GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of August 5 - 9, 2024

SPOTLIGHT: Next Day Allies: Levonorgestrel and Piroxicam Guard Against Pregnancy

Next Day Allies: Levonorgestrel and Piroxicam Guard Against Pregnancy

Oral Emergency Contraception with Levonorgestrel Plus Piroxicam: A Randomized Double-Blind Placebo-Controlled Trial

Li RHW, Lo SST, Gemzell-Danielsson K, Fong CHY, Ho PC, Ng EHY. Oral emergency contraception with levonorgestrel plus piroxicam: a randomized double-blind placebo-controlled trial [published correction appears in Lancet. 2023 Sep 9;402(10405):850. doi: 10.1016/S0140-6736(23)01850-0]. *Lancet*. 2023;402(10405):851-858. doi:10.1016/S0140-6736(23)01240-0

KEY TAKEAWAY: Co-administering levonorgestrel with piroxicam as emergency contraception significantly improves pregnancy prevention compared to administering levonorgestrel alone.

STUDY DESIGN: Double-blind, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The two main methods of oral hormone emergency contraception are levonorgestrel 1.5 mg and ulipristal acetate 30 mg. Both function by inhibiting ovulation but are less effective in preventing pregnancy after ovulation has occurred. Prostaglandins affect ovulation, fertilization, and implantation. Therefore, this study hypothesized that adding a cyclo-oxygenase (COX) inhibitor, which is involved in prostaglandin production, will have a synergistic effect in preventing pregnancy as a form of emergency contraception after unprotected intercourse.

PATIENTS: Adult women seeking emergency contraception

INTERVENTION: Levonorgestrel with oral piroxicam

CONTROL: Levonorgestrel with oral placebo

PRIMARY OUTCOME: Percent of pregnancies prevented

Secondary Outcome: Subsequent cycle menstrual blood loss, the timing of menstrual cycle return, adverse events, subsequent menstrual periods

METHODS (BRIEF DESCRIPTION):

- Participants were recruited from the Family Planning Association in Hong Kong.
- Demographics:
  - Women ≥18 years old (mean age 31 years old)
  - 97% reported Chinese ethnicity
- Inclusion criteria:
  - Women requesting emergency contraception after a single event of unprotected intercourse who chose to use levonorgestrel.
  - Women with menstrual cycles between 24–42 days long.
  - Agreement to abstinence during the follow-up period.
- Exclusion criteria:
  - Breastfeeding or currently pregnant.
  - Menstruation that had not resumed after a recent pregnancy or abortion.
  - Uncertainty of last menstrual cycle.
  - Use of hormonal contraceptive (emergency contraception, sterilization, or IUD) in current or previous menstrual cycle.
  - Current use of NSAIDs or anticoagulants.
  - Significant past medical history, such as allergies to ingredients being used in the study, heart failure, and GI bleeds.
- Participants in the intervention group were given 1.5 mg levonorgestrel and 40 mg piroxicam orally.
- Participants in the control group were given 1.5 mg levonorgestrel and a placebo pill orally.
- The primary outcome of pregnancies prevented was calculated by taking the difference between expected pregnancies and observed pregnancies divided by expected pregnancies.
- To measure secondary outcomes, women were given a diary to keep track of subsequent cycle menstrual blood loss, the timing of menstrual cycle return, and/or adverse events.
- Follow-up occurred 1–2 weeks after the next expected menstrual period to measure the occurrence/change of subsequent menstrual period.

INTERVENTION (# IN THE GROUP): 430

COMPARISON (# IN THE GROUP): 430

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- The combination of levonorgestrel with piroxicam significantly improved pregnancy prevention compared to levonorgestrel with placebo (95% vs 63%, respectively; risk difference [RD] 31%; 95% CI, 26–36).

Secondary Outcome –

- The combination of levonorgestrel with piroxicam significantly affected subsequent cycle menstrual blood loss compared to levonorgestrel with placebo (24% vs 16%, respectively; *P*=.019).
- There were no significant differences in the timing of menstrual cycle return, adverse events (fatigue, nausea, abdominal pain, dizziness), and subsequent menstrual periods between the two groups

LIMITATIONS:

- Limited generalizability due to recruitment of all patients from a single location.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

Timing the Tides of Adjunctive Antidepressants in Bipolar 1

Duration of Adjunctive Antidepressant Maintainence in Bipolar I Depression

Yatham LN, Arumugham SS, Kesavan M, et al. Duration of Adjunctive Antidepressant Maintenance in Bipolar I Depression. *N Engl J Med.* 2023;389(5):430-440. doi:10.1056/NEJMoa2300184

KEY TAKEAWAY: For patients with bipolar I and depression in remission on adjunctive antidepressants, there is no difference in the incidence of mood events between patients whose antidepressant was discontinued at eight weeks and those whose antidepressant was continued until 52 weeks.

