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RESEARCH UPDATES

Tirzepatide for the Treatment of Obesity. Is it a Weight Loss Game-changer?[1]

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Background: Obesity is the most prevalent disease worldwide, which can lead to a myriad of health issues for patients and is a significant cause of morbidity and mortality. Tirzepatide, an injectable medication with a novel dual mechanism of action, may help promote weight loss in patients with obesity. Secondary outcomes in the SURPASS trials demonstrated that tirzepatide exhibited a greater reduction in weight loss in participants when compared to various standards of care treatment options for type 2 diabetes. The safety and efficacy of this glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 receptor agonist (GLP-1 RA) in obese patients without type 2 diabetes is unknown.

Purpose: This trial sought to evaluate the efficacy and safety of tirzepatide in adults with obesity (BMI >30) or who are overweight (BMI >27) with one or more weight related comorbidities, not including diabetes.

Study Design: This study was a phase 3 multicenter, double-blind, randomized, placebo-controlled trial conducted at 119 sites across nine countries. The study included adults 18 years or older with BMI >30 kg/m2 or BMI >27 kg/m2 with at least one weight-related complication including hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Participants needed to report at least one unsuccessful dietary effort to lose weight to be included. Important exclusion criteria included diabetes, change in body weight more than 5 kg within 90 days prior to screening, previous or planned surgical intervention for obesity, and treatment with medication that promotes weight loss within 90 days prior to screening. Upon conclusion of a 2-week screening period, trial participants were randomly assigned in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, 15 mg, or placebo. Treatment regimens were administered subcutaneously once a week for 72 weeks. The treatment regimens were used in adjunction to lifestyle changes including a daily deficit of 500 calories and 150 minutes of weekly physical activity. The two primary outcomes of the study were the percentage of change in weight from baseline and a weight reduction of 5% or more. Key secondary endpoints included weight reduction of 10% or more, 15% or more, and 20% or more at week 72. Also included was the change in weight from baseline to week 20 and change from baseline to week 72 in waist circumference, systolic blood pressure, fasting insulin and lipid levels, and physical function score on a 36-item short form survey. Safety outcomes including serious adverse events were also evaluated during the reporting period.

Results: The trial ran from December 2019 through April 2022. It included 2539 participants. Adherence during the trial was higher in the treatment groups (83.5% to 85.7%) compared to placebo (73.6%). The rate of discontinuation of treatment due to adverse effects was 4.3%, 7.1%, and 6.2% with the 5 mg, 10 mg, and 15 mg doses

respectively, compared to 2.6% with placebo. Demographic characteristics were similar across all treatment groups: mean age of participants was 44.9 years, 67.5% were female, 70.5% were White, mean starting weight was 104.8 kg, mean BMI was 38.0 kg/m2, and 94% had a BMI >30 kg/m2. Across participants, the average duration of obesity was 14.4 years, 40.6% had prediabetes at baseline, and approximately 66% of patients had one or more weight-related comorbidities. For the treatment estimand, the mean change in weight at week 72 was -15.0% (95% CI, -15.9 to -14.2) in the 5 mg group, -19.5% (95% CI, -20.4 to -18.5) in the 10 mg group, -20.9% (95% CI, -21.8 to -19.9) in the 15 mg group and -3.1% (95% CI, -4.3 to -1.9) in the placebo group. For the efficacy estimand, the mean change in weight at week 72 was -16.0% (95% CI, -16.8 to -15.2) in the 5 mg group, -21.4% (95% CI, -22.2 to -20.6) in the 10 mg group, -22.5% (95% CI, -23.3 to -21.7) in the 15 mg group and -2.4% (95% CI, -3.2 to -1.6) in the placebo group. Weight reduction was 16.1 kg, 22.2 kg, 23.6 kg, and 2.4 kg respectively. Roughly 78.9% to 81.8% of participants treated with tirzepatide reported at least one adverse event that occurred during the treatment period, compared with 72.0% of participants in the placebo group. Frequently reported adverse events included nausea, diarrhea, and constipation. Adverse events were more common in the tirzepatide group, though they were generally self-limiting and non-severe. Severe adverse events included pancreatitis and cholecystitis. There were four cases of pancreatitis evenly distributed across treatment groups including placebo. Cholecystitis and acute cholecystitis were reported more frequently in the tirzepatide group than the placebo group although incidences were low.

