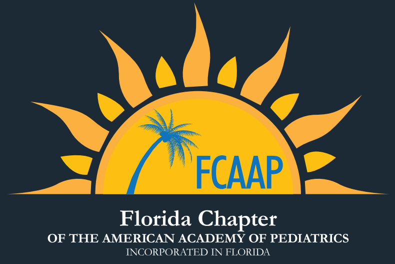
The Florida Pediatrician



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TREATING

PEDIATRIC OBESITY

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An Outstanding Article Lineup for April!

In this issue of *The Florida Pediatrician*, we present three outstanding review articles and an intriguing case report. While pediatricians are well informed about the rise in obesity prevalence in the patient populations they serve, a problem affecting millions worldwide, leading to an increasing incidence of serious health challenges, such as diabetes, hypertension, and psychosocial issues, student author Kalie Nass and her mentor, Dr. Patricia Emmanuel, provide an outstanding review of GLP-1 agonists in pediatrics with an emphasis on their use in overweight and obese children. They take us through an academic history lesson of pharmacological development and the current recommendations for the application of GLP-1 medications in pediatrics. Their review is rooted in current evidence and is mindful of what is well-known and what has yet to be defined.

Pediatricians are also acutely aware of the rise of dental caries in children, set to drastically worsen in municipalities with the inadvisable removal of fluoride from drinking water due to fears of harm to cognitive functioning. As an aside, a very recent longitudinal study of 10,317 subjects followed since 1957 (!) in Wisconsin who either had or did not consume fluorinated water growing up (and getting old like me!) was published in PNAS (*Proc. Natl. Acad. Sci. U.S.A.* 2026;123), and it conclusively showed no neurologic risks at fluorination levels used water supplies in the USA. *Primum, non nocere; et ne sinas noceri.* Student author Kashish Sachdeva and mentor, Dr. Frank Catalanotto, from the University of Florida College of Dentistry, comprehensively present the harmful social and psychological consequences of tooth decay beyond immediate medical considerations. We learn that the latter constitutes just the tip of the comorbid pediatric dentistry iceberg.

In a solicited opinion review, Dr. Mobeen Rathore outlines the rare biallelic genetic defects of Mendelian susceptibility to mycobacterial diseases (MSMD), a condition of which pediatricians may be unaware. He expertly reviews the fascinating and often missed clinical presentations and provides us with the recommended management.

Lastly, a case report of three female patients with autism spectrum disorder-related aggression who were treated with oral contraceptives is provided by Dr. David Matsibekker and colleagues of the Department of Pediatrics, University of Florida, Gainesville, and by Dr. Sanjeev Tuli of the Department of Pediatrics, University of Texas Medical Branch, Galveston. All of the characteristics of high-impact case reports are embodied in this manuscript. Publishing case reports can be challenging. Many well-known journals no longer accept them, and the ones that do have set high bars in their peer-review criteria, as does *The Florida Pediatrician*. Dr. Matsibekker and co-authors have passed with excellence the perennial "So what?" question applied to case reports as a first test of case report impact. While case report results should never be generalized to populations, high-quality reports lead to important research questions, and this paper does exactly that. Students and residents trying to publish a case report should use this article as an example of what passes muster for significance. When I was Associate Dean for Clinical Research at Florida State University, I wrote a primer for medical students titled "The Case with Case Reports" that detailed important principles and considerations of such manuscript undertakings. If any of you are interested in the primer, contact me at michaeljmd156@gmail.com, and I will be happy to share it with you.

Michael J. Muszynski, MD, FAAP, FPIDS
Editor, The Florida Pediatrician

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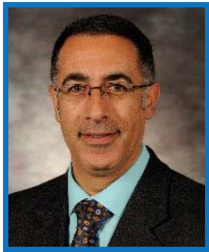

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REVIEW ARTICLE

Glucagon-like Peptide 1 Receptor Agonists in the Treatment of Pediatric Obesity

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ABSTRACT

Pediatric obesity is increasing globally. While numerous lifestyle interventions, pharmacologic therapies, and surgical options are widely available for adults, these options are limited in pediatric patients. Obesity in this population is especially detrimental as it can impact the child's social and physical health as well as put them at risk for the development of several other comorbidities in adulthood. Within the last decade, novel therapies, including glucagon-like peptide 1 receptor agonists, have been studied for their use as adjuvants to weight loss therapy. Over the last few years, many of these medications have been approved for widespread use in adults with obesity and have had heralding success. As such, glucagon-like peptide 1 receptor agonists are being more carefully studied for use in pediatric patients with obesity. Several trials have been completed, and as of this review, two glucagon-like peptide 1 receptor agonists have been approved for some cases in this population. Many trials are still in progress, testing the utility and safety of these medications in younger children. However, there is still concern regarding the effects of these medications on the child's growth and development and their proposed long-term consequences.

INTRODUCTION

In 1997, pediatric obesity was declared an epidemic by the World Health Organization, and currently, in the United States, 1 in 5 children and adolescents meet the definition of obesity.[1] Obesity is defined as having a body mass index (BMI) at or above the 95th percentile for age and sex. Unfortunately, this number is still on the rise, and it has been predicted that one-third of children and adolescents will be overweight or have obesity by 2050.[2] Many factors contribute to this trend including, social and economic determinants such as, access to healthy foods, food deserts, access to safe spaces for recreation, excessive screentime, bullying, and the child's perception of food security. The recent pandemic has also contributed to social isolation and the popularization of the sedentary lifestyle. Other factors that influence childhood obesity include the weight of the child's parents, race and ethnicity, and the child's birth weight.[3] There are many other genetic and environmental factors that may also contribute to childhood obesity.

