



GEMs of the Week

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Week of February 15 - 19, 2021

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Ubrogepant for treatment of Migraine – Heading in the Right Direction

Ubrogepant for treatment of Migraine

Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for treatment of migraine. *N Engl J Med*.2019; 381:2230–41. Copyright © 2020 by Family Physicians Inquiries Network, Inc.

KEY TAKEAWAY: Compared to placebo, a higher percentage of patients who took Ubrogepant experienced relief of migraine pain and associated symptoms.

STUDY DESIGN: Double blinded RCT placebo controlled
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Migraines are characterized by recurrent headaches which can be severe and debilitating affecting patient’s work performance, relationships, and quality of life. Not everyone responds to currently available medications and Ubrogepant may be consider as an alternative pain reliever in these patients.

PATIENTS: Patients 18–75 years old with a >1 year history of migraines and initial headache occurring before age 50 years

INTERVENTION: Ubrogepant 50mg & 100mg

CONTROL: Placebo

OUTCOME: freedom from pain and absence of most aggravating migraine-associated symptoms (photophobia, phonophobia and nausea) 2 hours after initial dose; degree of pain relief at 2 hours, sustained pain relief from 2–24 hours, and sustained freedom from pain (pain relief defined as changes in severity of pain after initial dose from moderate to severe to mild or no pain)

METHODS (BRIEF DESCRIPTION):

- Patients were randomized to 1:1:1 ratio to receive placebo, ubrogepant 50mg or 100mg orally to be taken at time of qualifying migraine (defined as moderate to severe intensity)
- Placebo group was given 2 tablets of placebo; ubrogepant 50mg group was given one tablet of 50mg and one placebo; ubrogepant 100mg group was given 2 tablets of 50mg
- Efficacy was determined on the basis of electronic diary rating headache severity (mild, moderate, severe) and presence of associated symptoms at various times frames up to 48 hours after initial dose

INTERVENTION (# IN THE GROUP): 556 (50mg); 557 (100mg)

COMPARISON (# IN THE GROUP): 559

FOLLOW UP PERIOD: 2–7 days after initial dose, and telephone visit at 14 days; approximately 21% of patients were withdrawn as they did not have a qualifying migraine within 60 days of randomization.

RESULTS:

Primary Outcomes:

- Freedom from pain 2 hours after initial dose greater in ubrogepant groups compared to placebo:
 - 12% with placebo
 - 19% with ubrogepant 50mg (OR 1.83; 95% CI, 1.2–2.6)
 - 21% with ubrogepant 100mg (OR 2.04; 95% CI, 1.4–2.9)
- Absence of most bothersome migraine-associated symptom greater in ubrogepant groups compared to placebo:
 - 27% with placebo
 - 38% with ubrogepant 50mg (OR 1.7; 95% CI, 1.2–2.2)
 - 37% with ubrogepant 100mg, (OR 1.63; 95% CI, 1.2–2.1)

Secondary Outcomes:

- Pain relief at 2 hours greater in ubrogepant groups compared to placebo:
 - 49% in placebo group
 - 60% with 50mg ubrogepant (OR 1.69; 95% CI, 1.2–2.2)
 - 61% with 100mg (OR 1.69; 95% CI, 1.2–2.2)
- Sustained pain relief (defined as change in severity of pain from moderate to severe intensity to mild or no pain) 2–24hr greater in ubrogepant groups compared to placebo:
 - 20% with placebo
 - 36% with 50mg (OR 2.25; 95% CI, 1.6–3, P<0.002)
 - 38% with 100mg (OR 2.39; 95% CI, 1.7–3.2, P<0.002)
- Sustained freedom from pain 2–24 hr was greater in ubrogepant groups compared to placebo
 - 8.6% with placebo
 - 12% with 50mg dose (OR 1.63; 95% CI, 1–2.4)
 - 15% with 100mg dose (OR 1.8, 95% CI, 1.3–2.4)

LIMITATIONS:

- The majority of participants were white and female.
- No direct comparison with standard therapies or with repeated use.
- Safety and side effect profile were based on single use.
- Study funded through Allegerm, producer of ubrogepant.

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Look to the Microbiome: Lactin-V may reduce recurrence of bacterial vaginosis

Randomized Trial of Lactin-V to Prevent Recurrence of Bacterial Vaginosis

Cohen CR, Wierzbicki MR, French AL, et al. Randomized Trial of Lactin-V to Prevent Recurrence of Bacterial Vaginosis. *N Engl J Med.* 2020; 382(20):1906–1915. Copyright © 2020 by Family Physicians Inquiries Network, Inc.