Conclusions: Weight reduction of 5% or more has been considered the threshold for clinical significance on the improvement of metabolic health. In this trial, 88% of patients in the tirzepatide 10 mg group and 91% of patients in the tirzepatide 15 mg group achieved the benchmark. In clinical practice, there has been an uptake in the demand for higher doses of semaglutide, a once weekly, GLP-1 RA to promote A1C lowering and weight loss. A recent trial of semaglutide (2.4 mg) demonstrated a mean weight reduction of 12.4% with approximately one-third of participants achieving a weight reduction of 20% or greater. In comparison, the tirzepatide 5 mg group had a mean placebo-adjusted weight reduction of 11.9% from baseline, with 30% of participants reaching the weight loss target of 20% or more. It is clear tirzepatide's dual mechanism of action targeting both the GIP and GLP-1 receptors may have additive effects for weight loss. Tirzepatide was also accompanied by greater improvements with respect to metabolic and cardiovascular risk factors including waist circumference, blood pressure, fasting insulin, and liver enzymes compared to placebo. Going forward, tirzepatide could serve as a key tool for the management of obesity.

Key Point: In this trial, all three doses of once weekly tirzepatide demonstrated both substantial and sustained weight reduction in adults with obesity. It has not been FDA approved for weight loss yet. This novel medication could provide great benefit to a significant subset of the population in the United States and can be a valuable tool for practitioners moving forward.

Does Double Dosing Levonorgestrel-Based Emergency Contraception for Obese Patients Affect Clinical Results?[2-3]

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Background: Obesity, defined as a BMI >30 kg/m2, is a risk factor for failure of emergency contraception (EC) containing levonorgestrel (LNG). This is pertinent given the global obesity epidemic. Glasier et al. reanalyzed data from two large randomized control trials and noted risk factors for EC failure. Individuals with BMIs in the obese range who used EC containing LNG had more than a fourfold greater risk of pregnancy compared with individuals with BMI 17-23.9 kg/m2 (OR 4.41, 95% CI 2.05–9.44); individuals with BMIs in the overweight range (25–29.9 kg/m2) were twice as likely as individuals with BMI 17-23.9 kg/m2 to experience failure. EC that contains LNG appears to have a ceiling of efficacy at 70 kg and no EC efficacy for those weighing 80 kg or more.

Purpose or Objective: To assess whether doubling the dose of EC that contains LNG improves pharmacodynamic outcomes in individuals with obesity.

Study Design: The researchers conducted a randomized controlled trial with participants between 18 and 35 years of age who possessed a regular menstrual cycle lasting from 21 to 35 days, had a BMI of greater than 30 kg/m2, and weighed at least 80 kg (176 lbs). Researchers first confirmed ovulation in the participants by measuring luteal progesterone levels >3 ng/mL. Participants were monitored utilizing transvaginal ultrasonography and blood samples were measured for progesterone, luteinizing hormone, and estradiol every other day until a dominant follicle appeared (minimum 15 mm in width). Upon reaching this point, the participants were randomized into two groups. Group 1 received LNG 1.5 mg and Group 2 received 3 mg LNG. Both groups were then monitored daily for up to seven days. The primary outcome of this study was the difference between groups in the proportion of participants with no follicle rupture for five days following EC dosing. The main secondary outcome compared timing of follicle rupture between the two groups and was assessed using Kaplan-Meier and log-rank tests.
Results: A total of 70 participants enrolled and completed the study procedures. Baseline demographics were similar: mean age 28, mean BMI 38 kg/m2, 77% of participants identified as White non-Hispanic, 50% of participants reported never experiencing a pregnancy. No difference in the intention-to-treat analysis was detected between groups in the proportion of participants without

follicle rupture more than 5 days post-LNG dosing (LNG 1.5 mg: 18/35 (51.4%); LNG 3.0 mg: 24/35 (68.6%), P=0.14). For the secondary outcome, in the participants with follicle rupture before 5 days, time to rupture also did not differ between groups.