ADVERSE EFFECTS AND LONG-TERM CONSEQUENCES OF PEDIATRIC OBESITY

It is well known that obesity in adults causes a cascade of metabolic derangements, including type 2 diabetes (T2DM), chronic inflammation, and cardiovascular disease. Similar to adults, children with obesity have a higher chance of being diagnosed with T2DM and hypertension during childhood. One study shows that as high as 37% of hypertension (HTN) in children is associated with childhood obesity.[4] Additionally, there is a higher prevalence of non-alcoholic fatty liver disease in children with obesity, a higher incidence of asthma, and a higher fracture rate in these patients.[4] It appears that obesity also influences puberty, especially in females, due to higher levels of adrenal androgen production that are converted to estrogens. Furthermore, higher levels of leptin in children with obesity may lead to CNS stimulation that also impacts the onset of puberty.[5] It has also been demonstrated that children with obesity live with a chronic low level of inflammation, which has been detected in children as young as preschool age. This inflammation, as well as other changes caused by obesity, leads to a worse quality of life in the future and has been linked to higher levels of insulin resistance in adulthood. Obesity and chronic inflammation have also been linked with a higher chance of developing rheumatoid arthritis and inflammatory bowel disease. Children with obesity have a higher risk for issues in adulthood, including osteoarthritis, multiple sclerosis, T2DM, and several cancers.[4] The complex nature of this disease and its long-term consequences warrant a multifactorial approach to treatment.

CURRENTLY AVAILABLE THERAPIES AND GUIDELINES FOR MANAGING PEDIATRIC OBESITY

The American Academy of Pediatrics (AAP) has carefully evaluated various therapies for managing pediatric obesity and has subsequently designed specific guidelines to help providers decide optimal treatment plans.[6] The suggested therapies and their supporting evidence have been listed in Table 1. The United States Preventive Services Task Force (USPSTF) currently recommends that children and adolescents over the age of 6 years should receive comprehensive, intensive behavioral interventions such as interventional health behavior and lifestyle treatment (IHBLT) as described by the AAP.[7] However, this therapy is time-intensive, requiring frequent visits, involves the other members of the family unit, and can be difficult to coordinate. Additionally, IHBLT is not widely offered, and few primary care physicians receive adequate training to administer such therapy. Because IHBLT may be challenging to implement, other forms of therapy, such as bariatric surgery and pharmacotherapy, are available to assist with weight loss, especially for patients who do not respond to IHBLT. Bariatric surgery may be available to pediatric patients with a BMI of >35 Kg/m^2 and a comorbidity such as T2DM, polycystic ovary syndrome, or patients whose BMI exceeds 40 Kg/m^2.[6] Usually limited to age 13 years and above, bariatric surgery has demonstrated success but still has limited uptake (Table 1). Pharmacotherapy is typically used as an adjunct treatment, and the evidence supporting its use varies among patients. As it stands, no medication is included in the USPSTF recommendation, and more research is needed into promising new therapies, such as glucagon-like peptide-1 receptor agonists (GLP-1RA), which will be the focus of this review.

GLP-1RAs have gained popularity in treating obesity in adults, and there is sufficient evidence supporting their use for weight loss. Because of their recent popularity, these drugs are also being heavily considered and currently studied for their use in treating pediatric obesity as well. This review will discuss GLP-1RAs and their current and future use in pediatric patients with obesity, and it will address barriers to and concerns regarding their use as a therapy for weight loss in this population.

RATIONALE FOR GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONIST USE IN OBESITY MANAGEMENT

The human body constantly measures and assesses its blood glucose levels and activates various pathways to maintain homeostasis. After a meal, when blood glucose levels increase, insulin is released and sets off a cascade of events to help the body properly store glucose and keep it from releasing added endogenous glucose into the bloodstream. The converse happens through the actions of glucagon, cortisol, and growth hormone, which promote endogenous glucose release during periods of starvation.

There are many other molecules involved downstream of these pathways, and even more that help initiate these pathways. One such molecule, glucagon-like peptide 1 (GLP-1), is released from L-cells in the intestinal tract and plays a role in stimulating insulin secretion. The most well-understood mechanism for the release of GLP-1 involves nutrients such as lipids and carbohydrates coming into contact with microvilli in the intestinal tract. However, there may also be neurohormonal mechanisms for its release involving stimulation from the vagus nerve that are less understood.[12] Once GLP-1 is released, it acts on the G-protein coupled receptor, GLP-1 receptor (GLP-1R), which is located on a variety of cell types, including pancreatic beta cells and cells of the brain, heart, gastrointestinal tract, and kidneys. Due to the widespread distribution of GLP-1R, GLP-1 has a multitude of effects throughout the body, though its primary functions include reducing gastric motility and amplifying meal-associated insulin secretion while reducing glucagon secretion. As such, targeting GLP-1R has become a prominent method for increasing insulin secretion in the treatment of T2DM, and it has been recently approved in adults as a therapy for obesity due to its ability to slow gastric emptying. In the body, GLP-1 is rapidly degraded by dipeptidyl peptidase IV (DPP-4), another target used in the management of T2DM. Because of its rapid degradation and removal from the body, giving GLP-1 as a therapy was unsuccessful. The molecule was modified to be resistant to DPP-4 and to decrease its renal clearance, while retaining the same blood glucose-lowering properties. This novel therapy was first approved for the treatment