KEY TAKEAWAY: Use of *Lactobacillus crispatus* (Lactin-V) reduces bacterial vaginosis recurrence after metronidazole treatment by 34% at 12 weeks compared to placebo.

STUDY DESIGN: Multicenter, randomized, double-blind, placebo-controlled, phase 2b trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Bacterial vaginosis (BV) affects many women worldwide. Recurrence of BV within 3 months of antibiotic treatment is common ranging from 25-75%. New agents are needed to reduce this high rate of recurrence. The efficacy of Lactin-V on BV recurrence is unknown.

PATIENTS: Women ages 18–45 years diagnosed with BV who were within 48 hours of completion of vaginal metronidazole gel treatment

INTERVENTION: Lactin-V, a live biotherapeutic product containing 2x10⁹ colony-forming units (CFU) of *Lactobacillus Crispatus*.

CONTROL: Matching placebo

OUTCOME: Percentage with recurrent BV at any follow-up visit including the week 12 visit

Secondary outcomes: percentage with recurrent BV at any visit including the week 24 visit; percentage of the Lactin-V group with detectable *L. crispatus* at 12 and 24 weeks; acceptability of Lactin-V.

METHODS (BRIEF DESCRIPTION):

- Participants randomly assigned 2:1 via permuted blocks to receive Lactin-V or placebo.
- Lactin-V or placebo vaginally self-administered four consecutive daily doses during week 1 followed by twice-weekly doses for 10 weeks.
- Participants logged administration of Lactin-V/placebo, menstruation, sexual activity, symptoms, and adverse events.
- Follow-up visits at 4, 8, 12, and 24 weeks after. Vaginal swabs obtained at each visit for the assessment of Amsel criteria, determination of

Nuget score, and detection of *L. crispatus* by PCR assays.

- Analysis via intention-to-treat.
- Power analysis and allocation/concealment described.

INTERVENTION (# IN THE GROUP): 152 intended to treat, 112 included in final results

COMPARISON (# IN THE GROUP): 76 intended to treat, 54 included in final results

FOLLOW UP PERIOD: Primary outcome measured at week 12 visit. Participants followed to 24 weeks.

RESULTS:

Primary Outcome:

- Recurrence of BV at week 12 was significantly lower in the Lactin-V group compared to placebo (30% (n=46) vs. 45% (n=34); Risk Ratio 0.66; 95% CI, 0.44–0.87; NNT=7).

Secondary Outcomes:

- Recurrence of BV at week 24 was significantly lower in the Lactin-V group compared to placebo (12% (n=13) vs. 17% (n=7); Risk Ratio 0.73; 95% CI, 0.54–0.92).
- Significantly greater amount of *L. crispatus* CFUs detected in the Lactin-V group at each follow-up compared to placebo group.
- No significant difference in adverse events between the groups.

LIMITATIONS:

- Small sample size with power <80% for primary outcome due to dropouts/loss to follow-up
- Pregnant women and <18 years of age excluded
- No test confirming BV eradication after initial metronidazole treatment

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Pelvic Floor Muscle Training to Treat Urinary Incontinence Works in Groups Too

Group-Based vs Individual Pelvic Floor Muscle Training to Treat Urinary Incontinence in Older Women: A Randomized Clinical Trial

Dumoulin C, Morin M, Danieli C, et al. Group-Based vs Individual Pelvic Floor Muscle Training to Treat Urinary Incontinence in Older Women. *JAMA Internal Medicine*. 2020; 180(8):E1–E10.

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KEY TAKEAWAY: Utilization of group-based pelvic floor muscle training is non-inferior to currently recommended individual pelvic floor muscle training for the treatment of both stress and mixed urinary incontinence in older women.

STUDY DESIGN: Single-blind, randomized, multicenter, non-inferiority trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Urinary incontinence is a common medical problem among aging women. First-line treatment for both stress and mixed urinary incontinence consists of individual pelvic floor muscle training, however, this is costly both with regard to human and financial resources, and may lead to early referral for surgical intervention as a costly but time efficient alternative. Group-based pelvic floor muscle training may represent a more efficient alternative, both with regards to human and financial resources, and may promote peer support and healthy discussion while reducing patient stigma and isolation.

PATIENTS: Women greater than 60 years of age with stress or mixed urinary incontinence.