Conclusions: The researchers concluded that individuals who possess a high BMI are at higher risk of failure of EC with LNG. These participants had an altered pharmacokinetic profile, as women with BMIs in the obese range were found to have ~50% reduction in plasma exposure to LNG. Doubling the LNG dose was not an effective intervention to improve outcomes based on the study results. A study limitation was follicle rupture being used as a substitute for ovulation; a more meaningful outcome of interest would be pregnancy rate.

Key Point: The findings of this study have important clinical relevance for individuals possessing BMIs in the obese range who desire to use EC. The results of this study do not support double dosing of EC with LNG in individuals with BMIs >30 kg/m2 or a weight of ≥80 kg (176 lbs).

Albuterol-Budesonide Fixed Dose Combination Rescue Inhaler for Asthma – The MANDALA Trial[4]

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Background: Patients with asthma typically rely on a short-acting β2-agonist (SABA) for rescue therapy when experiencing symptoms such as cough, wheezing, or shortness of breath. However, SABAs are not effective at treating the underlying airway inflammation associated with asthma. An overreliance on SABAs alone may leave patients at risk for severe asthma exacerbations. The Global Initiative for Asthma (GINA) has recently updated their recommendations to include inhaled corticosteroid (ICS)/formoterol therapy as the preferred rescue therapy in patients with a range of asthma severities. However, data regarding use of ICS/SABA rescue therapy in patients with moderate-to-severe asthma is still limited.

Purpose: The primary objective of this trial was to evaluate the safety and efficacy of albuterol-budesonide combination rescue therapy versus use of albuterol-alone rescue therapy in patients with uncontrolled moderate-to-severe asthma.

Study Design: This multinational, double-blind, event-driven, phase 3 study was designed to take place for a minimum of 24 weeks and continue until ≥570 first events of severe asthma exacerbation had been reported. Inclusion criteria was as follows: ≥4 years of age, ≥1 severe asthma exacerbation in the previous 12 month, and moderate-to-severe asthma (defined as previous treatment with medium-to-high doses of ICS or low-to-high doses of ICS/LABA combination for ≥3 months, with stable dosing for at least 4 weeks). Adults and adolescents (≥12 years of age) were randomly assigned in a 1:1:1 ratio to one of the three treatment groups: high-dose combination inhaler (180 µg albuterol and 160 µg budesonide), low-dose combination inhaler (90 µg albuterol and 40 µg budesonide), or albuterol-alone inhaler (180 µg). Children 4 to 11 years of age were not assigned to the high-dose combination treatment group due to concerns regarding high-dose ICS use in younger populations. Patients were assessed for inhaler competency and instructed to only use trial medications for rescue therapy. The primary efficacy endpoint was the first event of severe asthma exacerbation. Secondary efficacy endpoints were the annualized rate of severe asthma exacerbations, total systemic glucocorticoid exposure for asthma during the treatment period, and treatment response via various asthma evaluation questionnaires. Safety endpoints included incidence of adverse events and serious adverse events.

Results: Between December 27, 2018 and July 30, 2021, a total of 3132 patients underwent randomization, of which 3123 were evaluated for efficacy endpoints and 3127 were evaluated for safety endpoints. The trial had a low dropout rate, with 93% of patients completing the 24-week treatment period. Intention-to-treat analysis of the primary endpoint showed that for adults and adolescents ≥12 years, the risk of a severe asthma exacerbation was significantly lower in the high-dose combination group than in the albuterol-alone group (HR 0.74; 95% CI, 0.62 to 0.89; P=0.001). The hazard ratio in the lower-dose combination group, which included children 4 to 12 years of age, versus the albuterol-alone group was 0.84 (95% CI, 0.71 to 1.00; P=0.052), which was insignificant. Secondary endpoints showed similar results in that the high-dose combination therapy was numerically superior to albuterol-alone. The rate of any adverse event was similar among the three trial groups (46.2% in the higher-dose combination group, 47.1% in the lower-dose combination group, and 46.4% in the albuterol-alone group).

