REVIEW

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Update in Outpatient General Internal Medicine: Practice-Changing Evidence Published in 2025

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ABSTRACT

The continually evolving nature of evidence-based medicine requires clinicians to update their practice in response to new data. Integrating new research is essential for advancing clinical practice. To this aim, a panel of seven internists screened articles from seven high-impact internal medicine journals deemed most relevant to general outpatient care: *New England Journal of Medicine, The Lancet, Annals of Internal Medicine, Journal of the American Medical Association (JAMA), JAMA Internal Medicine, British Medical Journal (BMJ),* and *Public Library of Science (PLoS) Medicine*. The review also included curated summaries and evidence databases, including *American College of Physicians Journal Club, NEJM Journal Watch, BMJ Evidence-Base Medicine, McMaster ACCESSSS/DynaMed Evidence Alerts,* and *Cochrane Reviews*. Consensus was achieved using a modified Delphi process that emphasized outpatient relevance, impact on clinical practice, and overall quality of evidence. Related articles addressing the same clinical topics were evaluated together. Ultimately, seven practice-changing articles were included.
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KEYWORDS: 2025 update; General internal medicine; Outpatient; Practice-changing evidence

Treating partners with oral plus topical antibiotics reduces bacterial vaginosis recurrence[1]

Bacterial vaginosis is common and has a high rate of recurrence.[1] Prior research has suggested that treatment of sexual partners may reduce bacterial vaginosis recurrence, but studies were of low quality, with variable results.[2] This study used a standardized method for determining bacterial vaginosis diagnosis. Researchers randomized 164 monogamous heterosexual couples to a control group in which women received standard first-line therapy alone, or an intervention group in which women received the same therapy plus treatment of their male partners with oral metronidazole and topical clindamycin. The primary outcome was recurrence of bacterial vaginosis within 12 weeks.

Results

The woman-only treatment group showed 43 of 68 women (63%) with recurrent bacterial vaginosis within 12 weeks, which was equivalent to a recurrence rate of 4.2 per person-year (95% confidence interval [CI], 3.2 to 5.7). The mean time to recurrence was 54.5 days in the control group. The woman plus partner treatment group had recurrence in 24 of 69 (35%) of women within 12 weeks, which was equivalent to a recurrence rate of 1.6 per person-year (95% CI, 1.1 to 2.4). The mean time to recurrence was 73.9 days in the intervention group (difference was 19.3 days; 95% CI, 11.5 to 27.1; $p < 0.001$). This corresponds to an absolute risk difference of −2.6 recurrences per person-year (95% CI, −4.0

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to −1.2) and a lower risk of recurrence in the partner-treatment group over 12 weeks (hazard ratio, 0.37; 95% CI, 0.22 to 0.61).

Limitations

Microscopists assessing the diagnosis were blinded, but researchers and participants were not. No placebo cream was used for control group men (since it could alter penile skin flora). Planned recruitment was 342 couples, but the trial was stopped early by the data safety monitoring board due to efficacy of the intervention. 14% of male partners took less than 70% of the prescribed doses of medication.

Implications for practice

Treating male partners with oral metronidazole plus topical clindamycin reduced bacterial vaginosis recurrence in their female partners. The lowest recurrence rates were seen when male partners were 100% adherent to treatment.

CLINICAL SIGNIFICANCE

- Treating male partners reduces bacterial vaginosis recurrence.
- Oral GLP-1 medications are effective for type 2 diabetes and weight loss.
- Sublingual cyclobenzaprine improves pain in patients with fibromyalgia.
- Pramipexole can improve treatment-resistant depression.
- Reduced-dose direct oral anticoagulants for secondary prevention of venous thromboembolism may be effective and reduce bleeding risk.
- Semaglutide is effective in treating metabolic dysfunction-associated steatohepatitis (MASH).
- Continue SGLT-2 inhibitors after incident urinary tract infection.

