



Updates in Pharmacotherapy

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RESEARCH UPDATES

Insulin in Capsule - Safety and Efficacy Study in Patients with Early-Stage Type 2 Diabetes¹⁻²

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Background: The most common method of administering insulin to people with diabetes is through injections. Insulin is also available as an inhaled formulation but is not used widely in practice. Despite its efficacy, insulin is generally considered as one of the last pharmacotherapy options due to the risk of hypoglycemia and weight gain. New et al. explains the oral formulation can deliver insulin directly to the liver and avoid peripheral hyperinsulinemia. The author describes this delivery method as the major advantage over injectable insulin as one can avoid hypoglycemia and weight gain. Insulin is a poly-peptide protein that is normally broken down by digestive enzymes and loses its physiological ability when ingested orally. However, a novel delivery technology called Axcress™ developed by Diabetology Ltd increases the absorption of peptides across the intestinal wall without any chemical modification of the active compounds and thereby maintaining its physiological effect. Capsulin™ is a novel drug in the capsule form that contains regular human insulin in the form of dry white powder with excipients such as natural bile salt and an antioxidant to prevent degradation in the gut, to penetrate the mucin layer, and to aid its uptake by and across intestinal cells.

Purpose: The primary objective of this study was to evaluate the safety and efficacy of Capsulin™, an oral insulin capsule formulation, in patients with uncontrolled type 2 diabetes treated with metformin.

Study Design: This was a phase 2b open-label, randomized, comparative study that was conducted at 15 centers across India. The study included male or female patients aged 35-60 years old with type 2 diabetes diagnosed less than two years prior to enrollment with HbA1c of 7-9.5%, with body mass index (BMI) = 18-30 kg/m² at baseline, treated with metformin (1000 to 2500 mg per day), and on regular diet and exercise regimen at least 12 weeks prior to enrollment. The study excluded patients who received treatment with insulin or any other oral diabetic medications besides metformin within three months prior to enrollment. The participants were randomized into three groups in a 1:1:1 ratio: Capsulin™ 75 IU (2.5 mg) twice daily (BID), 150 IU (5 mg) BID, and 300 IU (10 mg) BID for 12 weeks. The participants in the 150 IU BID and 300 IU BID groups underwent a run-in period of one week with each previous lower dose before receiving the assigned dose. After the run-in period, participants received the same dose without titration during the entire study period. Adherence was assessed through the patient diary and on the basis of the number of capsules dispensed versus the number of capsules used and returned in the capsule strips. The primary endpoint of this study was the change in HbA1c level after 12 weeks from baseline. The secondary endpoints were change in fasting blood glucose, 2-hour postprandial glucose, adverse events, total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol.

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Results: The study was conducted from January 2019 to July 2020, and it was originally intended to include 195 participants. However, the trial was terminated early with 132 participants because of logistical difficulties with recruiting patients during the COVID-19 pandemic. Of these, 32 participants were excluded from the analysis because they were unable to attend the central clinic mainly due to lockdown from the COVID-19 pandemic. Thus, 100 patients were included in the analysis: 75 IU BID group (n=33), 150 IU BID group (n=29), and 300 IU BID group (n=38). The 150 IU BID and 300 IU BID groups met the primary endpoint with mean change in HbA1c of -0.52% (P=0.004) and -0.42% (P=0.009), respectively. The 75 IU BID group had a mean change in HbA1c of -0.11% but did not reach statistical difference (P=0.522). For the secondary endpoint of change in fasting blood glucose, only the 150 IU BID group reached a statistical difference of -18.8 mg/dl (P=0.017). Although all groups showed a reduction in 2-hour postprandial glucose ranging 17 to 31 mg/dl, they were not statistically significant. No hypoglycemia, gastrointestinal side effects, or significant weight gain were observed throughout the 12 weeks of the study. Mean reduction of total cholesterol, LDL, and triglycerides were -15 mg/dl, -9.9 mg/dl, and -40 mg/dl, respectively in 150 IU BID group. The results from other groups were not reported. The average adherence was calculated as 97%. In addition, a sub-group analysis suggested the potential of the 150 IU BID group to lower HbA1c levels by as much as 1.58% in patients with starting values of 9-9.5%.

Conclusions: Capsulin™ 150 IU administered orally twice daily reduces HbA1c by 0.52% and fasting blood glucose level by 18.8 mg/dl over a 12-week period without causing significant weight gain or hypoglycemia. One limitation of the study is the absence of a placebo-controlled group to limit the potential bias of metformin on the results.

Key Point: This study shows a promising future of orally administered insulin for the treatment of type 2 diabetes by improving HbA1c without causing hypoglycemia or weight gain. However, it is unclear if the HbA1c lowering effect of Capsulin™ is affected by dose or baseline HbA1c as the study results showed no difference between the 150 IU and 300 IU groups but showed a much greater HbA1c reduction in patients with higher HbA1c baseline levels. The author explained orally administered insulin works directly on the liver where the level of glucose control is determined by the level of glucose itself rather than dose of insulin. Therefore, Capsulin™ works in a glucose-dependent manner without hypoglycemia risk and causes greater A1c reduction in patients with higher glucose level at baseline. More studies will be needed to test this hypothesis.

