GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: A New Prophylactic Agent Against Influenza in Household Contacts

A New Prophylactic Agent Against Influenza in Household Contacts

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts

Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts. *N Engl J Med*. 2020 Jul 23; 383(4):309–320. doi:10.1056/NEJMoa1915341. Epub 2020 Jul 8.

KEY TAKEAWAY: Baloxavir marboxil (baloxavir) prevents influenza A in patients exposed to an infected household contact.

STUDY DESIGN: Randomized, placebo controlled clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Influenza is highly transmissible between individuals within a household. Baloxavir is an effective influenza treatment, but efficacy as pre-exposure prophylaxis is unknown.

PATIENTS: Asymptomatic household contacts
INTERVENTION: Single dose of baloxavir
CONTROL: Placebo
OUTCOME: Positive influenza test, fever, and one other respiratory symptom
Secondary Outcome – Positive PCR with fever, positive PCR test, asymptomatic infection, or other illness; adverse events

METHODS (BRIEF DESCRIPTION):

- Study conducted in Japanese primary care clinics between November 2018 and March 2019.
- 545 Index Patients: Diagnosed with influenza by RT-PCR test
  - 74% were less than twelve years old.
  - 96% had influenza A.
  - Index patients received an antiretroviral treatment.
- 752 Participants: Asymptomatic, lived with index patients for at least 48 hours, and tested negative before treatment
  - 19% less than 12 years old and 3% over 65 years old
  - 13% high risk and 66% unvaccinated against influenza
  - 7% tested positive for influenza before first dose.
  - Participants received a single dose of baloxavir within 24 hours of index patient's diagnosis.
- Nasopharyngeal swabs were completed before dose, on day 5 (± 2), and day 11 (± 2).
- Primary End Point: Positive swab for influenza, fever, and one other respiratory symptom during days 1–10.
- Secondary End Point: Positive PCR with elevated body temperature (at least 37.5 degrees), positive PCR regardless of symptoms, asymptomatic infection, or any other symptoms or illness.
  - Other secondary end points were adverse events.
  - Monitored temperature and URI symptoms were rated on a 4-point scale as none, mild, moderate, or severe.

INTERVENTION (# IN THE GROUP): 374
COMPARISON (# IN THE GROUP): 375

FOLLOW UP PERIOD: 10 days

RESULTS:

- Baloxavir protected against influenza infection in participants with household contact with influenza compared to placebo (1.9% vs 14%, respectively; RR 0.14; 95% CI, 0.06–0.3; NNT=9).
- Baloxavir may delay influenza protection, where 46 of the 51 participants in the placebo group who tested positive for influenza, were positive before day 5 and all seven of the infected individuals in the baloxavir group tested positive after day 5.
- Adverse reactions were observed in 22% of treatment group patients compared to 21% of placebo group patients.
  - The most common adverse reactions were headache, hematuria, pharyngitis, and ALT increase.
- Authors reported similar efficacy to oseltamivir, but numerical and statistical results were not provided.

LIMITATIONS:

- The drug sponsor employed the statistician.
- The efficacy against Influenza B was not tested.
- There was no significant change during influenza (about 1 day) and resulted in some new resistant viral strains.
- Follow up samples to adequately assess resistant viral strains were not collected.

- The product is more expensive than oseltamivir ($90–$185 vs $14–$18).
- The drug was not studied as a prophylaxis outside of household contacts.

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Donanemab an Option for Dementia?

Donanemab in Early Alzheimer's Disease

Mintun MA, Lo AC, Duggan EC, et al. Donanemab in Early Alzheimer's Disease. *N Engl J Med*. 2021; 384(18):1691–1704.

KEY TAKEAWAY: Donanemab for the treatment of Alzheimer's dementia results in less of a decline in cognition impairment and activities of daily living than no treatment; however, additional research is needed to understand clinical efficacy and disease progression.

STUDY DESIGN: Multisite, placebo controlled, double blinded trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Alzheimer's disease is highly associated with accumulated amyloid beta peptide. Donanemab is an antibody that targets deposition of amyloid beta epitope and is being studied as a method to slow or halt Alzheimer's disease. This phase 2 trial evaluates efficacy and safety of Donanemab in early Alzheimer's disease.