INTERVENTION: Group-based pelvic floor muscle training

CONTROL: Individual pelvic floor muscle training

OUTCOME: Percentage reduction in number of urinary incontinence episodes at 1 year

Secondary Outcomes:

- Number of daily urinary leakages at 12 weeks and 1 year
- Number of micturitions per day and night
- Amount of leakage on 24-hour test pad
- 5 International Consultation on Incontinence Questionnaire (ICIQ)
- Geriatric Self-Efficacy Index
- Patient Global Impression of Improvement Questionnaire
- Satisfaction with treatment

METHODS (BRIEF DESCRIPTION):

- Women were included if greater than 60 years of age with stress or mixed urinary incontinence with at least 3 episodes of involuntary urine loss per week during the 3 months preceding the study.
- Patients performed either group-based or individual pelvic floor muscle training exercises 5 days per week for 12 weeks, and then 3 days per week for an additional 9 weeks.
- Primary and secondary outcomes were measured at 12 weeks and 1 year after the start of each respective intervention.
- Patients in both arms initially received individual physiotherapist sessions on effective contraction of pelvic floor muscles (PFM) prior to beginning.
- Weekly sessions consisted of a 15-minute educational period followed by a 45-minute exercise component.
- The primary and secondary outcomes were measured through the use of a bladder diary to record the number and timing of daily incontinence episodes. A 24-hour pad test was used to quantify the amount of leakage. Additionally, multiple questionnaires were used to assess patient's subjective symptoms and overall satisfaction.

INTERVENTION (# IN THE GROUP): 178

COMPARISON (# IN THE GROUP): 184

FOLLOW UP PERIOD: 12 weeks and 1 year

RESULTS:

No difference in reduction of incontinence episodes between individual and group therapy:

- 70% vs 74%; Difference: -4% (95% CI, -10% to 7%; P = .58)

Note: The difference in the percentage reduction of leakage episodes correlated with an upper boundary of the 95% CI that was lower than the pre-specified margin for non-inferiority of 10%.

Secondary Outcomes: No significant difference with reduction in leakage episodes per day and all symptom measurements

LIMITATIONS: Some patients in each group reported receiving care at outside health professionals, taking medications, and receiving other forms of treatments.

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Does early ACL reconstruction prevent meniscal and chondral lesions in the knee?

Does a delay in anterior cruciate ligament reconstruction increase the incidence of secondary pathology in the knee? A systematic review and meta-analysis

Matthewson G, Kooner S, Rabbani R, et al. Does a delay in anterior cruciate ligament reconstruction increase the incidence of secondary pathology in the knee? A systemic review and meta-analysis. *Clinical Journal of Sport Medicine*. 2019; 00:1–8.

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KEY TAKEAWAY: In skeletally mature patients randomized to ACL reconstruction at less than 3 weeks versus 4 to 12 weeks after injury, there were no differences in rates of meniscal or chondral lesions of the knee.

STUDY DESIGN: Meta-analysis of 4 RCTs; N=303

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: ACL injuries are common but the optimal timing of ACL reconstruction is unclear. Experts suspect benefits of early reconstruction include decreased rehabilitation time and a decreased risk of a secondary injury due to persistent instability. Experts also believe delayed reconstruction may allow time for improved range of motion and strength before surgery. Chondral lesions and meniscal tears predict development of osteoarthritis later in life, and previous studies have suggested that timing of ACL reconstruction could impact the incidence of these lesions. However, this is unknown due to variability in defining early and delayed reconstruction and in study quality.

PATIENTS: Skeletally mature males and females (mean age 21–31.2 years) undergoing primary ACL reconstruction (ACLR)

INTERVENTION: ACLR less than 3 weeks after injury

CONTROL: ACLR 4 to 12 weeks after injury

OUTCOME: Incidence of meniscal tears and chondral injuries identified at time of surgery

METHODS (BRIEF DESCRIPTION):

- Authors searched MEDLINE, EMBASE, and CINAHL databases and major North American orthopedic organization conference proceedings from 2016–2018 systematically for randomized control trials comparing ACL reconstruction (ACLR) at different points in time.
- Included RCTs were published between 2003 and 2017. The four RCTs included patients aged 18–43 years (73% male, mean age range 21–31.2 years).

The majority of patients had suffered their injury playing sports.

- Included studies defined early ACLR as less than 1 to 3 weeks after injury, and delayed ACLR as occurring greater than 4 to 12 weeks after injury. Risk of bias in randomization, blinding, and outcomes data reporting was assessed with the Cochrane Collaboration Risk of Bias tool and methodologic quality was evaluated with the Detsky score.

INTERVENTION (# IN THE GROUP): 151

COMPARISON (# IN THE GROUP): 152

FOLLOW UP PERIOD: Follow-up at a minimum of 6–26 months and a maximum of 5 years after ACLR.