Pemafibrate in Hypertriglyceridemia: Treating Patients or Numbers³

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Background: Triglycerides are atherogenic and a component of very low-density lipoprotein. Hypertriglyceridemia has been shown to increase atherosclerotic cardiovascular disease (ASCVD) risk. Previous studies of medications used to lower triglycerides have found no reduction in cardiovascular risk despite significant improvements in triglyceride levels. Pemafibrate is a potent and selective peroxisome proliferator-activated receptor alpha (PPAR α) modulator that is known to decrease triglyceride levels. Previous subgroup analyses suggest that this medication could improve cardiovascular outcomes in patients with hypertriglyceridemia and low levels of low-density lipoprotein (LDL).

Purpose: To determine if triglyceride-lowering with pemafibrate is also associated with an improvement in cardiovascular outcomes in adults with type 2 diabetes and mild-to-moderate hypertriglyceridemia.

Study Design: This double-blind, randomized, placebo-controlled, event-driven trial was conducted in 24 countries with enrollment taking place between March 2017 and September 2020. The study included two cohorts: the primary-prevention cohort included men ≥ 50 years and women ≥ 55 years without a history of ASCVD, and the secondary-prevention cohort included adults ≥ 18 years with established ASCVD. To be eligible, participants had to have a diagnosis of type 2 diabetes, a fasting triglyceride level of 200-499 mg/dL, high-density lipoprotein (HDL) of ≤ 40 mg/dL, and LDL of ≤ 70 mg/dL with or without lipid-lowering therapy or LDL ≤ 100 mg/dL and unable to receive statin therapy. Those with type 1 diabetes; poorly controlled diabetes or thyroid disease; or severe heart failure, kidney disease, or liver disease were excluded. Participants were randomized to receive either pemafibrate 0.2 mg twice daily or placebo. The initial primary outcome was a composite of myocardial infarction, ischemic stroke, hospitalization for unstable angina needing unplanned coronary revascularization (later modified to include any coronary revascularization event), or death from cardiovascular causes. Notable secondary outcomes included the original primary outcome, composite of the primary outcome or hospitalization for heart failure, and new or worsening peripheral artery disease.

Results: A total of 10,497 patients were included in the intention-to-treat population. Baseline characteristics between the two treatment groups were balanced: the median age was 64 years, 27.5% were female, 85.8% were white, and 19.4% were Hispanic or Latinx. One-third of participants were part of the primary-prevention cohort. At baseline, 95.7% of the the trial population was on a statin, and 80.1% were on an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. The median fasting lipid profile showed a triglyceride level of 271 mg/dL, HDL of 33 mg/dL, and LDL of 78 mg/dL. The median HbA1c was 7.3% in both groups. At four months, the pemafibrate group saw a 31.1%

reduction in triglycerides compared to 6.9% with placebo. There was a 14.0% increase in LDL cholesterol in the pemafibrate group; however, no change in total or non-HDL cholesterol. With regard to clinical outcomes, the primary composite endpoint occurred in 572 patients in the pemafibrate group and 560 patients in the placebo group (HR, 1.03; 95% CI, 0.91-1.15; P=0.67). The original primary composite endpoint occurred in 432 patients in the pemafibrate group and 417 patients in the placebo group (HR, 1.04; 95% CI, 0.91-1.19). There was no statistical difference in any other secondary cardiovascular endpoints between the two groups. The pemafibrate group demonstrated an increase in renal adverse effects (HR, 1.12; 95% CI, 1.04-1.20; P=0.004) and venous thromboembolism (HR, 2.05; 95% CI, 1.35-3.17; P<0.001) compared to placebo. However, the treatment group experienced fewer hepatic adverse events (HR, 0.83; 95% CI, 0.69-0.99; P=0.04), including fewer reported nonalcoholic fatty liver disease (HR, 0.78; 95% CI, 0.63-0.96; P=0.02).

Conclusions: Despite previous subgroup analyses suggesting that triglyceride-lowering therapy could improve cardiovascular risk in patients with hypertriglyceridemia, low HDL, and concomitant type 2 diabetes, this study continues to support previous conclusions that statistically significant triglyceride-lowering is not associated with reduction in cardiovascular risk.

Key Point: This trial demonstrated that despite significant reductions in triglycerides in the treatment group, pemafibrate was not associated with a statistically or clinically significant reduction in ASCVD risk. These conclusions support current treatment guidelines which recommend initiation or intensification of statin therapy and lifestyle modifications to manage hypertriglyceridemia prior to initiation of fibrate therapy.

Does Antidepressant Use During Pregnancy Increase Risk of Neurodevelopmental Disorders in Children?⁴

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Background: Researchers have attempted to understand the safety of prenatal antidepressant use for many years, with a particular focus on neurodevelopmental disorders (NDD) in children exposed to these medications during pregnancy. Evidence has been conflicting which has kept the topic controversial, despite 6-8% of pregnant women in the United States taking antidepressants (correlating to approximately 280,000 births yearly). Many studies across the world have looked at this issue, but outcomes have been too heterogeneous to draw conclusions. This study looked closer at confounding variables within prenatal antidepressant use to further tease out potential for risk of NDDs.