PATIENTS: Elderly patients with early symptomatic Alzheimer's disease

INTERVENTION: Donanemab

CONTROL: IV placebo

OUTCOME: Cognition and physical function

Secondary Outcomes: Dementia severity and biomarker amyloid burden

METHODS (BRIEF DESCRIPTION):

- Patients 60–85 years old from 56 sites in US and Canada met diagnostic criteria for Alzheimer's disease.
  - The mean age was 75 years old.
  - Participants had early dementia.
  - Patients with SUVR (measurement of PET scan tau protein) >1.5 (advanced disease) and <1.1 (no disease) were excluded.
- Treatment Group: 700 mg IV Donanemab every 4 weeks for the first three doses, then 1,400 mg IV Donanemab every 4 weeks for 72 weeks.
  - Comparison group received matching placebo.
- Cognitive impairment and activities of daily living were measured via iADRS (0–144 lower levels indicating more cognitive impairment) every 12 weeks.
- Dementia severity was measured via CDR-SB (0–18 with higher scores indicating more impairment) every 12 weeks.
- Amyloid plaque levels were measured by PET scan in centiloids every 12 weeks.

INTERVENTION (# IN THE GROUP): 131

COMPARISON (# IN THE GROUP): 126

FOLLOW UP PERIOD: 72 weeks of treatment and follow-up at 76 weeks

RESULTS:

Primary Outcome –

- At 76 weeks, the treatment group had less cognition and activities of daily living deficits than the placebo group (–6.9 vs –10, respectively; MD –3.2; 95% CI, –0.12 to –6.3).

Secondary Outcomes –

- At 76 weeks, the treatment group had no clinical difference in dementia severity compared to the placebo group (1.2 vs 1.6, respectively; MD –0.36; 95% CI –0.83 to 0.12).
- At 76 weeks, the treatment group had greater reduction in amyloid plaque level than the placebo group (–84 vs 0.93, respectively; MD –85; 95% CI, –93 to –77).

LIMITATIONS:

- Funded by drug manufacturer.
- Lack of diversity with few non-White participants.
- Incidence of trial discontinuation higher in treatment than control.
- Minimum clinical score of iADRS to show effectiveness is undetermined.

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Don't Forget: Pimavanserin for Dementia-Related Psychosis

Trial of Pimavanserin in Dementia-Related Psychosis
Tariot PN, Cummings JL, Soto-Martin ME, et al. Trial of Pimavanserin in Dementia-Related Psychosis. *N Engl J Med*. 2021; 385(4):309–319.

KEY TAKEAWAY: Dementia patients maintaining Pimavanserin treatment were less likely to have a psychosis relapse than those who were discontinued from the medication.
STUDY DESIGN: Multisite, double blind randomized, placebo controlled, discontinuation trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with dementia often suffer from psychosis and providers prescribe antipsychotics to control their symptoms; however, these medications have many serious adverse side effects. Trials on Pimavanserin reveal decreased psychosis in patients with Parkinson's and Alzheimer's dementias. This study reports a phase III trial evaluating patients treated with Pimavaserin and rates of psychosis relapse when medication was discontinued.

PATIENTS: Adults with dementia and psychotic symptoms
INTERVENTION: Pimavanserin treatment throughout trial
CONTROL: Pimavanserin treatment then switched to placebo
OUTCOME: Relapse of psychosis
Secondary Outcome: Discontinuation of trial

METHODS (BRIEF DESCRIPTION):
- Patients were 50–90 years old and met criteria for dementia.
  - Included dementias: Parkinson's, Lewy body dementia, Frontotemporal dementia, Vascular, and Alzheimer's
  - The mean age was 75 years old.
- For 12 weeks, all patients received oral, daily, 20 or 32 mg Pimavanserin. For the next 25 weeks, the treatment group continued Pimavanserin while the control group was switched to placebo.
- Outcomes were evaluated every 2–4 weeks at clinic visits.
- Researchers assessed outcomes of relapse by meeting one or more criteria:
  - Increase in psychosis, measured by a SAPS-H+D increase of 30% (scale 0 to 10 with higher score indicating greater psychosis).
  - Increase in psychosis and impairment measured by CGI- score of 6 or 7 (scaled score 1 to 7 with higher score representing higher degree of psychosis and impairment).
  - Hospitalization due to dementia related psychosis.
  - Stopping the medication or trial withdrawal.
- Statistical analysis of primary and secondary outcome was done with hazard ratio with alpha level of 0.05.

