metered dose) two inhalations twice daily plus additional inhalations as needed.
  - Fixed-dose fluticasone/salmeterol (500/50 ug dry powder) one inhalation twice daily, plus salbutamol 100 µg as needed.
- The primary outcome of the number of moderate and severe COPD exacerbations was measured if patients presented to the study center or other health center meeting the following criteria:
  - Moderate exacerbation: Increase in dyspnea, cough, and sputum production for which prednisolone or antibiotics were given and absence of pneumonia diagnosis.
  - Severe exacerbation: Hospital admission required or result in death.
- Secondary outcomes were measured as follows:
  - Average daily ICS exposure: Inhaler use was self-documented by participants with a diary which they were instructed to use twice daily. In addition, pharmacy data such as the number of inhalers dispensed and the amount of medicine remaining in the inhaler upon return to the pharmacy were utilized in measurement.
  - As-needed medication use: Inhaler use was self-documented by participants with a diary which they were instructed to use twice daily.
  - PFTs and eosinophil level: Baseline PFTs and eosinophil levels were measured before study initiation. Changes from baseline values were reported in the study, though it is not explicitly stated in the paper exactly when or how the baseline and post-experiment values were obtained.

INTERVENTION (# IN THE GROUP): 103

COMPARISON (# IN THE GROUP): 92

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- Participants in the budesonide/formoterol MART arm demonstrated no significant difference from those in the fixed-dose arm for moderate/severe COPD exacerbation rates (1.3 exacerbations/patient-year; rate ratio [RR] 1.1; 95% CI, 0.79–1.4).
- Both groups demonstrated no significant difference in moderate COPD exacerbation rate (1.2 vs 1.2 exacerbations/patient-year, *p*=.963) or severe COPD exacerbation rate (0.15 vs 0.14 exacerbations/patient-year, *p*=.936) separately.

Secondary Outcome –

- Participants in the budesonide/formoterol MART arm had lower ICS exposure compared to those in the fixed-dose arm (928 ug/day vs 1747 ug/day, *p*<0.001)
- The two groups demonstrated no significant difference in terms of as-needed medication frequency per day.
- There was no significant difference in terms of PFTs, though it is noted that the MART group demonstrated near statistically significant improvement from baseline of RV/TLC when compared to the fixed-dose group (–3.6%, *p*=.053)
- Due to the low sample size, no formal statistical analyses were performed regarding blood eosinophil levels.

LIMITATIONS:

- Subjective nature of moderate exacerbation criteria
- Absence of analysis of increased pneumonia rate in the MART group
- Loss of funding part-way through the study led to a smaller sample size than expected.
- Lack of analysis for eosinophilia
- Unclear methods regarding PFT and lab testing.
- Self-reported patient data for as-needed medication use. Difficulty in maintaining a diary when hospitalized.
- A large number of participants were lost to follow-up (30% in the MART group, 37% in the fixed-dose group)

Brian Lin, MD
Medstar Georgetown/Washinton Hospital Center FMRP
Washington, DC

Labor of Love: Oxytocin's Exit Strategy and Neonatal Morbidity

Impact of Discontinuing Oxytocin in Active Labor on Neonatal Morbidity: An Open-Label, Multicenter, Randomized Trial

Girault A, Sentilhes L, Desbrière R, et al. Impact of discontinuing oxytocin in active labor on neonatal morbidity: an open-label, multicentre, randomized trial [published correction appears in Lancet. 2024 Feb 3;403(10425):438]. *Lancet*. 2023;402(10417):2091-2100. doi:10.1016/S0140-6736(23)01803-2

KEY TAKEAWAY: Compared with continuous oxytocin, discontinuing oxytocin upon reaching active labor does not reduce neonatal morbidity among patients receiving oxytocin in early labor.

STUDY DESIGN: Large, multicenter, randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Oxytocin is frequently used in labor induction and augmentation to enhance the frequency and intensity of uterine contractions, thereby reducing the duration of labor. However, excessive uterine contractions induced by oxytocin (tachysystole) can result in non-reassuring fetal heart tracings and lead to neonatal acidosis, contributing to neonatal morbidity. Discontinuing oxytocin upon reaching active labor could potentially mitigate neonatal morbidity.

PATIENTS: Pregnant women

INTERVENTION: Discontinuation of oxytocin upon active labor

CONTROL: Continous oxytocin

PRIMARY OUTCOME: Neonatal morbidity

Secondary Outcome: Neonatal and delivery characteristics and maternal well-being

METHODS (BRIEF DESCRIPTION):

- RCT was conducted at 21 sites in France.
- Participants were 28–35 years old (mean 32 years old), with a mean BMI of 24 kg/m^2, and approximately 50% were nulliparous.
- Pregnant women ≥18 years old, with cephalic singleton pregnancies (≥37 weeks), and oxytocin received before 4 cm of cervical dilation, regardless of labor onset method were included in the study.
- Individuals with a uterine scar, fetal abnormalities, abnormal fetal heart rate, and lack of medical insurance were excluded from the study.
- Patients were randomly assigned in a 1:1 ratio to either:
  - Discontinuous oxytocin: Oxytocin was stopped beyond 6 cm dilation, restarting after two hours if necessary.
  - Continuous oxytocin: Oxytocin was continued during the active phase and second stage of labor, with cessation if needed due to abnormal fetal heart rate or uterine tachysystole
- Oxytocin administration adhered to national guidelines, involving low-dose oxytocin infusion of less than 4 mUI/min with increments every 30 minutes, ensuring that the flow rate did not exceed 20 mUI/min.
- The primary outcome was neonatal morbidity, defined as a composite variable comprising umbilical arterial pH <7.1, base excess >10 mmol/L, umbilical arterial lactates >7 mmol/L, five-min Apgar score <7, or admission to the neonatal intensive care unit.
- Secondary outcomes were measured as:
  - Neonatal and delivery characteristics were measured using neonatal pre-acidosis, acidosis severity, other neonatal complications (hypoxia), mode of delivery, labor characteristics, maternal fever, postpartum hemorrhage, uterine tachysystole, oxytocin doses, and reasons for treatment discontinuation/resumption.
  - Maternal well-being was assessed based on women's experiences, which were measured postpartum using the Labor Agentry Scale (LAS) at day two. Scores range from 29–203, with higher scores indicating a greater sense of control during the birthing process.
  - Maternal well-being was further assessed at two months using the Edinburgh Postnatal Depression Scale (EPDS). Scores range from 0–30 with a score >12 indicating a higher likelihood of experiencing depressive symptoms.

INTERVENTION (# IN THE GROUP): 1,067

COMPARISON (# IN THE GROUP): 1,103

FOLLOW-UP PERIOD: Two months

RESULTS:

Primary Outcome –

- There was no difference in neonatal morbidity between the discontinuous and continuous oxytocin groups (9.6% vs 9.2%, respectively; relative risk [RR] 1.0; 95% CI, 0.8–1.4).

Secondary Outcome –

- There were no significant differences in neonatal and delivery characteristics and maternal well-being between the two groups.

LIMITATIONS:

- Nonblinded treatment team
- Limited generalizability

Ulysses Fernandez-Miro, DO
St. Louis University Southwest Illinois FMR
O'Fallon, IL