Conclusion: In patients with uncontrolled moderate-to-severe asthma receiving ICS-containing maintenance therapy, risk of severe asthma exacerbation was significantly lower for those using the high-dose combination inhaler as rescue therapy compared to albuterol-alone inhaler. The use of the trial medications were consistent among all three groups, which limits potential bias and adds validity to the results. Children between 4 and <12 years of age only made up 2.7% of all patients and the next age bracket (patients ≥12 to <18 years) at 3.2% respectively, limiting the external validity to children.

Key Points/Clinical Impact: The primary endpoint (first event of severe asthma exacerbation) was significantly lower for the high-dose combination group compared to the albuterol-alone group in both the pre-specified and pre-planned analyses. The results of this trial may lead to a shift in practice for adult patients with uncontrolled moderate-to-severe asthma who are receiving ICS-

containing therapy. Patients may now see more benefit with an ICS/SABA combination rescue therapy versus an albuterol-alone therapy. Astra-Zeneca and Avillion were major funders of this trial and have filed New Drug Application for this combination product.

THERAPEUTIC THOUGHT

The Impact of Systemic Racial Inequities on Asthma[5-6]

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Background: While Minnesota is consistently ranked as one of the most livable states, it also ranks as one of the worst states for Black, Indigenous, and People of Color (BIPOC) to live in according to Schuler et al., 2022, in terms of unemployment rate gaps, income inequality, homeownership/housing quality disparities, increased exposure to pollution, reduced life expectancy, and much more. Each of these factors are part of a person's social determinants of health. Looking deeper at increased exposure to pollution alone impacts a variety of conditions like ischemic stroke, lung cancer, hypertension, atrial fibrillation, and heart disease. Parfieniuk's 2022 report focuses specifically on the links between asthma, air pollution, and systemic racism in the Twin Cities. While these disparities and racial injustices are well known, little has been done to act on mitigation and adaptation strategies which address the underlying racial, class, and income disparities in Minnesota.

Evidence and Discussion: Schuler et al., 2022, notes that Minnesota's first racial covenant, a clause incorporated into property deeds to prevent non-White individuals from being allowed to buy or occupy land, occurred in the 1910s. From the 1930s onward, redlining practices increased as BIPOC were denied home loans/insurance in certain areas. According to Parfieniuk, I-94 was intentionally built through St. Paul's predominantly Black Rondo neighborhood in the 1950s. In the 1960s, I-35W was built through a Black south Minneapolis neighborhood. Today, the racial distribution of Minnesota residents has changed little and air pollution maps show that these freeways produce significant pollution in these historically Black Twin Cities neighborhoods. Ninety-three percent of Minnesotan BIPOC live in an area above the Minnesota Pollution Control Agency's air quality risk recommendation compared to the 51% statewide average. In 2015-2018, asthma emergency department visit rates were two to five times higher in these historically Black neighborhoods, as reported by Parfieniuk. Indigenous Minnesotans experience over double the rate of asthma than White Minnesotans, and Black Minnesotans are six times more likely to die from asthma than White Minnesotans. While compounding climate change factors and historical injustices have larger impacts still permeating the Minnesota community today, the disparities in asthma control alone demonstrates the need for change in policy.