Therapy	Description	Efficacy	Adverse Effects/Challenges
Motivational Interviewing[6]	Counseling centered on the patient and reinforcing their own motivation for change[6]	Change in BMI ranged between -4.3 to -0.1 with the most change observed with more contact hours[6]	Access to training and time
Interventional health behavior and lifestyle treatment[6,7]	Therapy involving family and patient visits focused on sustained healthy eating and making a habit of physical activity[6]	Range of 3.5-18lbs of weight loss over 1yr for 26hrs of therapy[6]	Access, scheduling
Pharmacotherapy[6]	Use of medication as an adjunct to health behavior and lifestyle treatment[6]		
Metformin	Biguanide that acts by decreasing glucose production by liver and increasing insulin sensitivity[6]	Less than 1 BMI unit but some inconsistencies; not currently approved as a weight-loss drug[6]	Dose-dependent flatulence, nausea, bloating, and rarely lactic acidosis[6]
Orlistat	Pancreatic and gastric lipase inhibitor; blocks fat absorption[6]	26.5% of orlistat-treated patients had 5% decrease in BMI compared to 15.7% of placebo group; 13.3% of orlistat-treated patients had >10% reduction in BMI compared to 4.5% of placebo group[8]	Steatorrhea, fecal urgency, flatulence[6]
Phentermine and topiramate	Phentermine is a norepinephrine, dopamine, and serotonin reuptake inhibitor; topiramate is a carbonic anhydrase inhibitor that suppresses appetite centrally[6]	BMI reduction by 10.44% in high dose and 8.11% in mid dose groups of adolescents 12-17; currently only approved in adults[6]	Elevated blood pressure, headache, dry mouth, difficulty concentrating[6]
Glucagon-like peptide-1 receptor agonists	Slow gastric emptying through action on central nervous system[6]	Liraglutide linked to 5% BMI reduction over 1yr in patients 12yrs or older who did not respond to lifestyle treatment[9] Exenatide in children >10yrs showed BMI reduction by 2.9%[10] *Currently liraglutide is approved for obesity alone in children >12yrs old; exenatide only for T2DM >10yrs old	Gastrointestinal symptoms[6]
Metabolic and Bariatric Surgery[6]	Performing surgeries including laparoscopic Roux-en-Y gastric bypass and vertical sleeve gastrectomy to assist with weight loss	Of adolescents 13-18, BMI reduced on average by 13.1 over 5 years after bariatric surgery; cardiovascular risk factors improved[11]	Postoperative nausea and dehydration, micronutrient deficiencies, need for subsequent surgeries[6]

Table 1: AAP Recommended Therapies for Pediatric Obesity

Legend: This table provides a list of AAP-recommended therapies to use when considering treatment options for pediatric obesity. A brief description of each therapy, in addition to evidence supporting its use and any adverse effects noted in the literature, has been included to provide a broader understanding of available treatment options.

of T2DM in 2005. In 2014, the first GLP-1RA, liraglutide, was approved for weight loss in adults, even without a diagnosis of T2DM.[13] Since then, several other GLP-1RAs have undergone clinical trials and have been approved for this use in adults, and they have become increasingly readily available to the public over the last few years.

CURRENT STATE OF GLP-1RA USE IN PEDIATRIC MEDICINE

Because of the widespread success of GLP-1RAs in adults and in light of treatment challenges, there has been significant motivation to learn more about how they may benefit the pediatric population. As of the time of this review, several GLP1-RAs, including dulaglutide, liraglutide, exenatide, and semaglutide, have been approved to be used in the treatment of T2DM in children older than 10 years when insulin and metformin do not provide sufficient glycemic control. Nonetheless, little is known about the effects of their long-term use in children younger than 10 years, therefore their use in young children is not recommended. More research is needed to determine safety and efficacy.

Recently, two of these drugs were also approved to manage obesity in children 12 years and older. Novel research regarding these compounds focuses on confirming their safety and efficacy in this population and seeking approval for use in younger children as well. There are also several ongoing clinical trials assessing the long-term effects of these medications, especially in pediatric patients. Due to the newness of these compounds and a lack of sufficient research on possible side effects in pediatric patients, several concerns remain regarding their broad-scale use as a weight loss therapy.

APPROVED USE OF GLP-1RAS IN PEDIATRIC PATIENTS WITH OBESITY

Until lately, there were very few drugs approved by the Food and Drug Administration (FDA) for weight loss in pediatric patients. However, in recent years, several GLP-1RAs have been shown in clinical trials to increase weight loss in pediatric patients as an adjunct therapy when lifestyle modifications alone have proven insufficient. As such, two GLP-1RAs have been FDA-approved for weight loss in pediatric patients aged 12 years and older due to their demonstrated benefits and limited side effects.