STUDY DESIGN: Multisite, double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Studies on the use of adjunctive antidepressants in bipolar I indicate that as many as 57% of patients receive adjunctive antidepressants, and prescriptions are often continued for months after remission. There is limited research regarding the efficacy, safety, and duration of adjunctive antidepressant use in bipolar I. This study compares the continuation of antidepressants for 52 weeks vs discontinuation at eight weeks after remission.

PATIENTS: Adults with bipolar I on adjunctive antidepressant

INTERVENTION: Continuation of adjunctive antidepressants

CONTROL: Placebo

PRIMARY OUTCOME: Time to first mood episode

Secondary Outcome: Time to depressive episode, time to manic/hypomanic episode, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients ≥18 old were recruited from outpatient clinics in India, Canada, and Korea.
- All patients had received a diagnosis of bipolar I disorder and were treated with escitalopram at 10–30 mg per day or bupropion XL at 150–450 mg per day for 2–8 weeks along with an adjunctive therapeutic dose of a mood stabilizer and/or a second-generation antipsychotic agent with remission of symptoms for at least 2–8 weeks.
- Patients who had received treatment with other psychotropic medications (aside from benzodiazepines) were excluded.
- The mean age of those enrolled was 41 years old with 52% women, ethnicity comprised of 87% Asian, 12% White, and 1% Black, and the baseline average age of diagnosis of bipolar 29 years old, average duration of bipolar diagnosis of 12 years and average duration of the index depressive episode of 74 days.
- In the intervention arm, patients received continued adjunctive antidepressive therapy with escitalopram or bupropion administered orally, daily for 52 weeks.
- The comparison group underwent eight weeks of continued adjunctive antidepressive therapy with escitalopram or bupropion administered orally, daily, with down-titration initiated at six weeks and subsequent discontinuation and initiation of placebo at eight weeks.
- The primary outcome of a mood episode was defined by scores on mood screeners using the following scales:
  - Clinical Global Impression Severity Scale for Bipolar Disorder (CGI-S-BD): Scores range from 1–7 with higher scores indicative of greater severity; with a mood episode defined as a score of ≥4.
  - Young Mania Rating Scale (YMRS): Scores range from 0–60 with higher scores indicative of greater severity; with a mood episode defined as a score of ≥16.
  - Montgomery-Asberg Depression Rating Scale (MADRS): Scores range from 0–60 with higher scores indicative of greater severity; with a mood episode defined as a score of ≥20.

INTERVENTION (# IN THE GROUP): 90

COMPARISON (# IN THE GROUP): 87

FOLLOW-UP PERIOD: 52 weeks

RESULTS:

Primary Outcome –

- 52 weeks of adjunctive therapy did not affect the incidence of mood events compared to control (hazard ratio [HR] 0.68; 95% CI, 0.43–1.1).

Secondary Outcome –

- Patients treated with adjunctive antidepressant therapy until 52 weeks had no significant difference in the incidence of manic or hypomanic events when compared to those discontinued at eight weeks.
- Patients treated for 52 weeks of antidepressant therapy had a lower incidence of depressive events compared to control (HR 0.43; 95% CI, 0.25–0.75).
- Patients treated for 52 weeks of antidepressant therapy may have had higher rates of adverse events when compared to those treated for eight weeks, including weight gain (14% vs 7%), memory problems (16% vs 8%), and fatigue (20% vs 15%).
    - Statistical analysis was not completed.

LIMITATIONS:

- There was a significant loss to follow-up as well as withdrawal of consent.
- The study was a largely homogenous study population.
- The trial selected patients who had already responded to antidepressant therapy and thus cannot be applied to patients who have not yet reached remission.
- The trial was stopped early and may be underpowered to detect a difference in treatment due to low recruitment.

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Osteopathic Manipulation Helps in Total Knee Replacement

Preoperative Osteopathic Manipulative Therapy Improves Postoperative Pain and Reduces Opioid Consumption After Total Knee Arthroplasty: A Prospective Comparative Study

Barral P, Klouche S, Barral N, Lemoulec YP, Thés A, Bauer T. Preoperative Osteopathic Manipulative Therapy Improves Postoperative Pain and Reduces Opioid Consumption After Total Knee Arthroplasty: A Prospective Comparative Study. *J Am Osteopath Assoc.* 2020;120(7):436-445. doi:10.7556/jaoa.2020.071

KEY TAKEAWAY: Osteopathic manipulation prior to total knee arthroplasty decreases pain one month after surgery and decreases opioid pain medication use one week after surgery.