Oral GLP-1 based medications are effective for diabetes management and weight loss[3]

Glucagon-like peptide 1 (GLP-1) based medications have transformed treatment of diabetes, obesity, and associated conditions. Most GLP-1s are injectable with implications for cost, storage, and adherence. Four large, multi-center, placebo-controlled randomized trials assessed the efficacy of daily oral GLP-1-based medications for type 2 diabetes and obesity. In a trial of 9650 older adults with type 2 diabetes and hemoglobin A1c (HbA1c) between 6.5%-10% plus atherosclerotic cardiovascular disease and/or chronic kidney disease, patients were randomized to oral semaglutide (a GLP-1 agonist) or placebo to assess a composite primary outcome of major cardiovascular events.[3] In a trial of 205 adults without diabetes with BMI ≥ 30 or ≥ 27 with at least one obesity-related complication, patients were randomized to oral semaglutide or placebo to assess percent change in body weight.[4] In a trial of 559 adults with type 2 diabetes with HbA1c between 7 and 9.5%, patients were randomized to oral orforglipron (a nonpeptide GLP-1 agonist) at different doses or placebo to assess change in HbA1c.[5] In a trial of 3127 adults with BMI ≥ 30 or ≥ 27 with at least one obesity-related complication, patients were randomized to oral orforglipron or placebo to assess percent change in body weight.[6]

Results

The trial of oral semaglutide and cardiovascular outcomes showed that, at median follow-up of 49.5 months, composite major cardiovascular events occurred in 12% of patients with diabetes taking oral semaglutide versus 13.8% of patients taking placebo (hazard ratio, 0.86; 95% CI, 0.77 to 0.96; $P = 0.006$).[3] In the trial of oral semaglutide for weight loss, at 64-week follow-up, percent body weight loss was −13.6% in the oral semaglutide group and −2.2% in the placebo group (estimated difference, −11.4%; 95% CI, −13.9 to −9.0; $P < 0.001$).[4] The trial of orforglipron for type 2 diabetes showed that, at 40-week follow-up, the mean change in HbA1c was −1.48% with the highest dose of oral orforglipron and −0.41% with placebo. All three doses of orforglipron were superior to placebo, and mean difference from placebo was −0.83% (95% CI, −1.10 to −0.56).[5] In the trial of orforglipron for weight loss, at 72-week follow-up, percent body weight loss was −11.2% (95% CI, −12.0 to −10.4) with the highest dose of orforglipron, compared with −2.1% (95% CI, −2.8 to −1.4) with placebo ($P < 0.001$ for all comparisons with placebo; higher orforglipron doses resulted in more weight loss than lower doses).[6]

Limitations

Only one of the four studies addressed cardiac, metabolic, or renal outcomes, which may initially limit indications for oral GLP-1 based medications. The percent body weight loss for oral semaglutide and orforglipron was lower than in clinical trials for injectable semaglutide and tirzepatide.

Implications for practice

The health benefits of oral GLP-1 medications will make them a viable and convenient option for patients and clinicians. Oral semaglutide was FDA approved in 2025 for weight management and reduction of cardiac events among patients with an overweight/obesity diagnosis and cardiovascular disease. FDA approval for orforglipron is expected in 2026.

Bedtime sublingual cyclobenzaprine improves pain and function in patients with fibromyalgia[7]

Fibromyalgia is a chronic, nociplastic pain syndrome defined by widespread pain, fatigue, and non-restorative sleep. It is difficult to treat, and patients often report

dissatisfaction with treatment modalities.[8] Impaired sleep is a major contributor to symptom burden.[9] Oral cyclobenzaprine has historically shown limited efficacy for fibromyalgia pain, but symptom improvement can be seen with increased sleep quality. Sublingual cyclobenzaprine was engineered to induce diurnal variation in blood levels, with maximal concentrations optimized during the sleep cycle.[10] This multicenter study randomized 456 patients to receive sublingual cyclobenzaprine or placebo and followed them for 14 weeks. The primary endpoint was a change in pain using Numeric Rating Scale (NRS) scores. Secondary endpoints included sleep disturbance and fatigue, assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires.