One of the currently approved GLP-1RAs is liraglutide, which has been shown to reduce BMI when added to lifestyle modifications in adolescents over the age of 12 years. In one randomized, double-blind trial involving 251 adolescents aged 12-18 years with obesity who did not respond well to lifestyle modification alone, adding liraglutide was shown to increase weight loss.[9] Liraglutide therapy featuring a 3.0 mg dose subcutaneously once a day in addition to lifestyle therapy was compared to a placebo treatment in patients also adhering to the same lifestyle modifications. Participants received therapy for 56 weeks, followed by a 26-week follow-up period. In this trial, liraglutide yielded a significantly greater reduction in BMI, with an average loss of 4.64 percentage points in the treatment group compared to placebo. In addition, more participants in the treatment group experienced a 5% reduction (43.3% treatment vs 18.7% in placebo) and a 10% reduction (26.1% treatment vs 8.1% placebo) in BMI. Participants receiving liraglutide also lost, on average, 4.5 kg more weight than those in the placebo group. Few participants in either group noted serious adverse events, but gastrointestinal side effects were more common in the treatment group.[9]

The only other GLP-1RA that is currently FDA-approved to be added to lifestyle therapy in the treatment of pediatric obesity in adolescents between the ages of 12 and 17 years is semaglutide. This drug was approved after liraglutide, and its efficacy was demonstrated in several clinical trials. In one double-blind, parallel-group, randomized, placebo-controlled trial, semaglutide was assessed as a weight-loss therapy in children 12-18 years of age with obesity (BMI in the 95th percentile or higher) or who were overweight (BMI in the 85th percentile or higher) but who had at least one comorbid condition related to their weight.[14] Participants either received a 2.4 mg subcutaneous dose of semaglutide once a week or a once-weekly placebo in addition to lifestyle interventions for 68 weeks. Two hundred and one participants were enrolled, and 180 completed the study. This study demonstrated that the addition of semaglutide to lifestyle therapy produced a greater decrease in BMI than lifestyle modification alone. Participants receiving semaglutide experienced a BMI reduction of 16.0 percentage points compared to those in the placebo group, where the BMI increased by 0.6. Furthermore, 95 out of 131 (73%) participants in the treatment group achieved 5% or more weight loss compared to only 11 out of 62 (18%) participants in the placebo group. Additionally, improvement of cardiometabolic risk factors, including glycated hemoglobin, lipids, alanine aminotransferase levels, and waist circumference, was noted in the semaglutide group compared to placebo. There was a greater incidence of gastrointestinal adverse events (62% vs 40% placebo) and cholelithiasis (4% compared to 0% of placebo) in the group that received semaglutide. Only a small percentage of participants experienced serious adverse events in either group (11% in the treatment group, 9% in the placebo group).[14] While there are several ongoing clinical trials assessing the use of semaglutide in younger children, there has been some evidence of its success in reducing BMI in children as young as 10 years. One retrospective observational study investigated the effect of semaglutide on the BMI of children aged 10-18 years in the UK who were receiving treatment in addition to lifestyle management.[15] The treatment produced a reduction in BMI standard deviation scores at 6 and 12 months of 0.32 ± 0.27 and 0.54 ± 0.52, respectively. Patients also achieved an average of 7.03 ± 7.50 kg of weight loss. The most common side effects were mild gastrointestinal issues, and of the 50 patients studied, one patient developed gallstones.[15] Though semaglutide appears to be safe and efficacious in children as young as 10 years, it remains unapproved, as more research is needed. Despite this, it has been occasionally prescribed off-label in younger children on a case-by-case basis.

FUTURE DIRECTIONS AND UPDATE ON CURRENT CLINICAL TRIALS FEATURING GLP-1RA USE IN PEDIATRIC PATIENTS WITH OBESITY

Though currently only two GLP-1RAs have been officially FDA-approved for the purpose of aiding in weight loss in adolescents, several others have been undergoing clinical trials. Such trials include investigating other GLP-1RAs' use in adolescents, the use of GLP-1RAs in young children, and trials involving various possible adverse effects of using these medications in pediatric patients.

As discussed, liraglutide is approved for adolescents aged 12-18 years as an adjunct to lifestyle modification for children who have had an insufficient response to lifestyle therapy alone. The SCALE Kids trial, published in 2024, aimed to assess the efficacy of liraglutide in children aged 6 to less than 12 years as an alternative therapy for children of this age group who are unable to achieve weight loss with traditional treatments.[16] This study is similar to the trials conducted in adolescents, featuring the same 3.0 mg daily subcutaneous dosage in addition to the lifestyle modifications compared with placebo for 56 weeks, followed by a 26-week follow-up period. It featured 82 participants randomized to receive either a 3.0 mg dose of liraglutide or a placebo and demonstrated that among children in this age range with obesity, treatment with liraglutide resulted in a greater BMI reduction than lifestyle modification alone. After 56 weeks, the mean changes in BMI for the treatment and placebo groups were -5.8% and +1.6%, respectively. One difference between the results of the liraglutide study in this age group and in children 12-18 years was the rate of adverse effects.[16] In this trial, 80% of participants receiving liraglutide endorsed gastrointestinal adverse events, whereas in the previously mentioned trial, only 64.8% of participants receiving liraglutide had these symptoms.[9,16] Additionally, this trial reported 12% of participants receiving treatment experienced serious adverse events, while only 2.4% of children ages 12-18 years in the other study had these effects.[9,16] Though this trial suggests that liraglutide is effective in children ages 6-12 years, more research is required regarding long-term effects and to confirm liraglutide's efficacy in this age group before it could be approved for use by the FDA. Semaglutide, which is also approved for adolescents ages 12-18 years, will also be studied as a weight management therapy in children as young as age 6 years. Though this study, STEP Young, has not yet begun recruitment, it plans to follow children and teenagers for 132 weeks as they receive once weekly semaglutide to assess the medication's effect on BMI.[17]