Clinical Impact: Health professionals are in a great position to invest in their local communities and organizations, use their voices to support climate justice and equity policy, and bring patient stories to legislators. It is important for health professionals to educate themselves on these underlying disparities in order to recognize how their patients' social determinants impact their health. Schuler et al. recommends health professionals promote policies that invest in neighborhoods hit hardest by climate change and reduce social inequities, such as the Next Generation Climate Act. This Act would update Minnesota's current climate goals with a commitment to provide jobs and business opportunities within the clean energy sector to people living within at-risk communities, prevent further climate change, and invest in the neighborhoods most impacted (and least responsible) for climate change. Other local resources to address climate justice include Minnesota's Climate Action Framework, Twin Cities Boulevard, the East Phillips Neighborhood Institute, 100%MN, and Community Members for Environmental Justice. Per Parfieniuk, one policy proposal that includes wind energy in the energy grid and increases use of plug-in electric vehicles would reduce environmental health impacts by 50%. With these actions, systemic racial inequities leading to poor public health can start to be corrected, allowing for all people in Minnesota to live in healthy communities.

Gabapentin's Impact on Drug-related Overdose Deaths[7-12]

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Background: Gabapentin is a medication approved by the Food and Drug Administration (FDA) for two clinical indications: postherpetic neuralgia and as an adjunctive therapy for partial seizures. Gabapentin is structurally similar to the inhibitory neurotransmitter GABA, however the exact mechanism of action is not known. It has been suggested it may decrease the effects of an excitatory synapse while also increasing the synthesis of the GABA neurotransmitter. Non-FDA approved (i.e. off-label) indications include maintenance of abstinence with alcohol dependence, fibromyalgia, hemodialysis-associated pruritus, hot sweats, neuropathy due to diabetes mellitus, preemptive therapy for acute postoperative pain, and trigeminal neuralgia. This list has continued to grow over the last several years, and according to Pauly et al., prescribing rates of gabapentin have doubled from 2009 to 2016. Moreover, according to IQVIA Institute, in 2019 it was the seventh most prescribed medication in the US.

Due to the overall inhibitory nature of gabapentin, some of the most common side effects include somnolence, ataxia, fatigue and dizziness. Gabapentin is generally considered safe on its own and can potentially have only mild to moderate toxicity even at doses as high as 35 to 40 grams. However, when used with other prescribed and non-prescribed central nervous system (CNS) depressants, such as an opioid like fentanyl or hydromorphone, CNS depression can become fatal.

Evidence: Over the last few years, there has been an increase in patient death related to gabapentin usage, driven partly by misuse. Buttram et al. states gabapentin is being misused to assist in opioid withdrawal management, self-detoxification from opioids, and the self-management of mental health or pain-related stress. Misuse of gabapentin often occurs at doses between 3600 mg and 12,000 mg. The Centers for Disease Control and Prevention analyzed data from the State Unintentional Drug Overdose Reporting System (SUDORS) and found there were 58,362 overdose deaths with toxicology reports in the 24 jurisdictions that use the reporting system (23 states and the District of Columbia) in 2019 and 2020. Of these overdose deaths, 5,687 (9.7%) had gabapentin detected in postmortem toxicology, and of those deaths, gabapentin was determined to be the cause of death in 49% of people at the beginning of 2019, with an increase to 55% by the end of 2020. This report also collected information on concomitant medication use. Of the 58,362 overdose deaths, 90% also involved opioids as the cause of death and this percentage remained stable from 2019 to 2020. Interestingly, prescribed opioid involvement decreased during this time period while illicit opioid use, particularly fentanyl, increased. An important limitation from this review: gabapentin is not always included on death certificates. This leads to an unknown amount of overdose deaths not indicated as associated with or caused by gabapentin which could potentiate an underestimate of gabapentin involvement.

Discussion and Clinical Impact: As health care professionals, we must find a way to decrease these overdose deaths. One way to find a solution to this is by looking at the patient care process and the indication, effectiveness, safety, and convenience (IESC) framework. For patients seen during day-to-day appointments, ensure gabapentin is a medication that is indicated for their condition and consider all alternative options for the condition. From a broader view, off-label indications for gabapentin need to be reevaluated and stronger recommendations need to be made in favor of or against the use of gabapentin. The other crucial part of the IESC framework is, of course, safety. Regular monitoring of adverse effects needs to be assessed in patients, especially those taking concomitant opioids. With the use of collected data and effective patient-provider relationships, we can help reduce these types of overdose deaths.