STUDY DESIGN: Prospective, cohort, comparative study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Approximately 20% of patients who have a total knee arthroplasty (TKA) are not satisfied with their level of pain relief one year or more post-surgery. This study examines the role of preoperative osteopathic manipulation and its role in postoperative pain after TKA.

PATIENTS: Patients with knee osteoarthritis undergoing unilateral TKA

INTERVENTION: Preoperative osteopathic manipulation

CONTROL: No osteopathic manipulation

PRIMARY OUTCOME: Postoperative pain

Secondary Outcome: Opioid analgesia use

METHODS (BRIEF DESCRIPTION):

- Patients included were those undergoing primary TKA for osteoarthritis.
- Exclusion criteria included a history of surgery on the operated knee, bilateral TKA in the same operation, and patient refusal.
- Osteopathic manipulation was performed three weeks and one week prior to unilateral TKA on patients without any history of prior knee surgery.
- At the three-week preoperative session, the physician performed rhythmic mobilization of all the body joints using long-lever manipulation.
- The one-week preoperative session focused on myofascial relaxation of the involved lower limb and pelvis by applying pressure to the areas being treated and allowing for relaxation of the tissues.
- Pain levels were assessed by giving the study participants notebooks with a visual analog scale (VAS) from 0 (no pain) to 100 (worst pain imaginable).
- During the first postoperative month, patients filled out the VAS daily on awakening and at the end of the day. Patients also noted the use of analgesics (name and dose), night pain, and the use of sleeping aids.
- Patients were followed up at one month, six months, and one-year post-surgery.
    - The International Knee Society (IKS) function scores and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index were completed at the six-month and one-year follow-up visit.

INTERVENTION (# IN THE GROUP): 35

COMPARISON (# IN THE GROUP): 35

FOLLOW-UP PERIOD: One year

RESULTS:

Primary Outcome –

- Osteopathic manipulation resulted in less pain at rest at one month post-surgery compared to traditional preoperative management (mean 6.8 vs 21, respectively; *P*=.001).
- The osteopathic manipulation group had less pain while walking one month post-surgery compared to traditional preoperative management (mean 7.9 vs 24, respectively; *P*=.001).

Secondary Outcome –

- Fewer osteopathic manipulation group patients used opioid analgesics at one week post-surgery compared to traditional preoperative management (15 vs 34, respectively; *p*=.001).
    - The difference was not found over the next three weeks.
- There was no statistically significant difference between osteopathic manipulation and traditional preoperative management in pain (IKA or WOMAC), stiffness, and function at six months or one year post-surgery.

LIMITATIONS:

- There was no comparison to sham techniques.
- Osteopathic manipulation was standardized across the participants, which does not always correspond to osteopathic manipulation treatment (OMT) used in daily practice.

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Keeping Players on the Ice: Factors Associated with Concussions in Youth Ice Hockey Players

Factors Associated with Concussion Rates in Youth Ice Hockey Players: Data From the Largest Longitudinal Cohort Study in Canadian Youth Ice Hockey

Eliason P, Galarneau JM, Shill I, et al. Factors Associated With Concussion Rates in Youth Ice Hockey Players: Data From the Largest Longitudinal Cohort Study in Canadian Youth Ice Hockey. *Clin J Sport Med.* 2023;33(5):497-504. doi:10.1097/JSM.0000000000001177

KEY TAKEAWAY: Females, sub-elite, and forward players are at higher risk for game-related concussions. Concussions are less common in leagues prohibiting bodychecking, and previous concussions increase the risk of a new concussion and extend recovery time.

STUDY DESIGN: Five-year prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Ice hockey is a popular sport for young athletes, and though participating in sports is common for young athletes, there is a high burden of injury associated with ice hockey. Previous studies have evaluated potential risk and protective factors for concussions but have had variable definitions and methodologies. Concussions are an injury that warrants significant concern due to the potential for long-standing effects on a young athlete, including delayed return to play and dropping out of sports. This study aims to inform policymakers and players of the risk and protective factors associated with concussions in youth ice hockey.

