GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Finasteride for Female Patterned Hair Loss

- Why So 'Mab'? Pre-Surgical treatment with Pembrolizumab in Melanoma
- Should We Reconsider Using Proton Pump Inhibitors in Young Children?
- Prescribe NSAIDs with Caution for Patients on Hormonal Contraception
- Investigating the Side Effects of GLP-1 Agonists

Finasteride for Female Patterned Hair Loss

A Systematic Review of Clinical Trials Using Single or Combination Therapy of Oral or Topical Finasteride for Women in Reproductive Age and Postmenopausal Women with Hormonal and Nonhormonal Androgenetic Alopecia

Nobari NN, Roohaninasab M, Sadeghzadeh-Bazargan A, et al. A systematic review of clinical trials using single or combination therapy of oral or topical finasteride for women in reproductive age and postmenopausal women with hormonal and nonhormonal androgenetic alopecia. *Adv Clin Exp Med.* 2023;32(7):813-823. doi:10.17219/acem/157990

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KEY TAKEAWAY: Finasteride, may be effective for treating female pattern hair loss (FPHL) in women, with promising results reported in several studies, however, with extreme caution in women of childbearing age since finasteride is categorized as pregnancy category X by the Food and Drug Administration in the United States.

STUDY DESIGN: Systematic review (SR) of 14 studies including four randomized control studies, five uncontrolled prospective studies, four retrospective studies, and one case report (N=735)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to the quality and variety of studies included in the SR)

BRIEF BACKGROUND INFORMATION: Hair loss is a natural part of the hair growth cycle, but when the balance between hair growth and loss is disrupted, it can lead to excessive hair loss known as alopecia. FPHL or androgenetic alopecia (AGA) is the most common cause of hair loss in women, often genetic and worsened during menopause. Finasteride is an important medication for treating hair loss by preventing the conversion of testosterone to dihydrotestosterone and is used in both male and female pattern hair loss.

PATIENTS: Women with FPHL

INTERVENTION: Finasteride

CONTROL: Not specified

PRIMARY OUTCOME: Effectiveness of finasteride in scalp hair regrowth

METHODS (BRIEF DESCRIPTION):

- This systematic review, conducted from 1999–2020 included women 21–65 years old, treated with finasteride for hair loss, and used in-vivo therapy only.
- Included studies had at least one group treated with finasteride, results on its effectiveness, and only in vivo therapy.
- Both oral and topical finasteride therapy were examined.
  - Dosage:
    - The oral dosage varied from 1 mg/day to 5 mg/day.
    - The topical dosage included 0.25% and 0.5% finasteride solutions.
  - Duration:
    - The duration of treatment ranged from 3.5 months to 12 months for most studies.
    - Three studies' treatment periods were beyond 12 months, two for 18 months, and one for 3 years.
  - Frequency:
    - Daily for both oral and topical forms
    - Effectiveness was measured using various study methods, including hair density and thickness, patient satisfaction, and scalp hair count.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 3.5–3 years

RESULTS:

Primary Outcome –

- Results were not pooled in this review due to heterogeneity. The use of 5 mg/day dose of finasteride has been shown to effectively manage FPHL in both postmenopausal women and women of reproductive age.
- The highest FPHL improvement was seen after 12 months of finasteride treatment (in only 3 of the trials).
- The effectiveness of finasteride, whether used topically or orally, ranged between 15–65% of hair regrowth.
- Side effects included decreased libido, increased liver enzymes, headache, menstrual irregularities,

dizziness, and increased body air growth in some cases

LIMITATIONS:

- Lack of a systematic review of side effects.
- Lack of caution on the use of finasteride in women of childbearing age which is categorized as pregnancy category X by the Food and Drug Administration in the United States.
- No meta-analysis performed.
- Lack of numbers of patients in intervention group and comparison group.
- No calculation of heterogeneity.
- Scarcity of well-designed prospective clinical trials.