Another GLP-1RA, tirzepatide, that has had recent success in adults, is currently undergoing several trials for use in pediatric patients. This drug is a dual GLP-1RA and glucose-dependent insulinotropic peptide (GIP) agonist, which means it also functions like GIP to increase insulin secretion and slow gastric emptying. One trial aimed to investigate the efficacy, safety, and pharmacokinetics of tirzepatide in pediatric and adolescent patients in the age range of 6-11 years with obesity. This study began in 2023 and is set to be completed by January 2025, though the results have not yet been released.[18] Another trial featuring tirzepatide, SURMOUNT-ADOLESCENTS-2, is currently in phase III. This trial enrolled pediatric patients between 12 and 17 years of age with obesity and at least 2 weight-related comorbidities such as HTN, prediabetes, or hypertriglyceridemia. In addition, participants must have had at least one unsuccessful dietary attempt at weight loss. The primary outcome of this study will be the percent change from BMI at week 72 compared to baseline, and several secondary outcomes related to BMI, including waist circumference, and other weight-related conditions. This trial is estimated to be completed by the end of May in 2027.[19]

Exenatide is yet another relevant GLP-1RA in this discussion, as it has been approved for use in children aged 10-18 years for the treatment of T2DM, but it has not yet been approved as a weight loss therapy. One randomized, double-blind, parallel, placebo-controlled clinical trial conducted in 2020 investigated the effects of extended-release (ER) exenatide primarily on the BMI of children in that age group with a BMI above 30 Kg/m^2. Forty-four participants were selected to receive 2 mg ER exenatide or placebo once weekly for 6 months along with lifestyle therapy. At the end of the trial, it was determined that treatment with exenatide led to a moderate reduction in BMI and improvement in glucose tolerance and cholesterol. The study additionally reported that the medication was well-tolerated.[10] Another trial was conducted in 2022 to assess ER exenatide at a dose of 2.0 mg as an adjunct to meal replacement therapy and also focused on children 12-18 years of age with obesity. The study followed 100 participants who had been enrolled in meal replacement therapy and experienced BMI reduction before the addition of weekly exenatide or placebo to determine if exenatide would influence BMI rebound in these adolescents. The results of the study, however, were not statistically significant, but they do in part suggest that exenatide could help reduce BMI rebound in adolescents who had lost weight initially with dietary interventions.[20]

CONCERNS ABOUT THE USE OF GLP-1RAS IN PEDIATRIC PATIENTS

In the current literature, the most commonly reported adverse effects associated with the use of GLP-1RAs in pediatric patients are gastrointestinal, including vomiting, diarrhea, abdominal pain, or hypoglycemia. More severe side effects include gallstones and pancreatitis, and they are contraindicated in patients at risk for medullary thyroid cancer. As the number of adults using GLP-1RAs expands, rare side effects have been reported, such as severe gastroparesis and non-arteritic ischemic optic neuropathy.[21] Since their recent increase in popularity and approval for use in some pediatric patients, more concerns have arisen regarding their effects on growth and development, mental health, and possible long-term consequences.

Pediatric patients differ from adult patients in many ways, one being energy expenditure. In children, additional energy is needed for growth and development. There is a delicate balance of energy intake and expenditure required in this population for sufficient growth and development to occur. One concern of using these medications, which inherently reduce energy intake through various satiety mechanisms, is that this delicate balance could be upset.[22] It has been postulated that this may result in defective growth and musculoskeletal development. There is currently a clinical trial to determine how GLP-1RAs may alter bone density, structure, and strength in adolescents. This trial will follow children and young adults aged 12-21years who are taking semaglutide for two years to assess the impact of GLP-1RAs on skeletal integrity.[23]

Another area of concern being discussed in the current literature addresses the abuse potential of these medications and their effects on the mental health of adolescent patients. Because of the widespread nature of their effectiveness portrayed in the media, GLP-1RAs have a reputation for inducing quick and effective weight loss. As such, it is likely that older adolescents at least have heard of these medications and know about their use in weight loss. Adolescents are generally a vulnerable population when it comes to body image and self-perception, and for them, these drugs provide another possible method of quickly achieving their ideal weight status, resulting in a high potential for abuse. In a similar fashion, it has been proposed that these medications may be misused by student athletes and other highly competitive students who must meet specific weight requirements for competitions or to enhance athletic performance.[22] Though these medications are not widely prescribed to the pediatric population currently, there has been a recent trend of increasing medicalization of pediatric conditions.[22] As such, if these drugs gain approval, it logically follows that pediatric obesity could become one of these conditions, leading to widespread use and availability of these medications to an already vulnerable population.

As GLP-1RAs have gained popularity, some cases involving rarer adverse effects have been reported in recent literature. One case report from 2024 involved an obese adolescent on low-dose liraglutide who presented with vomiting, epigastric pain, and decreased urine output and was diagnosed with an acute kidney injury (AKI) in addition to hepatic dysfunction. It was determined that liraglutide was the cause of his presentation, and the medication was discontinued.[24] A study conducted in 2022 demonstrated a correlation between GLP-1RAs and AKI in adult patients. Of the cases of AKI reported, liraglutide was the most common GLP-1RA culprit, most commonly occurring in patients between the ages of 45 and 84 years. AKI is a possible serious adverse effect associated with GLP-1RA use and should be considered when deciding whether to prescribe this medication.[25]

CONCLUSIONS

Pediatric obesity is a serious condition that affects a significant portion of today's children and young adults, and it continues to rise in prevalence. Because this condition has detrimental long-term consequences that threaten the child's quality of life in adulthood, it is incumbent that new therapies be made available to help treat obesity in this population. It is a complex problem that requires a multifaceted approach. GLP-1RAs have become targets for new research into possible remedies for the pediatric obesity epidemic. Due to their success in reducing BMI in adults who have struggled to lose weight with lifestyle modification alone.