Bonus note: According to Premont, et al., as of July 2022, gabapentin is a C-V in Alabama, Kentucky, Michigan, North Dakota, Tennessee, Virginia, and West Virginia. Also, states that require gabapentin to be included in PDMP monitoring include Connecticut, Kansas, Massachusetts, Indiana, Washington DC, New Jersey, Minnesota, Nebraska, Ohio, Utah, Wyoming, and Oregon.

Addressing Modifiable Risk Factors in Heart Failure Management[13-16]

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Background: Heart failure (HF) and the risk of developing HF are common, estimated to affect roughly 6.2 million US adults. Despite preventative efforts, prevalence continues to increase globally. Specific modifiable risk factors include prediabetes or diabetes, uncontrolled hypertension, hyperlipidemia, atherosclerotic cardiovascular disease (ASCVD), tobacco and other substance use, as well as obesity, among other renal and cardiovascular complications. According to the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, patients who receive care from a multidisciplinary team benefit from improved guideline-directed medication therapy, reduced hospitalizations for HF, and improved survival. Though the guidelines specifically call out pharmacist intervention in Stages C and D due to the complexity of care for these patients, this also underscores the importance of pharmacist involvement in identifying and addressing modifiable risk factors in patients with heart failure beginning as early as Stage A.

Evidence: The management of modifiable risk factors including hyperlipidemia, poor glycemic control, obesity, and uncontrolled hypertension is imperative due to their role in the development of structural heart disease. The 2022 ADA Heart Failure Consensus Report describes one study that demonstrated how appropriate treatment with statins in patients with diabetes may decrease the incidence of HF. Optimal blood pressure targets for HF remain unknown, but the 2022 AHA/ACC/HFSA HF Guidelines recommend optimizing antihypertensive therapy according to ACC/AHA Hypertension Guidelines to decrease incident risk of HF in the general public. Additionally, HF is a common complication of diabetes with an estimated prevalence of up to 22% in those diagnosed with diabetes. Along with appropriate medication therapy, the implementation of lifestyle modifications such as optimal nutrition, regular physical exercise, and tobacco cessation are known to reduce the impact of these HF risk factors to treat and prevent HF.

Sodium restriction has historically been a common nonpharmacologic strategy to manage symptoms of congestive HF and reduce hospitalizations. However, more recently, concerns have been raised regarding diminished quality of nutrition with strict limitations on sodium intake. Of note, the recommendations

regarding sodium intake are supported by low-quality evidence of clinical benefit. A recent study by Li and colleagues found an association with worse outcomes including survival and HF hospitalization for patients with heart failure with preserved ejection fraction who follow an overstrict sodium restriction (defined as no salt added to homemade foods). Both the 2022 ADA Heart Failure Consensus Report and AHA/ACC/HFSA Guidelines for the Management of Heart Failure support the DASH diet for HF in combination with dietary counseling to achieve a diet low in sodium and fat, but rich in antioxidants, vegetables, and whole grains.

Physical activity, specifically aerobic exercise, has demonstrated benefit for the prevention and treatment of HF. Per the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure, incorporation of regular, structured exercise can improve functional capacity and prevent progression. Thus, consistent exercise can ultimately lead to reduced hospitalizations and improve patients' quality of life. Of note, cardiopulmonary exercise testing should be completed before recommending specific exercise in individuals with HF to ensure safety.

Smoking is considered a major modifiable risk factor, increasing the risk of HF in both current and former smokers. A 2022 study by Ding et al. demonstrated a decreasing risk of incident HF with tobacco cessation and further declining risk with longer duration of tobacco cessation. HF risk was significantly reduced after ≥20-30 years of tobacco cessation (HR 1.34; 95% CI 1.07-1.67). Incorporation of counseling, motivational interviewing, approved pharmacologic treatment, and/or appropriate referrals is encouraged at each contact.