Results

Sublingual cyclobenzaprine improved pain compared to the placebo at week 14 measured by least squares mean change from baseline (−1.8 versus −1.2, respectively; least squares mean difference [LSMD] versus placebo, −0.7 [95% CI, −1.0 to −0.3]; effect size, 0.38; $P < 0.001$), which is a comparable effect size to other FDA-approved fibromyalgia medications. Sleep disturbance and fatigue also improved with least squares mean changes from baseline in PROMIS scores (LSMD versus placebo [95% CI]: Sleep Disturbance, −4.2 [−5.8 to −2.7]; effect size, 0.50; $P <$ 0.001; Fatigue, −3.0 [−4.5 to −1.5]; effect size, 0.37; $P < 0.001$). The medication was well tolerated.

Limitations

Men were underrepresented, which limits the generalizability. Mean age of participants was 49, suggesting extrapolation to older patients requires caution. Patients with complex psychiatric histories or those taking opioids were excluded.

Implications for practice

Sublingual cyclobenzaprine improves pain, sleep, and fatigue in patients with fibromyalgia. Its FDA approval is a welcome addition for a condition with few effective therapies.

Pramipexole can improve treatment-resistant depression[11]

Treatment-resistant depression occurs in approximately 30% of adults taking antidepressant medication and is associated with significant morbidity and health-care cost.[12] Existing augmentation options come with efficacy and tolerability concerns.[13] Dopaminergic agents have been used off-label to augment treatment-resistant depression, but evidence about efficacy, tolerability, and duration of benefit is limited. In this randomized, placebo-controlled trial, 151 adults with treatment-resistant, unipolar depression already taking antidepressant medication were randomized to pramipexole (titrated to target dose of 2.5 mg) or placebo and followed for up to 48 weeks. The primary outcome, a 16-item Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$), was assessed at 12 weeks.

Results

At week 12, the $QIDS\text{-}SR_{16}$ was −6.4 (SD 4.9) in the pramipexole group compared with −2.4 (SD 4.0) in the placebo group, with a mean difference of −3.91 (95% CI, −5.37 to −2.45; $P < 0.0001$). Treatment response occurred in 44% (30/68) of pramipexole-treated patients versus 16% (11/67) receiving placebo (RR 2.72 [95% CI, 1.49 to 4.95]; $P = 0.0011$). Remission rates were 28% versus 8% respectively (RR 3.94 [95% CI, 1.61 to 9.64]; $P = 0.0026$). Symptom improvement was maintained at week 48 ($QIDS\text{-}SR_{16}$ mean difference −2.02 [95% CI, −3.73 to −0.31]; $P = 0.021$). Discontinuation rates related to adverse effects were higher with pramipexole (20%) than placebo (5%; RR 3.95 [95% CI, 1.35 to 11.57]; $P = 0.012$).

Limitations

The study sample was small and there is concern for functional unmasking, due to recognizable side effects of pramipexole. Tolerability concerns and prescribing complexity may limit broad implementation. Larger trials are needed to confirm findings and clarify patient selection, which would better define pramipexole's role compared to other existing augmentation options. Ethnicity data was not collected in this study.

Implications for practice

Pramipexole is an effective augmentation strategy in treatment resistant depression. The number needed to treat of 4 for improvement compares favorably to other augmentation options.[14] As a low-cost, generic medication, pramipexole is an appealing option for treatment of treatment resistant depression in primary care.

Reduced-dose direct oral anticoagulants for secondary prevention of venous thromboembolism may be efficacious and reduce bleeding risk[15]

In patients with cancer requiring extended treatment for secondary venous thromboembolism prevention, a recent study found that reduced-dose direct oral anticoagulant (DOAC) was non-inferior to full dose DOAC therapy.[16] For patients without cancer at high risk of recurrent venous thromboembolism (VTE), indefinite full-dose anticoagulation is a common recommendation. The optimal DOAC dose in patients at high risk for recurrence of venous thromboembolism without cancer is not clear.