Several trials have been conducted that demonstrate the promise of these medications in younger children, and still, more are set to be completed within the next few years, with the hope of gaining approval for additional GLP-1RAs. Today, two GLP-1RAs, liraglutide and semaglutide, are approved for the purpose of weight loss as an adjunct to lifestyle therapy. They are only approved for children over the age of 12 years. A recent MMWR study of national prescribing data demonstrated that less than 1% of obese adolescents have been prescribed GLP-1RAs.[1]

Even with FDA approval, there is limited insurance coverage for these agents, and Medicaid, which covers about 40% of children in the United States, does not cover this indication[26], at least in the state of Florida. Without insurance, patients may be required to pay $1000 per month out of pocket for these medications. This cost barrier creates a socioeconomic disparity for patients who cannot afford private insurance or the high costs of these medications. Aside from high costs, other reasons for such a low rate of GLP-1RA prescription include production shortages and concerns for possible adverse effects.[1]

Despite their demonstrated success in this population, there are still many concerns regarding long-term effects, and no data on outcomes are available concerning long-term use. While the main side effects noted in the trial are mild to moderate gastrointestinal effects, other serious events have been reported in the literature. There are clinical trials that are currently studying long-term complications. Because of the paucity of completed research and data regarding their performance and tolerance in this population in the long-term, it is essential to weigh the individual benefits and risks of using these medications on a case-by-case basis and to monitor long-term outcomes carefully.

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REVIEW ARTICLE

Is Poor Oral Health in Children the Tip of the Iceberg?

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ABSTRACT

Tooth decay is the most common chronic disease in children, with a prevalence five times higher than asthma and seven times more prevalent than hay fever. Untreated dental decay can cause pain, infection leading to hospital emergency department visits, impaired academic performance, problems with emotional development, and, in rare instances, death. The purpose of this paper is to review the current literature concerning the impact of dental caries on children, specifically related to school attendance, academic performance, and emotional health. Research highlights that students with poor oral health are more likely to miss school, whether due to tooth pain or the need for dental treatment. The frequent absences disrupt learning opportunities and place the child at a disadvantage compared to their peers, often resulting in diminished academic performance. Beyond academics, dental caries impairs children's emotional health by lowering self-esteem and hindering their ability to fully engage in daily activities. As these issues affect the upcoming generation, it is essential to prioritize their oral health. Further research is needed to broaden our understanding of the impact of poor oral health on children. Efforts to expand access to dental care must be intensified. Pediatric healthcare providers play a crucial role in fostering oral health awareness and ensuring children receive the care they need to thrive. Therefore, we urge pediatricians and other medical providers to increase their efforts to monitor and improve oral health in children.

INTRODUCTION

Dental caries (tooth decay) is the most common chronic disease in children, with a prevalence roughly five times higher than asthma and seven times more prevalent than hay fever.[1,2] Untreated dental decay can cause pain, infection that leads to hospital emergency department visits and even hospitalization, impaired academic performance, problems with emotional development, and, in rare instances, death. The purpose of this paper is to review literature about the impact of dental caries on children, specifically related to school performance and emotional health, and to urge pediatricians and other medical providers to increase their efforts to improve oral health in children.

EXTENT OF THE ORAL HEALTH CRISIS

The unmet needs for health care are critical indicators of access problems. Among children, the unfulfilled requirements for effective healthcare have special significance. Failure to obtain treatment can affect their health status and functioning in both the near- and long-term. Dental care is the most prevalent unmet need.[3,4] Florida leads the nation in many measures of poor access to dental care.[5]

IMPACT ON SCHOOL ATTENDANCE

Poor oral health has a significant impact on school attendance and academic performance, as demonstrated by multiple studies. Jackson, et al. found that children with poor oral health were nearly three times more likely to miss school due to dental pain, contributing to over 700,000 lost school hours in North Carolina alone.[6] Absences due to pain had a stronger negative effect on academic performance than those for routine dental care. Agaku and colleagues reported that 21.8% of U.S. children aged 6–17 experienced dental problems in the past year, and unmet therapeutic dental needs were linked to increased absences, especially among children without insurance and those living in poverty.[7] The study also highlighted higher unmet dental needs in Hispanic children and those not enrolled in school. Naavaal and Kelekar estimated that U.S. children missed 142 million school hours annually due to dental visits, with those from lower-income or less-educated families missing the most.[8] Children from lower-income families and those with worse oral health were found to miss significantly more school. These results highlight the importance of improving access to dental care to help reduce school absences and support students' learning.

IMPACT ON ACADEMIC ACHIEVEMENT

Academic performance is profoundly influenced by oral health, with the impact often felt most strongly in underserved communities. Seirawan, Faust, and Mulligan found that students with toothaches in the past six months were nearly four times more likely to have a grade point average lower than a median of 2.8 compared to students without a toothache in the past six months.[9] Students with toothaches in the past six months were found to be nearly six times more likely to miss school for dental reasons, while those lacking access to dental care were three times more likely. A study by Blumenshine et al. revealed that students with poor oral and general health were 2.3 times more likely to report poor academic performance, while those with only poor oral health were 1.4 times more likely to perform poorly.[10] They noted that poor dental health alone significantly impacts school performance, even when general health is good. A 2019 meta-analysis showed consistent links between poor oral health and academic challenges, with higher decayed, missing, and filled teeth index scores that reduced the likelihood of earning higher grades.[11] It demonstrated that untreated caries and a lack of school-based sealant programs significantly impacted academic performance. These findings highlight the importance of implementing targeted oral health strategies to enhance students' educational outcomes.