Clinical Impact: The specialized training and accessibility of pharmacists offers an opportunity for significant impact in the care of patients with HF. By intervening and educating on risk factors, pharmacists can play an important role in reducing the impact that HF has on patients' lives. In fact, the ADA specifically encourages pharmacist involvement as part of the care team for the treatment of individuals with HF. In addition to performing a comprehensive review of patients' regimens for use of appropriate guideline-directed medication therapies, pharmacists can contribute to management of these risk factors by assessing adherence and helping to address barriers such as noncompliance, affordability, tolerability, pill burden, and knowledge gaps. In fact, these are contributions that pharmacists already make on a daily basis in the ambulatory care setting. Modifiable risk factors and lifestyle changes should be assessed at every visit with resources, counseling, and motivational interviewing employed to encourage positive changes and lifestyle modifications such as medication adherence, tobacco cessation, regular physical activity, and reducing sodium intake through the DASH diet.

MISCELLANEOUS NEWS

Updates in Wearable Technology[17-19]

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M Health Fairview

Abbott's newest continuous glucose monitoring (CGM) system, the FreeStyle® Libre 3, received US Food and Drug Administration approval on May 31st, 2022, for patients four years of age and older diagnosed with type 1 and 2 diabetes that do not utilize an automated insulin dosing system. The new CGM offers an increased bluetooth range between smartphone and sensor from 20 to 33 feet and it is currently the thinnest, smallest, and most discrete sensor on the market being only the size of about 2.9 mm in height and 21 mm in diameter. With the new technology, patients no longer have to remember to scan their sensor every eight hours because the FreeStyle® Libre 3 will automatically store and send data to the user's device once the initial scan to link the sensor to the phone is completed. A potential limitation for use of the FreeStyle® Libre 3 is that it requires a smartphone, as a reader has not been approved for use in the United States. Like previous generations, the FreeStyle® Libre 3 will continue to integrate with the LibreLinkUp smartphone app and LibreView cloud-based data system and is compatible with most Apple IOS and select Android products. The FreeStyle® Libre 3 will continue to show glucose trends and allow patients to set optional glucose alarms to help with better hypoglycemic management.

According to Sabin 2022, the University of Texas and Texas A & M University have developed a new technology that takes "wearable technology" to a whole new level: temporary tattoos that measure blood pressure (BP). The tattoos are made with graphene, a carbon that promotes bioelectrical impedance analysis (BIA), which is similar to the technology used in smart scales that measure body fat. The graphene temporary tattoo lasts for approximately a week, during which it uses BIA to send data to a machine that will provide the results. Similarly to the devices used in ambulatory BP monitoring today, this technology will help identify the patient's BP throughout the entire day rather than just a moment in time. Testing has shown that this technology is accurate and could be available within the next five years.

Melatonin Safety Concerns and Dietary Supplements[20-23]

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Per a JAMA article by Kuehn, insomnia rates have risen over the past 20 years with nearly one third of US adults experiencing it. With rising rates in sleep difficulties and poor sleep hygiene, many people have turned to melatonin as a quick fix. Recently, melatonin use has become more prevalent among adult and pediatric patients. The 2017 American Academy of Sleep Medicines (AASM) practice guidelines suggest to not use melatonin in adults for insomnia. AASM recommends cognitive behavioral therapy for insomnia as first-line therapy in children and adults. Although melatonin is generally well tolerated and safe, it doesn't come without risks. There are very few long-term safety studies performed on melatonin. Additionally, the commonly used high doses of 5 mg or more may increase the risk of adverse effects. Common side effects include fatigue, dizziness, headache, and daytime sleepiness. An article by Lelak et al. reported that US poison control centers have noticed a 530% increase in calls about children ingesting melatonin between 2012 and 2021. Many of the melatonin products formulated as gummies are highly attractive to children and lack childproof packaging; however, melatonin is still a drug and should be kept out of the reach of children. Kuehn's article mentions that for children, medications or supplements such as melatonin for sleep may not be appropriate and may not address underlying issues that are typically behavioral.