The RENOVE trial was a non-inferiority, randomized, open-label, blinded endpoint study performed in 47 centers in France. Outpatient adults without cancer (2768 patients enrolled, 65% male) who had completed treatment (6-24 months) for acute venous thromboembolism (pulmonary

embolism or deep venous thrombosis) and had indications for extended treatment were randomized 1:1 to reduced-dose anticoagulation (apixaban 2.5 mg twice daily or rivaroxaban 10 mg daily) or full-dose anticoagulation (apixaban 5 mg twice daily or rivaroxaban 20 mg daily). Median follow-up was 37.1 months (IQR 24·0-48·3). The primary outcome was recurrent VTE. Key secondary outcomes were major bleeding or clinically relevant non-major bleeding.

Results

In the reduced-dose treatment group, recurrent venous thromboembolism occurred in 19 of 1383 participants (5-year cumulative incidence 2.2% [95% CI, 1.1 to 3.3]) versus 15 of 1385 participants in the full-dose treatment group (5-year cumulative incidence 1.8% [95% CI, 0.8 to2.7]; adjusted HR 1.32 [95% CI, 0.67 to 2.60]; absolute difference 0.40% [95% CI, −1.05 to 1.85]; $P = 0.23$ for non-inferiority). In the reduced-dose treatment group, major or clinically relevant non-major bleeding occurred in 96 patients (5-year cumulative incidence 9.9% [95% CI, 7.7 to 12.1]) versus 154 patients in the full-dose group (5-year cumulative incidence 15.2% [95% CI,12.8 to 17.6]; adjusted HR 0.61 [95% CI, 0.48 to 0.79]).

Limitations

The open label design could influence behaviors, although endpoints were adjudicated by a blinded committee. Statistical manipulation was used to extrapolate outcomes to 5 years. Patients with renal insufficiency, elevated bleeding risk, and concurrent antiplatelet therapy were excluded. Overrepresentation of men from a single country could limit generalizability.

Implications for practice

Reduced dose DOAC treatment is a consideration for patients without cancer at high risk for recurrent venous thromboembolism. Although non-inferiority was not achieved, overall venous thromboembolism rates were very low in both groups and the bleeding risk was significantly reduced in the lower dose treatment group. An additional recent study evaluating treatment duration for patients with venous thromboembolism in the setting of a transient provoking factor (e.g. surgery) and at least one additional risk factor found that low intensity apixaban therapy for 12 months lowered both venous thromboembolism recurrence risk and bleeding risk.[17] This body of evidence suggests that secondary prevention with reduced-dose DOAC may result in low VTE recurrence and less bleeding risk. Further research is needed to clarify practice guidelines and individualize treatment approaches.

Semaglutide is effective in treating metabolic dysfunction-associated steatohepatitis[18]

Metabolic dysfunction associated steatotic liver disease (MASLD) affects one-third of the adult population and is associated with increased hepatic and nonhepatic morbidity and mortality.[19] Metabolic Dysfunction-Associated Steatohepatitis (MASH) is a histologically defined subset of MASLD characterized by steatosis with inflammation and progressive fibrosis at higher stages. The current mainstay of treatment to reverse steatosis and improve outcomes are lifestyle interventions.

In a phase 3 randomized, double-blind, placebo-controlled trial of 1197 patients with biopsy-defined MASH and stage 2 or 3 hepatic fibrosis, patients received subcutaneous Semaglutide 2.4 mg weekly versus placebo for 240 weeks. The study was conducted at 253 centers in 37 countries. The first 800 patients completing 72 weeks of treatment were reported. The two end points were resolution of steatohepatitis without worsening of liver fibrosis, and a decrease in liver fibrosis without worsening of steatohepatitis.

Additionally, a smaller double-blind, randomized, placebo-controlled trial conducted in 6 tertiary hospitals in China compared response of dapagliflozin 10 mg to placebo in 548 participants with biopsy-proven MASH.[20]

Results

In the semaglutide trial, resolution of steatohepatitis without worsening of fibrosis was seen in 62.9% of the treatment group compared with 34.3% of the placebo group (95% CI, 21.1 to 36.2; $P < 0.001$). A decrease in hepatic fibrosis without worsening steatohepatitis occurred in 36.8% of the treatment group versus 22.4% of the placebo group, (95% CI, 7.5 to 21.3; $P < 0.001$). Resolution of steatohepatitis and reduction in liver fibrosis occurred in 32.7% of semaglutide group and 16.1% of placebo group (95% CI 10.2 to 22.8; $P < 0.001$).