IMPACT ON EMOTIONAL DEVELOPMENT

Oral health has a strong impact on children's behavior and emotional well-being, affecting their daily lives and interactions. Guarnizo-Herreño and Wehby surveyed children with varying levels of dental health to examine behavioral impacts.[12] They found that 19.25% of children frequently felt unhappy, 18.4% felt worthless or inferior, and 11.46% felt shy. These feelings were more common among those reporting poor or fair dental health compared to children with good or excellent dental health. Their analysis showed that better dental health alone was linked to improved school performance outcomes after adjusting for general health. Baseer et al. studied children experiencing oral health issues and found that these problems affected daily activities: 50% had difficulty drinking, 41.4% struggled to eat, 17.8% faced trouble speaking, and 16.9% missed school.[13] Beyond physical symptoms, many experienced emotional effects, with 39.2% feeling disturbed and 11% avoiding smiling, illustrating how dental pain impacts both behavior and well-being. A 2020 study of young children with early childhood caries anfoundd found widespread issues, including pain from hot and cold drinks (48%), sleep problems (41%), and difficulties playing (27%), before treatment.[14] Following full-mouth rehabilitation, most children showed significant improvement in quality of life, though a small group still struggled with self-esteem and smiling. These findings highlight the importance of early and effective dental care to improve not only children's physical health but also their emotional well-being and social experiences.

CONCLUSION

Pediatricians should view the above findings with a focus on the recent decision to ban community water fluoridation in Florida. A recently published study predicted that removal of fluoride from community water supplies would result in a significant increase in dental caries over a ten-year period and approximately 20 billion dollars in associated increased health care costs.[15] Dental caries significantly impact a child's well-being, influencing their school attendance, academic achievement, and emotional development. Research highlights that students with poor oral health are more likely to miss school, whether due to tooth pain or the need for dental treatment. These frequent absences disrupt learning opportunities and place them at a disadvantage compared to their peers. Combined with the challenges of managing dental pain, this often results in diminished academic performance. Dental caries also impair children's emotional health, lowering self-esteem and hindering their ability to fully engage in daily activities. As these issues affect the next generation, it is essential to prioritize their oral health.

Further research is needed to deepen our understanding of the full impact of poor oral health on children, and efforts to expand access to dental care must be intensified. Pediatricians and pediatric healthcare providers play a fundamental role in fostering oral health awareness and ensuring children receive the care they need to thrive. Pediatric clinicians can learn more about oral health and their role in managing and preventing dental disease in their patients. The free Smiles for Life online curriculum contains excellent

resources in self-paced individual modules that cover a wide range of oral health topics.[16]

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Disclaimer: The opinions expressed herein are those of the authors and do not necessarily reflect official positions of the UF College of Dentistry.

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REVIEW ARTICLE

Mendelian Susceptibility to Mycobacterial Diseases

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ABSTRACT

Mendelian susceptibility to mycobacterial diseases is a rare condition often diagnosed in countries where the Bacillus Calmette-Guérin vaccine is given routinely at birth. Although prevalence is difficult to determine, it is estimated that the global prevalence of Mendelian susceptibility to mycobacterial diseases is 1 per 50,000 to 1,000,0000 individuals. In the high-income countries where the Bacillus Calmette-Guérin vaccine is not routinely used, this condition may be diagnosed based on recurrent non-tuberculous mycobacterial infections or recurrent Salmonella infections, often in unusual anatomic sites.

INTRODUCTION

Mendelian Susceptibility to Mycobacterial Diseases (MSMD) is a group of genetic disorders that are an inborn error of immunity. Individuals with MSMD are otherwise healthy with no obvious immunological abnormalities. However, they are at increased risk for infections with environmental mycobacteria. These individuals can go undiagnosed for years unless there is a high index of suspicion due to recurrent infections with certain organisms or the identification of an infection in an uncommon site for that organism.

In countries where the Bacillus Calmette-Guérin vaccine is not routinely recommended, such as the United States, MSMD may go undiagnosed unless there is a high index of suspicion based on the occurrence of certain types and patterns of infections.

CONDITION

The underlying reason for MSMD is 35 separate genetic disorders resulting from mutations in 19 genes. Biallelic mutations are the most common. This condition affects an estimated 1 in 10,000 individuals. Fifty percent of the patients had IL-12Rβ1 or IL-12p40 deficiency. There may be an impaired response to interferon gamma (IFN-ϒ) or the production of IFN-ϒ may be impaired, and the severity of the disease depends on penetration.

Most of these individuals are identified in the first year of life, usually within the first six months of life if they received the Bacillus Calmette-Guérin (BCG) vaccine at birth.

These individuals have normal immunoglobulins and normal dihydrorhodamine and nitroblue tetrazolium tests. They may have lymphopenia, but usually have no other laboratory abnormalities on routine testing. Measuring IFN-ϒ in plasma or serum can help in identifying complete defects when no IFN-ϒ is detected. However, partial defects will not be diagnosed since some IFN-ϒ may be present with partial defects. IFN-ϒ levels should only be performed after an active infection resolves.