Purpose: This trial sought to determine whether antidepressant

use in pregnancy is associated with neurodevelopmental outcomes in children.

Study Design: Approximately 3.18 million patients aged 12 to 55 years with live birth deliveries were collected through Medicaid Analytic eXtract (nationwide Medicaid beneficiaries; 2000-2014) or MarketScan Claims Database (private commercial health insurance; 2003-2015). In order to be eligible, patients had to have insurance for at least three months prior to their last menstrual period and until one month after delivery. The exposed patients were also required to have at least one antidepressant dispensed between the 19th week of gestation to delivery. Confounding factors that were collected when available were: antidepressant indication, genetics, demographics (age, race, ethnicity, state, delivery year), healthcare visits (to aid in assessment of severity of mental health conditions), lifestyle factors (substance use), other medications, comorbidities, prenatal care, socioeconomic indicators, and dispensed outpatient prescriptions. The control group consisted of individuals who met the population criteria but were not exposed to antidepressants at least 90 days prior to pregnancy and up until the day prior to delivery. There was also a secondary study of siblings who were not exposed to antidepressants to compare to siblings who were exposed.

Of the approximately 3.18 million pregnancies, 198,496 of the patients had early-pregnancy exposure to antidepressants (dispensing in the first half of pregnancy; included in a secondary analysis), 145,702 of the patients had late-pregnancy exposure to antidepressants, and 3,032,745 patients were unexposed. The children were followed until diagnosis of collected NDD*, disenrollment, death, or end of 14 year study period. Analysis was then completed from August 2020 to July 2021. After weighting, characteristics were balanced.

*Collected NDDs: autism spectrum disorder, attention deficit/hyperactivity disorder, specific learning disorders, developmental speech/language disorder, developmental coordination disorder, intellectual disability, behavioral disorder; validated via claims algorithms

Results: By age 12, 46.8% of children (95% CI, 45.6% to 48.1%) in the Medicaid cohort and 24.9% (95% CI, 23.0% to 26.9%) in the commercial cohort with antidepressant exposure had any NDD, compared with 31.4% (95% CI, 31.1% to 31.6%) and 15.1% (95% CI, 14.7% to 15.4%), respectively, among unexposed individuals. Crude HRs (hazard ratios) for all NDD outcomes suggested an increase in risk, with HRs ranging from 1.32 (95% CI, 1.16 to 1.47) for specific learning disorders to 2.02 (95% CI, 1.96 to 2.08) for ADHD, among children exposed versus unexposed. These outcomes were further broken down into the specific type of NDD at age 12; crude data suggested increased risk with antidepressant use, but when other variables were accounted for, this did not persist.

Taking confounding factors into account, individuals in the experimental group were overall older and had more medication use. Cumulative incidence for all NDDs was higher in the Medicaid population compared to commercial health insurance groups.

Results for each exposure window were similar whether antidepressant exposure occurred only in early pregnancy or only in late pregnancy. Composite outcome of any NDD showed no significant increased risk for any drug class or specific medication (except potentially escitalopram, which showed slightly higher HRs; more research needed).

Conclusions: Rather than interpreting results in a typical significant versus non-significant lens, they used a qualitative approach to express the results as meaningful or not meaningful increases in risks. It initially appeared that children exposed to antidepressants during pregnancy had an increased risk of having a NDD compared to children not exposed to antidepressants during pregnancy. However, after adjusting for potential confounders, the results shifted away from this association. The comparison shifted even more towards no-difference when comparing to people who discontinued antidepressants prior to pregnancy or compared to unexposed sibling comparisons. There is a possibility that the increased risk is more related to the indication for taking an antidepressant and the environment during pregnancy than to the medication itself. The confounding factors were shown to carry an impact on the outcomes, which is what has largely been unexplored prior to this study.

Key Point: In this trial, children born after exposure to common antidepressant medications during gestation were not at higher risk for neurodevelopmental disorders after controlling for various confounding factors.

Baxdrostat: looking to BrigHTN the outlook for treatment-resistant hypertension⁵⁻⁶

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Background: Elevated blood pressure has been identified as the leading risk factor for cardiovascular disease, stroke, disability, and death. In the United States, about 10% of adults with hypertension (10 to 12 million) have treatment-resistant hypertension, defined as elevated blood pressure while on at least three antihypertensive medications of different classes, including a diuretic. Currently, spironolactone—a mineralocorticoid receptor antagonist—is recommended by the American Heart Association for treatment-resistant hypertension, but the potential for adverse effects limits its use. Despite a variety of antihypertensive medication options available, 40-50% of patients with hypertension remain inadequately treated. As a highly selective inhibitor of aldosterone synthase, baxdrostat prevents the body from producing

aldosterone (rather than blocking the mineralocorticoid receptor), making it an intriguing option for treatment-resistant hypertension due to a more limited side effect profile.