In the dapagliflozin trial, 53% of the treated group versus 30% of the placebo group had MASH improvement without worsening of fibrosis (risk ratio 1.73 [95% CI, 1.16 to 2.58]; $P = 0.006$). MASH resolution without worsening of fibrosis occurred in 23% treated group versus 8% of the placebo group (risk ratio 2.91 [95% CI, 1.22 to 6.97]; $P = 0.01$). Improvement of fibrosis without worsening of MASH occurred in 45% of the treated group compared with 20% of the placebo group (risk ratio 2.25 [95% CI, 1.35 to 3.75]; $P = 0.001$).

Limitations

The semaglutide trial was limited by lack of racial diversity, blood biomarkers to assess alcohol consumption, and data on changes in body composition with treatment. The dapagliflozin study was limited by small sample size and single-country participants. Future studies should assess both the cost effectiveness of treatment and impact on long term outcomes such as cirrhosis.

Implications for practice

Semaglutide is effective for treatment of MASH and has now been FDA approved for this indication. A smaller

study suggests that dapagliflozin may also result in histological improvement of steatosis and fibrosis, but more robust studies are needed.

Continue SGLT-2 inhibitors after incident urinary tract infection[21]

Sodium-glucose cotransporter-2 inhibitor (SGLT-2i) medications are widely used for treatment of type 2 diabetes, chronic kidney disease, and heart failure. They have cardiovascular and renal benefits, decreasing risk of major adverse cardiovascular events and progression of chronic kidney disease. Because of the glucosuria effect of SGLT-2is, urinary tract infections are a primary cause of medication discontinuation.[22]

This cohort study of 61,606 patients in Hong Kong with type 2 diabetes on an SGLT-2i compared cardiovascular composite outcomes (heart failure hospitalization, stroke, myocardial infarction, or all-cause mortality) and renal composite outcomes (50% decline in eGFR, end-stage renal failure, or all-cause mortality) in patients with and without incident UTI, and in patients in whom SGLT-2is were and were not discontinued following UTI diagnosis. Target trial emulation analysis was used to estimate the effect of discontinuing versus continuing SGLT-2i within 120 days after incident UTI. Median follow up was 0.94 years.

Results

Of the 61,606 study patients, 3921 (6.36%) had at least one urinary tract infection (UTI). Compared to patients without UTI, those with incident UTI had higher risk of cardiovascular composite outcomes (HR 3.18; 95% CI, 2.88 to 3.51) and renal composite outcomes (HR 2.51; 95% CI, 2.32 to 2.72). After incident UTI diagnosis, 1267 (32.31%) patients discontinued SGLT2i therapy. SGLT-2i discontinuation was associated with higher cardiovascular (HR 1.35; 95% CI, 1.20 to 1.53) and renal (HR 1.35; 95% CI,1.21 to 1.51) adverse events compared to continuation. However, the risk of recurrent UTI was similar between those who discontinued and continued SGLT-2i after UTI (HR 0.96; 95% CI, 0.22 to 4.29).

Limitations

This is an observational study, and although the study authors used target trial emulation, randomized controlled trials in more heterogeneous populations are warranted to confirm their results. Additionally, this study did not evaluate genital mycotic infections, which are well established adverse events of SGLT-2is and are also a reason for discontinuation of SGLT-2is.[23,24]

Implications for practice

Clinicians should attempt to continue SGLT-2i therapy in patients who develop UTIs, particularly if the patient has cardiovascular or renal disease. In patients on SGLT-2is for type 2 diabetes, UTI itself is associated with increased risk of both cardiovascular and renal adverse events. Recent meta-analyses have shown no increased risk of UTI in patients on SGLT-2is compared to placebo.[23,24] Discontinuation of SGLT-2is after UTI is associated with worse cardiovascular and renal outcomes without changing the risk of recurrent UTI.

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Authorship

All authors reviewed literature, had access to the data, and had a role in writing the manuscript. All authors approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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