PATIENTS: Youth ice hockey athletes

INTERVENTION: Ice-hockey related concussion

CONTROL: No reported concussion

PRIMARY OUTCOME: Risk factors for game-related concussions

METHODS (BRIEF DESCRIPTION):

- Participants were male and female ice hockey athletes 11–17 years old across all levels of play in leagues allowing and prohibiting bodychecking.
- Inclusion criteria:
  - Team members to report weekly data.
  - Written informed consent from players and parents.
  - Full participation of athletes at the beginning of the season.
- A previously validated youth hockey injury surveillance methodology was used, including a baseline questionnaire, tracking of sport-related time exposure, and an injury report form.
- The Baseline Sports Concussion Assessment Tool (SCAT) was utilized for preseason testing, as well as for postinjury testing.
- All injuries were validated by a study athletic therapist or physiotherapist; any suspected concussions were referred to a study sports medicine physician within 72 hours of injury.
- Injury follow-up based on recommendations from the International Conferences on Concussion in Sport was standardized and followed by all study physicians.
- Game-related concussion risk factors included the following:
  - Sex, level of play, bodychecking policy, history of previous concussions, and playing position.

INTERVENTION (# IN THE GROUP): 4,418

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Five years

RESULTS:

Primary Outcome –

- Game-related concussions were higher in females compared to males (incidence rate ratio [IRR] 1.8; 95% CI, 1.3–2.5).
- Game-related concussions were lower in leagues with policies prohibiting bodychecking compared to leagues allowing bodychecking (IRR 0.54; 95% CI, 0.4–0.72).
- Subelite players were more likely to have game-related concussions when compared to elite players (IRR 1.4; 95% CI, 1.1–1.8).
- Individuals with previous concussions were more likely to have game-related concussions (IRR 1.6; 95% CI, 1.3–2.0) and to have >10 days of time-loss (IRR 1.7; 95% CI, 1.3–2.2).
- Goalies had a lower rate of game-related concussions than forward players (IRR 0.57; 95% CI, 0.38–0.87).

LIMITATIONS:

- Participants self-reported covariate preseason baseline data, and participants did not always play

the same position in games and practices throughout the system.

- Not all suspected concussions were confirmed by a sports medicine physician participating in the study after referral.
- Variable return-to-play decisions based on individual players affected the timing of return to play, despite following the same protocol.
- Selection bias was noted for players who did not finish the season based on injury, leading to loss to follow-up, causing the players who remained in the group to have a lower underlying concussion risk profile.

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The Role of Glycemic Control in Rotator Cuff Tears Amongst Non-Diabetic Individuals

Associations of Normal Fasting Glucose Levels and of Insulin Resistance with Degenerative Rotator Cuff Tear: Normoglycemia and Rotator Cuff Tear

Park HB, Gwark JY, Jung J. Associations of normal fasting glucose levels and of insulin resistance with degenerative rotator cuff tear: Normoglycemia and rotator cuff tear. *BMC Musculoskelet Disord.* 2023;24(1):973. Published 2023 Dec 16. doi:10.1186/s12891-023-06899-5

KEY TAKEAWAY: Among normoglycemic individuals, increased blood glucose levels are associated with an increased risk of complete degenerative rotator cuff tear (RCT).

STUDY DESIGN: Cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Hyperglycemia has been linked to an increased risk of tendon damage and injury. However, no large studies have examined variations in glucose levels in normoglycemic populations on the risk of RCT. Due to the low quality of the study, further investigation is warranted to better understand the link between fasting glucose levels and complete degenerative rotator cuff tears. Musculoskeletal complaints are a common reason for primary care visits, hence better understanding of prevention strategies is of great interest.

PATIENTS: Normoglycemic agricultural workers of Korean nationality

INTERVENTION: Subjects with RCT and normoglycemia

CONTROL: Subjects with intact rotator cuff and normoglycemia

PRIMARY OUTCOME: Fasting glucose measure

METHODS (BRIEF DESCRIPTION):

- Patients were included in the study if they had either a full-thickness tendon tear or intact tendons.
- Participants were excluded if they had incomplete MRI data, a history of diabetes or pre-diabetes, took medication that could affect lipid profiles, had partial thickness rotator cuff tear, and history of shoulder trauma or surgery.
    - Individuals with a diagnosis of shoulder osteoarthritis, calcific tendinitis, frozen shoulder, isolated subscapularis tendon tear, and partial thickness posterosuperior rotator cuff tear were also excluded.
- Individuals were grouped with fasting glucose levels of <85 mg/dL, 85–89 mg/dL, 90–94 mg/dL, or 95–99 mg/dL, and the rate of full-thickness rotator cuff tears was determined in each group.
- Rotator cuff tears were identified via MRI on both shoulders.
    - Full-thickness tears were identified as images with high signal intensity passing through the entire thickness of the tendon.
    - If high signal intensity extended only to the bursal or articular surface, the tear was categorized as partial thickness and excluded from the study.
- Outcome: Univariate analyses were performed on multiple variables (age, waist circumference, dominant side involvement, manual labor, metabolic syndrome, fasting glucose, glucose category, TG/HDL ≥3.5, and other factors related to HDL) after which multivariable analysis was performed, which demonstrated an association between elevated glucose in normoglycemic range and complete degenerative rotator cuff tears.