INTERVENTION (# IN THE GROUP): 83
COMPARISON (# IN THE GROUP): 71

FOLLOW UP PERIOD: Median 18 weeks after initial 12 weeks

RESULTS:
Primary Outcome –
- Patients who continued Pimavanserin had significantly fewer relapses compared to placebo (13% vs 28%, respectively; HR 0.35; 95% CI, 0.17–0.73).

Secondary Outcomes –
- Patients who continued Pimavanserin were less likely to discontinue the trial for any reason compared to placebo (22% vs 38%, respectively; HR 0.45; CI 95%, 0.26–0.79).
- There were no statistically significant differences in adverse events between the groups.
  - The most common adverse events in the Pimavanserin group were constipation (3.1%), headache (4.1%), and UTI (6.4%).

LIMITATIONS:
- Small sample size completed trial.
- High dropout rate.
- Funded by the drug manufacturer.

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Bariatric Surgery vs Weight Watchers: A Showdown for Lowering Intracranial Pressure in Patients with Idiopathic Intracranial Hypertension

Surgery vs Community Weight Management Intervention for Treatment of Idiopathic Intracranial Hypertension: A Randomized Clinical Trial

Mollan SP, Mitchell JL, Ottridge RS, et al. Effectiveness of Bariatric Surgery vs Community Weight Management Intervention for the Treatment of Idiopathic Intracranial Hypertension: A Randomized Clinical Trial. *JAMA Neurol*. 2021; 78(6):678–686. doi:10.1001/jamaneurol.2021.0659

KEY TAKEAWAY: Bariatric surgery is superior to a community weight management intervention in lowering intracranial pressure.

STUDY DESIGN: Multicenter RCT

LEVEL OF EVIDENCE: STEP 3 (downgraded due to low power)

BRIEF BACKGROUND INFORMATION: Idiopathic intracranial hypertension (IIH) is a debilitating condition characterized by severe headaches, which mainly affects younger women (typically 25 to 36 years old). Excess body weight is the main risk factor and weight loss has been associated with disease remission. Case series suggest that bariatric surgery is associated with remission among patients with IIH, but no prior randomized controlled trials (RCTs) have addressed this question.

PATIENTS: Obese women 18–55 years old with IIH

INTERVENTION: Bariatric surgery

CONTROL: Weight watchers

OUTCOME: Intracranial pressure

Secondary Outcomes: Lumbar puncture (LP) opening pressure, visual function, quality-of-life, serious adverse events

METHODS (BRIEF DESCRIPTION):

- Women with BMI ≥35 meeting diagnostic criteria for IIH with normal brain imaging, who had not been successful in losing weight or maintaining weight loss were recruited from neurology and ophthalmology clinics from seven National Health Service hospitals in the UK.
  - Diagnostic criteria for IIH included baseline papilledema and LP opening pressure of at least 25 cm cerebrospinal fluid (CSF).
- Participants were randomized in a 1:1 ratio to receive either community weight management intervention (Weight Watchers) or bariatric surgery. The specific surgical type was determined by surgeon and patient preference.
- Randomization was stratified by acetazolamide (a headache reduction medication) use vs nonuse. Acetazolamide was used by 29% (19 of 66) of the patients.
- Difference in intracranial pressure (ICP) between the surgery arm and the weight management arm was measured by lumbar puncture (LP) opening pressure at 12 months.
- LP opening pressure was measured at 24 months.
- Visual function and quality-of-life (measured with the 36-item Short Form Health Survey, SF36, which includes physical and mental health components and 8 subscales each with scores 0–100, with higher scores indicating improvement) were measured at 12 months.