Purpose: The purpose of this study was to examine the safety and efficacy of baxdrostat treatment for patients diagnosed with treatment-resistant hypertension.

Study Design: BrigHTN is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase II trial that assigned patients to receive 0.5 mg, 1 mg, or 2 mg of once-daily baxdrostat or placebo. Participants were eligible to enroll if they were at least 18 years old, taking stable doses of at least three antihypertensive medications, including one diuretic, and had a mean blood pressure of at least 130/80 mmHg. Key exclusion criteria were mean seated systolic blood pressures of at least 180 mmHg or diastolic blood pressure of at least 110 mmHg, eGFR of <45 mL/min/1.73m², and uncontrolled diabetes. Patients receiving mineralocorticoid receptor antagonists and potassium sparing diuretics were required to discontinue these medications four weeks prior to randomization. Eligible participants entered a 2-week run-in period and patients with at least 70% adherence, as determined by pill counts, underwent randomization. The primary efficacy endpoint evaluated was the change in the mean seated systolic blood pressure from baseline to the end of the 12-week treatment period. The secondary efficacy endpoints included the change in seated diastolic blood pressure and the percentage of patients with a seated blood pressure of <130/80 mmHg at the end of the 12-week period. The safety endpoints evaluated were adverse effects of special interest, vital signs, and results of laboratory tests, electrocardiography, and physical examinations.

Results: The trial ran from July 30, 2020 to June 14, 2022 and 274 patients were included in the modified intention-to-treat analysis. Each trial group consisted of similar demographic and clinical characteristics at baseline. Approximately 44% of the patients were female, and mean patient age was 62 years old. The study population represented 70% White, 28% Black, 2% Asian, <1% American Indian or Alaska Native, and 43% identified as Hispanic or Latinx adults. The modified intention-to-treat analysis of the primary outcome showed that baxdrostat treatment was associated with dose-dependent changes in mean reduction of systolic blood pressure of -20.3 + 2.1 mmHg, -17.5 + 2.0 mmHg, and -12.1 + 1.9 mmHg at the 2 mg, 1 mg, and 0.5 mg doses, respectively, compared with placebo which had a -9.4 mmHg mean change in systolic blood pressure. Statistical significance was met for the 1 mg (P=0.003) and 2 mg (P<0.001) baxdrostat groups. Hypothesis testing was not performed for the secondary efficacy endpoint of change in mean diastolic blood pressure. No deaths occurred throughout the trial and a higher percentage of patients in the baxdrostat 1 mg and 2 mg groups experienced adverse events (52% and 48%) than in the 0.5 mg and placebo groups (35% and 41%), although hypothesis testing was not performed. Most were

considered mild (62%) and investigators determined 89% were unrelated to baxdrostat or placebo. The most common adverse effects that occurred in 5% or more of patients were urinary tract infections, hyperkalemia, headache, and fatigue. No patients discontinued the trial because of hyperkalemia and there were 10 adverse events of special interest: one case of hypotension, three cases of hyponatremia, and six cases of hyperkalemia.

Conclusion: In the BrigHTN trial, baxdrostat 1 mg and 2 mg displayed significant, dose-related reductions in the mean systolic blood pressures at week 12. Further studies are needed to confirm the benefit beyond 12 weeks and the long-term safety profile, and head-to-head studies are necessary to determine its place in placeholder.

THERAPEUTIC THOUGHT

Chronic Insomnia: Comparison of Non-Pharmacological & Pharmacological Treatment Approaches⁷⁻¹¹

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Background: Insomnia disorder is characterized by dissatisfaction with sleep quantity or quality related to difficulty initiating (sleep onset) or maintaining sleep (sleep maintenance), which results in associated daytime impairments. Insomnia is a highly prevalent sleep disorder with an estimated impact on 12 to 20% of the general population and is commonly encountered in clinical practice. Chronic insomnia is when sleep difficulties persist for three or more months with a frequency of three or more episodes per week. Uncontrolled chronic insomnia is associated with decreased quality of life; increased risk for depression, anxiety and substance use disorders; and elevated risk for cardiovascular disease and metabolic syndrome. General management measures include treatment of comorbid medical and psychiatric conditions, adjustment of sleep-interfering medications, and modification of behavioral and cognitive factors that may perpetuate insomnia. Despite its prevalence and the availability of approved pharmacotherapy options, a general consensus regarding the optimal approach to treatment of insomnia is lacking. The 2021 American Academy of Sleep Medicine (AASM) Guidelines recommend multicomponent cognitive behavioral therapy for insomnia (CBT-I) as first-line therapy for chronic insomnia. However, factors including lack of trained providers, cost of upfront treatment, delayed symptom relief, and ability and motivation to adhere to treatment recommendations limit its use in practice. Although both non-pharmacological and pharmacological treatment options are available, medications are more frequently used in practice and present safety concerns with significant risks for adverse events. More recently, a novel class of agents, dual orexin receptor antagonists (DORAs), have been brought to market. These agents promote sleep by antagonizing

therapy. Impacting millions of adults in the United States, treatment-resistant hypertension remains difficult to control with the current treatment options. Promising results from this phase II trial lend hope that baxdrostat will BrigHTN the outlook for treatment-resistant hypertension.