INTERVENTION (# IN THE GROUP): 71

COMPARISON (# IN THE GROUP): 347

FOLLOW-UP PERIOD: 1.5 years

RESULTS:

Primary Outcome –

- Individuals with complete RCT showed significantly higher fasting glucose levels, even within the normoglycemic range compared to control.
    - <85 mg/dL (odds ratio [OR] 0.27; 95% CI, 0.11–0.58)
        - 3% of individuals in this group had complete RCT
    - 85–89 mg/dL (OR 0.83; 95% CI, 0.45–1.6)
        - 11% of individuals in this group had complete RCT
    - 90–94 mg/dL (OR 1.9; 95% CI, 1.0–3.3)
        - 26% of individuals in this group had complete RCT
    - 95–99 mg/dL (OR 3.1; 95% CI, 1.3–7.3)

    - 33% of individuals in this group had complete RCT

LIMITATIONS:

- Relatively small sample size.
- Sampled blood glucose measures were obtained once as opposed to obtaining several samples or evaluating A1C.
- The general population was not represented.
- Individual fitness levels and participation in activities that may predispose individuals to rotator cuff tears were not accounted for.
- Individuals with partial rotator cuff tears were excluded from the study.

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Suffering at the End of Life: More Than Just an Illness

Iatrogenic Suffering at the End of Life: An Ethnographic Study

Green L, Capstick A, Oyebode J. Iatrogenic suffering at the end of life: An ethnographic study. *Palliat Med*. 2023;37(7):984-992. doi:10.1177/02692163231170656

KEY TAKEAWAY: Suffering as the result of overall clinical care experience is often overlooked and identified late in patients with terminal diagnoses. Factors that contribute to these experiences are interventional, interactional, and environmental.

STUDY DESIGN: Observational prospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to low-quality prognostic study design)

BRIEF BACKGROUND INFORMATION: Suffering at the end of life is variable and complex, often viewed in the context of disease burden. Less studied is the quality of suffering through the lens of the patient's hospital experience at the end of life. By understanding themes and patterns in different treatment settings primary care providers can aim to deliver a more comfortable and humanistic experience for patients and their families in stressful circumstances.

PATIENTS: Adults thought to be in the last weeks of life

INTERVENTION: Not applicable

CONTROL: Not applicable

PRIMARY OUTCOME: Factors contributing to suffering

METHODS (BRIEF DESCRIPTION):

- Hospitalized patients identified by staff to be in the last weeks of life were included in this study.
- There were no criteria for participant exclusion.
- Participant-observer role by the author.
- Field notes were taken in real-time on-site and reflexively off-site.
- The focus of data collection changed each observation period and was determined by concerns identified during nurse handoffs.
- In addition to observation, the author performed formal interviews with participants, reviewed chart notes and documents, and evaluated the physical environment.
- A reflexive approach was used to review field notes by the author, workshops involving seven "experts-by-experience" within the University of Bradford, and the author's doctoral supervisors.

INTERVENTION (# IN THE GROUP): 15

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: May 2016–August 2016 (There is no documented average that each patient was followed for, but it can be assumed that each patient was followed through the end of their life)

RESULTS:

Primary Outcome –

- Iatrogenic suffering was observed to be due to three categories of factors:
  - Interventional factors:
    - Suffering at end-of-life can be difficult to identify and failure to identify can lead to prolonged interventions.
    - Avoidance of discussion about death with relatives results in unnecessary interventions.
    - Partial or unclear discussion of prognosis, leaving family members confused about patient status.
  - Interactional factors:
    - Persons with dementia were often ignored and talked over by staff.
    - Staff verbal and non-verbal reactions to sights and smells of patient's condition.
  - Environmental factors:
    - Patients were unaccustomed to the smells and sounds of the hospital, resulting in added distress.
    - The physical layout of the room forced the overlap of the patient's daily activities (eating, defecation, and sleeping) to occur all in the same location.

LIMITATIONS:

- Small, single-site ethnographic observational project.
- No control/comparison groups.

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