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Why So 'Mab'? Pre-Surgical Treatment with Pembrolizumab in Melanoma

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Patel SP, Othus M, Chen Y, et al. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. *N Engl J Med.* 2023;388(9):813-823. doi:10.1056/NEJMoa2211437

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KEY TAKEAWAY: The use of neoadjuvant-adjuvant as opposed to adjuvant-only treatment in resectable stage III-IV melanoma provides longer event-free survival without an increase in adverse events.

STUDY DESIGN: Randomized, single-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pembrolizumab is a monoclonal antibody developed as either adjuvant or singular therapy for patients with a wide variety of cancers. The drug specifically binds to the PD-1 antibody on T-cells and helps the patient's immune system target cancer cells. Providers have used this medication with various timing and dosing techniques with no standard dosing regimen currently proven superior to others. Variations include the timing of dosing compared to surgery, dosing regimen, and other concurrent treatments.

PATIENTS: Patients with surgically resectable stage III or IV melanoma

INTERVENTION: Pre- and post-surgical treatment with pembrolizumab

CONTROL: Post-surgical treatment only

PRIMARY OUTCOME: Event-free survival time

Secondary Outcome: Incidence of adverse effects

METHODS (BRIEF DESCRIPTION):

- Patients >18 years old from 90 sites in the United States were included with pathologically confirmed, clinically detectable (per RECIST criteria), stage IIIB to IIID or oligometastatic resectable stage IV melanoma.
- Exclusion Criteria: Patients with HIV and CD4 count <350, previous treatment with immunotherapy for melanoma, an active autoimmune disease with systemic treatment within two years of entering the study, uveal melanoma, and any history of brain metastasis.
- Patients were randomized into two treatment arms:
  - Pre- and post-surgical treatment (intervention): One dose of 200 mg infusion of pembrolizumab was given every three weeks for a total of three doses before surgical resection.
    - No more than five weeks between the last neoadjuvant dose and surgery
    - Treatment then continued at the same dosing and interval for an additional 15 weeks for 15 total doses post-resection.
    - A total of 18 treatments of pembrolizumab were given.
  - Post-surgical treatment only (control): After surgical resection patients were started on one dose of 200 mg infusion of pembrolizumab given every three weeks for 18 total doses.
- Treatment efficacy was measured by:
  - "Event-free survival": Time to any of the following predetermined events: Disease progression, toxic effects of treatment, inability to resect all gross disease, recurrence of melanoma after surgery, or death from any cause.
  - Overall survival time was measured starting at the time of randomization to the date of death or for those still alive at the time of last contact.

INTERVENTION (# IN THE GROUP): 154

COMPARISON (# IN THE GROUP): 159

FOLLOW-UP PERIOD: Two years after completion of treatments

RESULTS:

Primary Outcome –

- Time to event-free survival was found to be significantly longer in the neoadjuvant-adjuvant group compared to the adjuvant group (*P*=.004) by the log-rank test.
  - At two years, event-free survival was 72% (95% CI, 64–80) in the neoadjuvant-adjuvant and 49% (95% CI, 41–59) in the adjuvant-only group.
  - Between-group differences showed consistent benefit in neoadjuvant treatment across all subgroups.

Secondary Outcome –

- Incidents of adverse reactions during adjuvant therapy between the two study groups were similar (12% neoadjuvant-adjuvant vs 14% adjuvant only).

LIMITATIONS:

- There were a small number of participants enrolled in the study.
- Many of the subgroups were too small to draw statistically significant between-group conclusions other than the tested outcome. May use additional outcome data for the basis of new studies with higher power to address additional between-group differences.

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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 view of the US Army Medical Department, the Army at Large, or the Department of Defense.

Should We Reconsider Using Proton Pump Inhibitors in Young Children?