Key Point: Baxdrostat is an aldosterone synthase inhibitor that showed promising blood pressure-lowering efficacy in a phase II trial of individuals with treatment-resistant hypertension. While the initial results are encouraging, comparison with other antihypertensives, especially mineralocorticoid receptor antagonists such as spironolactone and eplerenone, will be the real benchmark for the safety and efficacy of this medication.

orexin receptors responsible for excitatory responses and the release of neurotransmitters involved in arousal, wakefulness, and appetite. Suvorexant, lemborexant, and daridorexant have been FDA approved for the treatment of insomnia based on phase III randomized controlled trials. However, the clinical application of these agents have not yet been fully recognized. Moreover, optimizing the treatment of insomnia disorder is further complicated by the lack of evidence to support long-term use and the comparative effectiveness of pharmacological agents.

Evidence: The 2017 AASM Clinical Practice Guidelines recommend CBT-I as a primary intervention in patients with chronic insomnia and limiting the use of medications for patients who are unable to receive CBT-I, have persistent symptoms despite such treatments, or are in need of a temporary adjunct to CBT-I. The therapies applied for CBT-I go beyond traditional sleep hygiene techniques. CBT-I combines multiple cognitive and behavioral therapy strategies with sleep education to identify and address feelings and behaviors that contribute to sleep disruption. Compared to pharmacological interventions, CBT-I has demonstrated both non-inferior and superior effects in treating chronic insomnia, fewer safety risks, and treatment gains that are potentially durable long-term. However, despite the data, medications continue to be more commonly and inappropriately prescribed in practice. Physicians increasingly prescribe sedating antidepressants, antipsychotics and analgesics "off-label" (i.e., trazodone) despite the lack of evidence to support their effectiveness. Previous meta-analyses of benzodiazepines (BZDs) and non-benzodiazepines (non-BZDs), suggest small to moderate effect sizes for sleep outcomes with significant increases in adverse events, calling into question their relative risk-benefit ratio. A recent systematic review and network meta-analysis from Crescenzo et al. aimed to assess the comparative effects of pharmacological agents for the acute and long-term treatment of insomnia disorder. Provided the basis of evidence for approved insomnia medications are primarily short-

term placebo-controlled trials, pharmacotherapies are recommended only for the acute management of insomnia disorder. Crescenzo et al. concluded that, overall, eszopiclone and lemborexant were favorable in terms of long-term effects on sleep quality (>3 months); however, eszopiclone may cause substantial adverse events and safety data available for lemborexant were inconclusive. Comparatively, Zheng et al. established a data-driven pharmacodynamic model to estimate drug efficacy at different time points. Predicted drug efficacy at 24 weeks showed eszopiclone had the greatest reduction in sleep onset latency (SOL) of -16 minutes and increase in total sleep time (TST) of +34 minutes. Suvorexant had the greatest reduction in wake after sleep onset (WASO), a measure of time spent awake from when one falls asleep until awakening in the morning, of -27 minutes. Notably, eszopiclone had smaller effects on WASO reduction of -17 minutes and suvorexant had smaller effects on TST improvements of +20 minutes. Ramelteon was only associated with improvements in SOL of -28 minutes. Low-dose doxepin demonstrated greater reductions in WASO of -37 minutes and

increased TST by +62 minutes. The findings of this and other studies call out the need for selection of treatment based on predominant sleep onset versus sleep maintenance symptoms, as well as future studies to examine comparative efficacy and long-term safety of sleep medications.

Discussion & Clinical Impact: Given the findings of Crescenzo et al., numerous approved medications can be effective for short-term treatment of insomnia, but data to support long-term treatment is limited and inconsistent. Additionally, further randomized-controlled trials that directly compare the effectiveness and safety of sleep medications are needed to better guide the role of pharmacological agents in the treatment of chronic insomnia. The general approach to the treatment of chronic insomnia observed across the literature and guidelines reviewed has been interpreted and outlined below. The table below demonstrates a simplified stepwise approach that may be applied in clinical practice.

Stepwise Treatment Approach for Chronic Insomnia	
(1) Determine appropriateness of CBT-I and other non-pharmacological interventions	
Consider: cost, access, ability & motivation to adhere, severity of symptoms & distress	
(2) Evaluate & modify contributing factors when able	
Consider: sleep-interfering medications, medical & psychiatric conditions, behavioral & cognitive factors	
(3) Risk vs benefit discussion of treatment options	
Consider: goals of therapy (reduce daytime impairment, improve quality of life), risk of adverse events (increased in older adults), realistic expectations for efficacy	
(4) Consider appropriateness of melatonin supplement trial	
Consider: primary effect sleep onset, utility in circadian rhythm-based sleep disorders, administration time (1-2 hours vs 30-60 minutes before bedtime), minimal associated risks, quality of supplement	
(5) Select agent based on predominant symptoms of sleep onset vs sleep maintenance or mixed	
Consider: age, drug-drug and drug-disease interactions, cost, side effects, previous treatment responses, patient preference	
(5a) Sleep onset	(5b) Sleep maintenance or mixed
→ Ramelteon, or	→ DORA: lemborexant, suvorexant, daridorexant, or
→ Non-BZD: eszopiclone, zaleplon, zolpidem	→ Low-dose doxepin, or
	→ Non-BZD: eszopiclone, zolpidem
(6) Determine plan for monitoring & follow-up	
Consider: (i) effectiveness, (ii) adverse effects, (iii) need for continuation of therapy	
(7) Consider future trial off therapy with slow taper	
<ul style="list-style-type: none"> • Taper does not result in recurrence of symptoms → discontinue therapy & avoid restarting • Taper results in recurrence of symptoms → consider quality of life & option to resume treatment 	