One resource that may help address the increasing safety concerns of melatonin and other supplements is a new education initiative developed by the US Food and Drug Administration (FDA). "Supplement Your Knowledge" is a program that strives towards educating consumers, educators, and healthcare professionals about dietary supplements. The website provides patient- and educator-friendly fact sheets and infographics that can be downloaded in English and Spanish. There are educational videos that provide overviews of dietary supplements, dietary supplement interactions with medications, adverse effects and more. This website can be a quick and easy resource for patients with reliable information. Additionally, the website serves as an opportunity for free continuing medical education program for healthcare professionals.

Counseling Points for Progestin-Only, OTC Birth Control[24-27]

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On July 11, 2022, HRA Pharma (Perrigo) submitted an application to the United States Food and Drug Administration (FDA) for over-the-counter (OTC) approval of their prescription birth control medication, Opill®. This progestin-only-pill (POP), containing 0.075 mg of norgestrel, would be the first ever daily oral contraceptive available OTC in the United States. Advocates for reproductive access celebrated the prospect, including the American Medical Association, the American Academy of Family Physicians, and the American College of Obstetrics and Gynecology (ACOG). In a statement released shortly after Perrigo's announcement, ACOG president Iffath Abbasi Hoskins, MD highlighted the application's significance on the heels of the overturn of Roe vs Wade:

> "Amidst the current reproductive health crisis, today's news is positive. We know that birth control is not a solution to abortion bans, as people need abortion care for many reasons. However, by increasing access to birth control through over-the-counter oral contraception, we have an opportunity to empower more people to control their own reproductive futures, including avoiding pregnancy."

While accessibility is critical to effective reproductive health care, POPs come with their own considerations and risks. The FDA is expected to review Perrigo's application in the first half of 2023, and if approved, health care professionals will face an abundance of questions. The following review provides key counseling points for POPs, based on Morbidity and Mortality Weekly Report (MMWR), applicable to today's prescription patients and - potentially - to future OTC patients.

POPs do not protect against sexually transmitted infections (STIs)

- As with all hormonal contraceptives, POPs do not reduce the risk of STI transmission

Initiate at any time in the menstrual cycle

- If started ≤5 days from the beginning of most recent menstrual cycle, there is no need for backup contraception
- If started >5 days from the beginning of most recent menstrual cycle, advise the patient to use a backup contraceptive method (such as condoms) for 48 hours

There are no placebo pills

- Patients will take active pills every day with no breaks

Consistent timing is critical

- Counsel patients to take at the same time every day
    - Unlike combined oral contraceptives (COCs), which have a window of 24 hours before a dose is considered "missed", POPs have a window of only 3 hours
- If a patient misses a dose (>3 hours late for a dose):
    - Advise the patient to take one pill as soon as possible and the next dose at its regular time, even if it means taking two pills at once
    - Advise the patient to use a backup contraceptive method (such as condoms) for 48 hours
        - If a patient does have unprotected sex after a missed dose, emergency contraception can be considered

Take with or without food

- Taking POPs with food may reduce associated nausea/stomach upset

Menstrual changes are common

- POP patients may experience a prolonged or irregular menstrual cycle, or they may have little to no change in their menstrual cycle
    - "Spotting" (light instances of bleeding between cycles) is reported by many POP patients
- Patients should contact their provider if they experience repeated postictal bleeding, prolonged episodes of bleeding, amenorrhea, or severe abdominal pain

Other risks and adverse events

- Unlike with COCs, POPs are not associated with increased risk of cardiovascular disease or venous thromboembolism
- POPs may be associated with mood changes such as fatigue, depression, nervousness, and irritability
- Modest weight gain is possible
    - A 2016 Cochrane review concluded that there is some evidence for weight gain with POPs (less than 2 kg for most patients after 6-12 months), though authors noted some studies showed POPs to be weight-neutral

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