Proton Pump Inhibitors Use and Risk of Serious Infections in Young Children

Lassalle M, Zureik M, Dray-Spira R. Proton Pump Inhibitor Use and Risk of Serious Infections in Young Children. *JAMA Pediatr.* 2023;177(10):1028-1038. doi:10.1001/jamapediatrics.2023.2900

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KEY TAKEAWAY: Proton pump inhibitor exposure increases infections in young children.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Proton pump inhibitor (PPI) use has increased among young children in high-income countries. This is a cause of concern because only gastroesophageal reflux disease (GERD) needs treatment compared to regular reflux (spit up). PPI use can be linked to bone fractures, acute kidney injuries, allergies, asthma, and inflammatory bowel disease. It was previously proposed that PPIs may make children susceptible to infections by changing the stomach pH or acting on the immune system. This study aimed to investigate if there is an association between PPI use and infections in children.

PATIENTS: Children who received an antacid treatment

INTERVENTION: PPI exposure

CONTROL: No PPI exposure

PRIMARY OUTCOME: Any infection that required hospitalization

Secondary Outcome: Incidence of serious infections according to infection site

METHODS (BRIEF DESCRIPTION):

- The Mother-Child EPI-MEREs Register was created by the EPI-PHARE from the French National Health Data System (SNDS), which contains all pregnancies overseen in France since 2010.
- Participants were children born between January 1, 2010, and December 31, 2018, who had received a PPI, histamine type-2 receptor antagonist, or antacid/alginate between birth and December 31, 2019.
- Exclusion criteria: Any children who did not obtain outpatient care before the index date, (the first date any of the medications were dispensed), if their mother did not have outpatient care the year before she became pregnant, history of perinatal infections, and other infections before the index date.
- PPI use over time (exposure) was assessed through unexposed or exposed, history of PPI use, and duration of ongoing PPI use.
- A 30-day lag on exposure was applied to prevent protopathic bias.
- Crude incidence rates of serious infections (per 100 person-years) were computed.
- Cox models were used to approximate relations between PPI use and serious infections by crude and adjusted hazard ratios (aHR).

INTERVENTION (# IN THE GROUP): 606,645

COMPARISON (# IN THE GROUP): 655,779

FOLLOW-UP PERIOD: One year

RESULTS:

Primary Outcome –

- PPI use increased serious infections compared to no PPI use (aHR 1.3; 95% CI, 1.3–1.4).

Secondary Outcome –

- Compared to no PPI use, PPI use was associated with an increased risk of the following infection types:
  - Gastrointestinal tract (aHR 1.5; 95% CI, 1.5-1.6)
  - Ear, nose, and throat (aHR 1.5; 95% CI, 1.4–1.5)
  - Lower respiratory tract (aHR 1.2; 95% CI, 1.2–1.3)
  - Kidneys or urinary tract (aHR 1.2; 95% CI, 1.2–1.3)
  - Nervous System (aHR 1.3; 95% CI, 1.1–1.5)
  - Bacterial infections (aHR 1.6; 95% CI, 1.5–1.6)
  - Viral infections (aHR 1.3; 95% CI, 1.3–1.3)

LIMITATIONS:

- Treatment indications for PPIs were not reported.
- No information was provided regarding breastfeeding or social interactions.
- Residual confounding was present, but the study minimized it by calculating E-values and using negative control outcomes.
- Some children might have been left out because it is unknown how many PPIs are used in hospitals or over the counter in France.

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Prescribe NSAIDs with Caution for Patients on Hormonal Contraception

Venous Thromboembolism with Use of Hormonal Contraception and Non-Steroidal Anti-Inflammatory Drugs: Nationwide Cohort Study

Meaidi A, Mascolo A, Sessa M, et al. Venous thromboembolism with use of hormonal contraception and non-steroidal anti-inflammatory drugs: nationwide cohort study. *BMJ.* 2023;382:e074450. Published 2023 Sep 6. doi:10.1136/bmj-2022-074450

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KEY TAKEAWAY: Concomitant use of medium/high-risk hormonal contraception and NSAIDs increases the risk of venous thromboembolism (VTE) when compared to the use of either of them alone.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Hormonal contraceptives are an independent risk factor for the development of VTE. Studies demonstrate risk for VTE with NSAID use. The incidence of VTE with concomitant use of hormonal conception and NSAIDs is unknown. This study aims to address the risk of taking both hormonal contraceptives and NSAIDs, both frequently prescribed in primary care.