For the Treatment of HFpEF, are SGLT2is continuing to DELIVER?¹²⁻¹⁵

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) seem to be all the rage right now. They have become a mainstay in the management of type 2 diabetes and are now a pillar of treatment for heart failure with a reduced ejection fraction (HFrEF), classified as having an ejection fraction (EF) $\leq 40\%$. SGLT2is have been shown to reduce heart failure (HF) progression in patients with type 2 diabetes and HFrEF, and recent studies suggest they may provide some benefit for patients with HF with a preserved ejection fraction (HFpEF).

Prior to the 2022 AHA/ACC/HFSA guidelines there were little to no guideline-directed medication therapies for the treatment of HFpEF. Roughly 50% of HF cases are HFpEF, and commonly these patients are older adults. Patients with HF, regardless of EF, are at risk of greater mortality compared to patients who do not have HF. With few treatment recommendations for half of HF patients, some recent studies bring both excitement and suspicion to the treatment of HFpEF.

Evidence & Discussion: The 2022 AHA/ACC/HF Guideline for the Management of Heart Failure is the newest reference for the treatment of HF. HFpEF in this guideline is defined as having an EF $\geq 50\%$. This guideline provides 2a and 2b recommendations, representing moderate and weak strengths of recommendation respectively, for all medication treatment options for HFpEF. Angiotensin receptor/neprilysin inhibitors (ARNis) and mineralocorticoid receptor antagonists (MRAs) are now considered a 2b treatment recommendation with SGLT2is securing a 2a recommendation. Previous guideline renditions contained primarily recommendations for only management of other conditions that can affect HF such as hypertension, this revision provides broadened recommendations for treating HF more directly.

The trial that played a primary role in SGLT2is receiving the 2a recommendation was the 2021 EMPEROR-Preserved trial. This trial concluded that the SGLT2i, empagliflozin 10 mg daily, reduced the combined risk of cardiovascular death or HF hospitalization regardless of the presence or absence of diabetes for patients with symptomatic HFpEF (EF $> 40\%$) (hazard ratio, 0.79; 95% CI, 0.69 to 0.90; $P < 0.001$). However, the study did not find a significant difference in cardiovascular mortality between placebo or empagliflozin (hazard ratio, 0.91; 95% CI, 0.766 to 1.09). A subgroup analysis of EMPEROR-Preserved noted more favorable outcomes for patients with a EF $< 50\%$ (hazard ratio 0.71; 95% CI, 0.57 to 0.88) and EF $\geq 50\%$ to $< 60\%$ (hazard ratio 0.80; 95% CI, 0.64 to 0.99).

In 2022 the DELIVER trial was published. This trial looked at the

SGLT2i, dapagliflozin 10 mg daily, and its effectiveness in treating patients with preserved EF or mildly reduced EF. Like EMPEROR-Preserved, DELIVER reached its primary outcome and concluded that dapagliflozin reduced the composite risk of cardiovascular death and worsening HF (hazard ratio 0.82; 95% CI, 0.73 to 0.92). Unlike EMPEROR-Preserved, DELIVER did not find any significant heterogeneity in benefit for dapagliflozin based on EF subgroup analysis.

A prespecified analysis looking at safety and efficacy with regard to frailty of patients in the DELIVER trial was also published in 2022. As a large portion of patients with HFpEF are older and frailty is common among patients with HF, these are patients whom providers may be hesitant to start on new medications. This analysis found increasing frailty was associated with worse outcomes. However, it also found greater improvement with dapagliflozin in patients with a larger degree of frailty. Older patients may not always receive the newest therapy options, but with evidence for improvements in symptoms and quality of life near the end of life, SGLT2is are becoming an appealing option.

Clinical Impact: Both empagliflozin and dapagliflozin have been shown to reduce HF hospitalizations with promising safety profiles. However, neither therapy has been shown to decrease mortality for patients with HFpEF. The decision to treat HFpEF with a SGLT2i is highly patient specific involving a variety of factors including EF and comorbidities. SGLT2is provide a promising treatment avenue for patients with HFpEF who otherwise have few treatment options.

Six Years Later - How the 2022 CDC Clinical Practice Guidelines for Prescribing Opioids for Pain Compare to the 2016¹⁶⁻¹⁷

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Background: In 2016, the Centers for Disease Control and Prevention (CDC) released its first set of guidelines for opioid prescribing in the management of outpatient adults with chronic pain. These guidelines excluded treatment recommendations for pain management related to sickle cell disease, cancer-related pain treatment, palliative care, and end-of-life care. In 2022, the CDC updated the guidelines using new evidence to address the risks and benefits of prescription opioids and expanded them to cover acute, subacute, and chronic pain.