INTERVENTION (# IN THE GROUP):

- Roux-en-Y gastric bypass: 12
- Gastric banding: 10
- Laparoscopic sleeve gastrectomy: 5

COMPARISON (# IN THE GROUP): 33

FOLLOW UP PERIOD: 2 years

RESULTS:

Primary Outcome –

- The surgery group had a greater reduction in intracranial pressure compared to the placebo group at 12 months (adjusted mean difference [aMD] –8.7 cm vs –2.5 cm, respectively; between group aMD –6.0 cm; 95% CI, –9.5 to –2.4).

Secondary Outcomes –

- The surgery group had a greater reduction in intracranial pressure compared to the placebo group at two years (mean percent change –35% vs –6%, respectively; *P*<.001).
- The surgery group had a greater improvement in quality of life compared to the placebo group at 12 months (aMD 7.3; 95% CI, 0.2–14), with specific increases in the following areas.
  - Energy (aMD 15; 95% CI, 2.4–27)
  - Physical functioning (aMD 20; 95% CI, 6.9–34)
- There was no difference in visual function between the two groups at 12 months.
- During the two years, there were 24 serious adverse events with six in the treatment group.

LIMITATIONS:

- Primary outcome of LP opening pressure is not patient-oriented.
- The type of bariatric surgery was determined after randomization and number of participants in trial was too low to be able to determine if type of surgery affects outcomes.
- Underpowered for secondary outcomes.
- Unclear if findings are generalizable to women with BMI <35 or men.
- Lack of long-term follow up beyond 24 months to determine adverse effects or sustained improvement.

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Osteopathic Manipulation and its Influences on Cervical Range of Motion

Isometric Osteopathic Manipulation Influences on Cervical Ranges of Motion and Correlation with Osteopathic Palpatory Diagnosis: A Randomized Trial

Niewiadomski C, Bianco RJ, Arnoux PJ, Evin M. Isometric osteopathic manipulation influences on cervical ranges of motion and correlation with osteopathic palpatory diagnosis: A randomized trial. *Complement Ther Med*. 2020; 48:102278. doi:10.1016/j.ctim.2019.102278

KEY TAKEAWAY: Isometric osteopathic manipulative treatment (OMT) resulted in a small improvement in lateral flexion; however, patient-oriented outcomes were not assessed.

STUDY DESIGN: Single site, single-blind randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Osteopathic manipulation is considered standard care among osteopathic providers for treatment of cervicalgia. However, the impact of isometric manipulation on range of motion remains uncertain.

PATIENTS: Adults 18 to 60 years old without cervical spine pathology

INTERVENTION: Osteopathic manipulation with muscle-energy

CONTROL: Sham treatment

OUTCOME: Measured ranges of motion pre- and post-treatment

METHODS (BRIEF DESCRIPTION):

- A headband with four opto-electric sensors and three cameras was used to capture range of motion (flexion/extension, side-bending, and rotation).
  - Participants were asked to reach their physiologic barrier with active range of motion.
- An osteopathic practitioner palpated for restrictions, diagnosed a somatic dysfunction, and treated the patient using isometric techniques.
- The placebo group consisted of simple cervical muscle palpation without specific guidance aimed to target and treat the restriction.
- Following treatments, patients were again asked to reach their physiologic barrier in active range of motion.
  - These differences were then compared.

INTERVENTION (# IN THE GROUP): 50

COMPARISON (# IN THE GROUP): 51

FOLLOW UP PERIOD: None (pre/post OMT assessment only)

RESULTS:

- Isometric manipulation improved the following when comparing pre- to post-intervention:
  - Degree of incl. on the right (42.5 vs 43.4, respectively; *P*=.04) and left (–44.5 vs –46.4, respectively; *P*=.008)
  - Degree of flexion and extension (124 vs 127, respectively; *P*=.03)
  - Degree of lateral flexion (87 vs 90, respectively; *P*<.001)
- After treatment with Isometric Manipulation, 67% of subjects reported pain improvement versus 40% of the subjects in the placebo treatment group.
- No adverse events to either treatment or placebo group were noted.
- No direct comparison was done between OMT and placebo.

LIMITATIONS:

- The participants had to assume an anatomical position of reference assessed by the CodaMotion system, though how they positioned themselves and their true anatomical neutral position may not perfectly align.
- While the study had one practitioner and each participant in the treatment group of the study received nearly identical treatment for controlled assessment, that individual's techniques are not likely reflective of all practitioners.

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