PATIENTS: Women 15–49 years old

INTERVENTION: NSAID use and/or hormonal contraception use

CONTROL: Non-use of NSAIDs and hormonal contraception

PRIMARY OUTCOME: Incidence of VTE

METHODS (BRIEF DESCRIPTION):

- Participants were individuals living in Denmark between 1996–2017 with no significant past medical history or risk factors related to VTE.
- Only a limited number of participants (17%) had information on smoking and obesity status which can potentially be a confounding variable.
  - To adjust for this, women's education status was included in all analyses. In Denmark, smoking and obesity are highly associated with educational status. Less education means more likely to be obese and smoke cigarettes.
- Exclusion criteria included women with a history of bilateral oophorectomy, hysterectomy, sterilization, cancer, thrombophilia, fertility treatment, venous thromboembolism, and any arterial thrombosis.
- Women were stratified based on NSAID/hormonal birth control use into the following groups:
  - Non-use of hormonal contraception and NSAIDs
  - Hormonal contraception use only
  - NSAID use only
  - Concomitant use of NSAIDs and hormonal contraception
- NSAIDs use included ibuprofen, diclofenac, and naproxen.
- Hormonal contraception included contraceptives administered orally, by patch, injections, vaginal rings, and implants.
- Hormonal contraception was stratified as high, medium, or low risk based on the known association between their use and the formation of venous thromboembolism. Some forms of contraception are more likely to cause VTE, in particular the ones containing estrogen.
- Adjusted incidence rate ratios of VTEs were calculated for each group based on user status of hormonal contraception and NSAIDs using Poisson regression.
  - The analysis included an exposure variable with eight categories which were high-risk contraception only, high-risk + NSAID use, medium risk only, medium risk + NSAID use, low risk only, low risk + NSAID use, NSAID use only, and neither NSAID/contraception use.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 10 years

RESULTS:

Primary Outcome –

- Hormonal contraception use alone had an increased incidence of VTE compared to the non-use of NSAIDs and hormonal contraception.
  - High-risk hormonal contraception (incidence rate ratio [IRR] 4.2; 95% CI, 4.0–4.4)
  - Medium-risk hormonal contraception (IRR 3.0; 95% CI, 2.8–3.2)
- The use of any NSAIDs significantly increased the incidence of VTE compared to the non-use of

NSAIDs and hormonal contraception (IRR 8.1; 95% CI, 6.0–9.6).

- Concomitant use of hormonal contraception and NSAIDs increased the incidence of VTE compared to non-use of hormonal contraception and NSAIDs.
    - High-risk hormonal contraception and any NSAID (IRR 51; 95% CI, 44–58)
    - Medium-risk hormonal contraception and any NSAID (IRR 26; 95% CI, 20–35)

LIMITATIONS:

- NSAID dosage may have varied among users as the information on dosage was not available from the National Registry of Medicinal Product Statistics.
- Exposure was based on real-world data and was not randomized therefore residual confounding and unmeasured confounding variables exist.
- Information on smoking and obesity was only available in 355,086 of the 2,029,065 women in the study. Therefore, the study could not accurately account for these confounding factors but rather relied on the association between education level and smoking/obesity seen in Denmark.

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Investigating the Side Effects of GLP-1 Agonists

Adverse Drug Reactions of GLP-1 Agonists: A Systematic Review of Case Reports

Shetty R, Basheer FT, Poojari PG, Thunga G, Chandran VP, Acharya LD. Adverse drug reactions of GLP-1 agonists: A systematic review of case reports. *Diabetes Metab Syndr.* 2022;16(3):102427. doi:10.1016/j.dsx.2022.102427

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KEY TAKEAWAY: Gastrointestinal distress is the most common side effect of GLP-1 agonists with liraglutide and exenatide having adverse reactions most frequently.