Evidence: The 2016 guidelines had 12 recommendations for prescribing opioids. These recommendations were grouped into three categories that included when to initiate or continue opioids; opioid selection, including dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. The 2022 guidelines still include the original 12 recommendations; however, they have been adjusted to reflect

emerging evidence and now have four categories. The four categories are as follows: determining whether to initiate opioids for pain, selecting and determining opioid dosages, deciding duration of initial opioid prescription, and conducting follow-up and assessing risk and addressing potential harms of opioid use.

To start, the 2022 recommendations address the use of opioids for chronic, subacute, and acute pain whereas the 2016 recommendations were mainly focused on chronic pain management. Recall that the recommendation categories were developed on the basis of evidence type, cost, preferences, and values while balancing desirable and undesirable effects. Recommendation category A applies to all persons, and most should receive the course of action recommended whereas category B recommendations need individual decision making as choices will differ in appropriateness based on the patient. Initial changes from the 2016 guidelines include four recommendations being decreased from category A recommendation to category B recommendation. All the 2016 recommendations were labeled category A, aside from Recommendation 10, which addressed clinicians using urine drug testing before starting opioid therapy.

Taking a closer look into the 2022 guidelines, the first recommendation focuses on acute pain and how clinicians should use nonpharmacologic and nonopioid pharmacologic therapies initially for specific conditions. Previously, initiation of opioids for acute pain was not addressed. The 2022 recommendations still emphasize discussing expected benefits and risks of opioid therapy when used for both acute and chronic pain and include a statement for clinicians to consider how opioid therapy would be stopped should the benefits not outweigh risks. As for initiation of opioid therapy, the guidelines held steady with the recommendation to prescribe immediate-release opioids over extended-release or long-acting opioids when starting opioid therapy for chronic, acute, or subacute pain. Part of this recommendation is due to a fair-quality study that demonstrated a higher risk for overdose when patients were treated with extended-release or long acting (ER/LA) opioids rather than immediate release opioids. Additionally, use of ER/LA opioids have not been shown to be more effective or safer than intermittent use of immediate-release opioids. When it comes to dosage of opioids for pain, the 2022 recommendations reflect the desire to be more flexible. Previously, the recommendation had been to reassess risk

versus benefit when increasing to ≥ 50 morphine milligram equivalents (MME)/day and to avoid dosages above ≥ 90 MME/day. However, the updated guidelines state that caution should be used when prescribing opioids at any dosage and providers should carefully reassess evidence of benefits when increasing dosages to ≥ 50 MME/day as many patients do not experience benefit in pain or function from those doses. The 2022 guidelines continue to recommend assessing risks and benefits within 1-4 weeks of starting therapy and regularly with continued opioid use, as was recommended in the 2016 guidelines. However, an additional statement was added which recommends carefully weighing risks versus benefits any time a change in dosage occurs.

Another new statement in the 2022 guidelines discourages abrupt discontinuation or rapid dose reductions in opioids unless there are warning signs of impending overdose or other life-threatening issues. The 2016 guidelines did suggest tapering opioid dosages to lower doses or discontinuing altogether if benefits did not outweigh harms, but did not address abrupt discontinuation. As with the 2016 guidelines, clinicians should still evaluate patients for risk of opioid related harms and offer naloxone to mitigate risk, and should exercise caution when prescribing opioids in patients with concomitant benzodiazepines or other CNS depressants.

Another change is related to duration for opioid prescriptions for acute pain. In the 2016 guidelines, it was recommended that prescriptions for three days or less would be sufficient for most, and rarely would need to exceed seven days. The 2022 guidelines do not specify a duration but rather state prescriptions for opioids should be written for a quantity no greater than needed for the expected duration of pain (which is severe enough to require opioids). The final recommendation from the 2022 guideline notes clinicians should offer or arrange treatment for patients with opioid use disorder and discourage detoxification on its own without medications for opioid use disorder.

Discussion and Clinical Impact: It is clear the 2022 guidelines were updated from 2016 to provide more flexibility for both patients and clinicians. Some may struggle with the ambiguity of the 2022 guidelines as they may be familiar with more straightforward recommendations. These guidelines should be used as a clinical tool to help guide therapy recommendations and improve communication between clinicians and their patients.

MISCELLANEOUS NEWS

FDA Taking Steps to Approve OTC Naloxone for Opioid Overdose¹⁸⁻²⁰

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In November 2022, the United States Food and Drug Administration (FDA) issued a Federal Register notice. The notice included an assessment revealing specific naloxone drug products (naloxone 4 mg nasal spray and naloxone 2 mg auto-injector for intramuscular or subcutaneous use) may be safe and effective for

use without a prescription. This announcement was another support measure taken by the FDA to combat the ongoing opioid epidemic, with hopes to increase the accessibility of naloxone with the development and approval of over-the-counter (OTC) naloxone.