RESULTS:

- No difference in incidence of meniscal or chondral lesions identified at time of ACLR performed at <3 weeks versus >4 weeks.
 - Meniscal lesions: 4 trials; N=303; (RR 0.98; 95% CI, 0.74–1.29)
 - Chondral lesions: 3 trials; N=272; (RR 0.88; 95% CI, 0.59–1.29)

LIMITATIONS:

- Few studies fit inclusion and exclusion criteria, limiting power to detect differences in outcomes.
- Included RCTs had small sample sizes.
- Long term outcome information limited as most outcome measures recorded between 12 weeks and 1 year after surgery.
- 2 of 4 included studies excluded patients with meniscal lesions that required repair or chondral lesions that required more than simple debridement, as it altered rehabilitation protocol.
- No study monitored compliance with physical therapy post repair and only 2 reported duration of physical therapy.
- Included studies were all performed outside the United States.
- Included only studies published in English.
- One study was found to be at high risk of bias and another was found to have low methodologic quality.

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Antepartum Metformin use is associated with improved cardiovascular profile in offspring. Should we consider more routine use of Metformin in Obese Non-Diabetic Pregnant Women?



Metformin use in obese mothers is associated with improved cardiovascular profile in the offspring

Panagiotopolou O, Syngelaki A, Georgiopoulos G, et al. Metformin use in obese mothers is associated with improved cardiovascular profile in the offspring. *American Journal of Obstetrics and Gynecology*. 2020; 223(2):e1–10.

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KEY TAKEAWAY: Prenatal exposure to metformin improved cardiovascular profiles (blood pressure, aortic pulse pressure, left atrial area, and pulmonary vein systolic pressure), but it is not clear if there are any long term benefits.

STUDY DESIGN: Prospective cohort study of pediatric patients whose mothers participated in a previous randomized control trial

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Maternal obesity has been associated with increased pregnancy complications. Metformin is a commonly used agent in pre-diabetic and diabetic individuals regardless of pregnancy status, but few studies exist regarding long-term effects on offspring whose mothers were exposed to Metformin during pregnancy.

PATIENTS: Children of obese non-diabetic mothers taking Metformin

INTERVENTION: Children exposed to Metformin prenatally

CONTROL: Children not exposed to Metformin prenatally

OUTCOME: Body composition, peripheral blood pressure, arterial stiffness, central dynamics (including central blood pressure and augmentation index), left ventricular cardiac function and structure

METHODS (BRIEF DESCRIPTION):

- Study participants were offspring selected from the Metformin in Obese Pregnant Women randomized control trial. Mothers in this trial were randomized to receive metformin or placebo from 12–18 weeks gestation until delivery
- Participants were examined by a researcher blinded to all maternal information
- Body composition was recorded at various sites of body including arms, legs, waist, and gluteal areas
- Hemodynamic measurements were obtained peripherally using a blood pressure cuff on the right

arm and obtained centrally using Doppler echocardiography

- Metabolic analysis was performed using a nonfasting venous blood sample

INTERVENTION (# IN THE GROUP): 77

COMPARISON (# IN THE GROUP): 74

FOLLOW UP PERIOD: Study population born 2011–2016. This cohort follow up study conducted at 4 years post-trial.

RESULTS:

Children who were exposed to Metformin in prenatal period resulted in:

- Improved cardiovascular profile as evidenced by the following indices:
 - Lower aortic systolic blood pressure, mm Hg (94 vs 96, $P < .05$)
 - Aortic pulse pressure, mm Hg (33 vs 36, $P < .01$)
 - Smaller left atrial area, cm^2 (5.5 vs 6.1, $P = .001$)
 - Higher pulmonary vein peak systolic Doppler velocity value, cm/sec (56 vs 53, $P < .01$)
- No major difference in body composition compared to placebo group.
 - Body mass index, kg/m^2 (17 vs 17, $P = 0.27$)
 - Free fat mass, kg (16 vs 16, $P = 0.17$)
 - Waist circumference, cm (51 vs 52, $P = 0.12$)
- No significant differences in metabolic profile compared to placebo group.
 - Cholesterol, mmol/L (3.8 vs 3.7, $P = 0.32$)
 - Low-density lipoprotein, mmol/L (1.5 vs 1.5, $P = 0.43$)

LIMITATIONS:

- It remains undetermined if cardiovascular changes demonstrated in childhood will translate into any long-term cardiovascular benefit in adulthood.
- Only 38.5% of participants in the original study completed body assessments and only 19.8% completed blood sampling studies.

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