STUDY DESIGN: Systematic review of 120 case reports and case series (N=120)

LEVEL OF EVIDENCE: STEP 4 (downgraded due to the design of included studies)

BRIEF BACKGROUND INFORMATION: As GLP-1 agonists are becoming more utilized as a primary treatment option for diabetic patients, it is important to consider side effect profiles. Common side effects can include pancreatitis, hepatitis, and acute kidney injury. This study further assesses adverse drug reactions of GLP-1 agonists.

PATIENTS: Adults with type 2 diabetes

INTERVENTION: Treatment with GLP-1 agonists

CONTROL: Not applicable

PRIMARY OUTCOME: Adverse effects, side effect profile

METHODS (BRIEF DESCRIPTION):

- A literature search was conducted across several medical databases, including PubMed and Google Scholar, to identify case reports and case series of adult diabetic patients on GLP-1 agonists who had any adverse drug reaction.
- Case reports that described any adverse reaction to liraglutide, exenatide, dulaglutide, semaglutide, albiglutide, or lixisenatide were included.
- Reported adverse reactions were subsequently grouped by organ system: Gastrointestinal, renal, endocrine/metabolic, hepatic, dermatologic, immunologic, reproductive, cardiovascular, neurologic, psychiatric, and hematologic.
- Adverse reactions in each organ system were recorded as a frequency and percentage of the total number of case reports.
- To determine which GLP-1 agonist had the greatest number of side effects, adverse reactions were also grouped by the specific GLP-1 agonists and recorded as a frequency and percentage of the total number of case reports.
- 120 cases were identified.
  - 64 (53%) were male and 56 (47%) were female
  - Although most cases occurred in the US and UK, there were also cases from Asia, the Middle East, and Western Europe.
  - Cases were reported from 2007–2021.

INTERVENTION (# IN THE GROUP): 120

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The most common side effects of the GLP-1 agonists were gastrointestinal (GI) disorders, such as pancreatitis, nausea, vomiting, and diarrhea (N=40; 33%).
- Of these, pancreatitis was the most common (N=23; 19%).
- Additional GLP-1 side effects include:
  - Renal: Kidney injury, acute interstitial nephritis, acute tubular necrosis, and renal failure (N=23; 19%)
  - Dermatologic: Bullous pemphigoid and morbilliform rash (N=14; 12%)
  - Hepatic: Drug-induced liver injury and autoimmune hepatitis (N=10; 8.3%)
  - Immunologic: Eosinophilic panniculitis and anaphylaxis (N=13; 11%)
  - Metabolic: Hypoglycemia, diabetic ketoacidosis (N=7; 5.8%)
  - Hematologic: Thrombocytopenia, eosinophilia (N=3; 2.5%)
  - Angioedema (N=3; 2.5%)
  - Seizures (N=2; 1.6%)
  - Cardiovascular: Tachycardia, cerebral venous thrombosis (N=2; 1.6%)
  - Worsened depression (N=1; 0.8%)
  - Infertility (N=1; 0.8%)
  - Generalized edema (N=1; 0.8%)
- Liraglutide and exenatide had the greatest number of adverse reactions:
  - Liraglutide (N=46; 38%)

- Exenatide (N=46; 38%)
- Dulaglutide (N=20; 17%)
- Semaglutide (N=4; 3.3%)
- Albiglutide (N=2; 1.6%)
- Lixisenatide (N=2; 1.6%)

LIMITATIONS:

- This study shows a correlation between GLP-1 agonist use and certain adverse events, however, a causal relationship between the two cannot be fully established.
- A meta-analysis of randomized control trials or cohort studies would be more effective at showing a stronger association.
- Some adverse reactions were reported by only one person, which limits the side effect's generalizability.

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