As the assessment is preliminary, the next step in the process of OTC naloxone approval is for the FDA to collect data demonstrating the safety and efficacy of additional naloxone products not included in the original assessment. This would encompass products supplied as naloxone vials, ampules, and syringes, and the recently approved higher-dosed naloxone products (KLOXXADO, an 8 mg, prefilled, single-dose nasal spray, and ZIMHI, a 5 mg single-dose, prefilled syringe with an integrated needle for intramuscular or subcutaneous administration). In addition, the FDA asked for comments from the public discussing the impact of switching naloxone from prescription to non-prescription status. Comments were submitted electronically ([Safety and Effectiveness of Certain Naloxone Hydrochloride Drug Products for Nonprescription Use](#)) or written and mailed. The comment period ended January 17, 2023, 11:59 PM Eastern Time, with mailed comments being considered on time if received on or before January 17, 2023.

Other actions taken by the FDA include providing guidance to harm-reduction programs on distributing naloxone, exempting some of the requirements of the Drug Supply Chain Security Act, increasing the shelf-life of naloxone, and developing a Drug Facts Label for naloxone. Drug Facts labels are required for OTC products, and the development of such a label specific to naloxone was created in hopes of encouraging manufacturers to pursue OTC approval of naloxone. The FDA has also required that manufacturers of opioid analgesics and medications used to treat opioid use disorder include recommendations related to naloxone use in their prescribing information. In the future, the FDA intends to implement the FDA Overdose Prevention Framework. Its vision is aimed at preventing opioid overdoses and reducing deaths through four priorities to address this public health emergency. More about the framework can be found [here](#).

Hope for the Future: Finally an RSV Vaccine²¹⁻²³

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A new bivalent respiratory syncytial virus (RSV) protein-based vaccine (RSVpreF) for pregnant women is being studied to help limit the number of RSV cases in pediatrics. The purpose of vaccinations during pregnancy is to take advantage of passive immunity. Passive immunity occurs during the last three months of pregnancy and is when the antibodies from the mother are passed to the baby through the placenta. Those affected with RSV tend to be contagious for three to eight days and those with

weakened immune symptoms, such as newborns, are at greatest risk of serious complications from the virus. It is noted that in the United States, nearly 60,000 hospitalizations occur among children less than five years old, resulting in nearly 500 deaths per year. Currently, there is no treatment for RSV, only symptomatic support.

Per the phase III clinical trial, MATISSE (Maternal Immunization Study for Safety and Efficacy), Pfizer's RSV vaccination, which was given to expectant mothers in their late second trimester to third trimester of pregnancy, was approximately 82% effective (CI: 40.6%, 96.3%) at protecting babies against severe medically attended lower respiratory tract illness due to RSV for their first three months of life. At six months of life, the efficacy dropped to 69% (CI: 44.3%, 84.1%). No adverse events or safety concerns to either the mother or baby have been observed. Several companies currently have an RSV vaccine in their pipeline, but Pfizer and GSK have made the most progress with goals of seeking US regulatory approval in the near future. If approved, the RSV vaccine will be the first maternal vaccine against RSV.

Medicare Changes in 2023: Summing up the IRA²⁴

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On August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022 (IRA). In an effort to combat high inflation rates, this bill aims to lower the deficit, increase domestic clean energy production, and, most significantly for pharmacy practice, lower prescription drug prices. Changes taking effect in 2023 include reducing out-of-pocket costs for insulin, imposing rebates on drug manufacturers due to drug prices being raised faster than the rate of inflation, and eliminating copays for adult vaccines that are covered under Medicare Part D.

Previously, Part D plans were required to cover at least one short-, intermediate-, and long-acting insulin at \$35 monthly. Starting in 2023, all insulins covered by Medicare Part D must be available to Part D patients for a monthly copay of \$35 or less. Notably, insurers do not have to cover every insulin product on the market. The average monthly cost of insulin products for Medicare Part D insulin users was \$54 in 2020, so this provision will cut the average out of pocket cost for insulin by one third. Additionally, this means that patients in the coverage gap (or donut hole) will only spend \$35 monthly on each insulin product, rather than 25% of the cost of the insulin, which should improve medication access for patients in the coverage gap.

In 2019 and 2020, the prices of about half of branded prescription drugs covered by Medicare Part D rose more rapidly than inflation. The IRA will impose rebates on drug manufacturers equal to the difference, using 2021 as an inflation benchmark starting in 2023.

The funds accrued by these rebates will be placed into the Medicare Supplementary Medical Insurance fund. It is difficult to know what the exact impact of this change will be, it will almost certainly reduce out of pocket costs for many Medicare Part D beneficiaries.

Finally, the bill will eliminate cost sharing for adult vaccines

recommended by the Advisory Committee on Immunization Practices (ACIP) and covered under Part D. The most notable change here is the price of the Shingrix (recombinant zoster) vaccine. Previously, the average cost was \$57 per dose for Medicare Part D beneficiaries. Eliminating this cost should remove a huge barrier to vaccine uptake and shingles prevention.

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