The BCG vaccine is routinely recommended at birth in many countries globally where there is a high incidence of tuberculosis. BCG is administered on the left upper arm of the newborn. Currently, BCG is not recommended in the United States. Infants with MSMD can present with two types of diseases. The first is "BCG-itis" (also referred to as loco-regional or isolated infection), which

is a localized lymphadenitis that usually affects the axillary, cervical, or supraclavicular lymph nodes. The second is “BCG-osis” (also referred to as systemic BCG infection), which can cause infection of the lungs, skin, soft tissue, spleen, kidneys, gastrointestinal tract, bone, joints, or brain. In addition, it can result in lymphadenitis of the distant lymph nodes (mesenteric, mediastinal, and inguinal). *Mycobacterium bovis* is often isolated from the site of infection.

Individuals with MSMD are also susceptible to non-typhoidal Salmonella infections that cause gastroenteritis or sepsis. Patients may have recurrent Salmonella infections, especially at unusual sites, such as lymph nodes. In individuals with recurrent non-typhoidal Salmonella infections who have not received BCG, MSMD should be suspected, and the patient referred to a geneticist for evaluation. Infections with unusual or uncommon gram-negative enteric organisms, especially in otherwise healthy individuals, and severe *Mycobacterium tuberculosis* infections, have also been observed in individuals with MSMD. Fungal infections, including Paracoccidioidomyces, Candida, and Histoplasma, have been reported. Therefore, patients with the clinical presentation of chronic mucocutaneous candidiasis should be evaluated for MSMD. There does not appear to be a selective predisposition to severe viral infections.

Henoch-Schönlein purpura has also been reported in individuals with MSMD.

MANAGEMENT

There is no curative treatment for MSMD, although patients benefit from monthly subcutaneous or intravenous immunoglobulin therapy. The benefits of dialyzable leukocyte extracts have also been reported in MSMD patients. Some patients also undergo hematopoietic stem cell transplantation. As one might expect, recombinant human IFN-ϒ appears to be beneficial in many MSMD cases. There are no clinical trials that have shown a definitive benefit with any of these management modalities.

Management of infections with appropriate antimicrobials is critical since many patients with MSMD succumb to infections as a result of multiorgan failure. Lifelong azithromycin prophylaxis may be successful in preventing recurrences and should be done in consultation with an infectious diseases specialist. Gene therapy could be curative, but it is currently unavailable for MSMD.

Mortality risk in patients with MSMD is variable depending on the specific genetic defect and the clinical outcome of serious infections. In low-income parts of the world where children receive the BCG vaccine at birth, most patients with MSMD die from multiorgan failure secondary to serious infections before their fifth birthday.

To prevent life-threatening complications of BCG infection, BCG vaccination should not be administered to newborns and infants whose siblings or other relatives have had complications of the BCG vaccine, and MSMD was confirmed or suspected.

CONCLUSION

In the United States and other parts of the world where BCG is not routinely recommended, a high index of suspicion is necessary to make the diagnosis of MSMD. MSMD should be suspected in otherwise healthy individuals with recurrent mycobacterial and Salmonella infections or infections in unusual sites with these organisms. In addition, unexplained infections caused by endemic intracellular pathogens like Histoplasma and deep mycoses should raise concern for MSMD.

Author Disclosure: Dr. Rathore has disclosed no financial relationships relevant to this article. This article does not contain a discussion of an unapproved/investigative use of a commercial product/device.

RECOMMENDED READING

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CASE REPORT

Oral Contraceptives' Effect on Menstruation-Related Aggression in Children with Autism Spectrum Disorder

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ABSTRACT

Individuals with autism spectrum disorder often experience heightened difficulty managing menstrual symptoms, including increased aggression and self-injurious behaviors. Sensory sensitivities and limited communication abilities can exacerbate these behaviors. This case report evaluates the impact of oral contraceptive therapy on aggression associated with menstruation in post-menarche females with autism spectrum disorder. Three female patients with autism spectrum disorder and documented menstruation-related aggression were followed over an 8–10-month period after initiation of hormonal contraceptive therapy. The Modified Overt Aggression Scale was used to assess behavioral changes. All three patients demonstrated a significant reduction in aggression scores following hormonal therapy, with decreases ranging from 16 to 22 points. Menstrual suppression was achieved in all patients without adverse effects. Hormonal contraception may represent a viable adjunct therapy for managing menstruation-related aggression in females with autism spectrum disorder. Larger, prospective studies are warranted to validate these findings.

INTRODUCTION

Menstruation can present significant behavioral and emotional challenges for individuals with autism spectrum disorder (ASD). These challenges, including severe premenstrual syndrome (PMS) and dysmenorrhea, are often magnified by sensory sensitivities, communication deficits, and behavioral dysregulation. Notably, menstruation may exacerbate aggressive and self-injurious behavior, particularly in non-verbal or minimally verbal patients.[1-2]

Premenstrual dysphoric disorder (PMDD) is a severe, mood-related condition that is more commonly reported among individuals with ASD than in the general population, with reported prevalence ranging from 14% to 92% in some cohorts. Symptoms include irritability, mood swings, aggression, and social withdrawal.[4-6]

The American College of Obstetricians and Gynecologists (ACOG) supports menstrual suppression in individuals with cognitive or physical disabilities who desire or require fewer menses.[7] However, there is limited literature that has explored the impact of hormonal therapy on menstruation-related aggression in females with ASD.

This case report describes the clinical course of three adolescent females with ASD and aggression exacerbated by menses who were treated with oral contraceptive therapy and monitored using the Modified Overt Aggression Scale (MOAS).[8]

CASE PRESENTATIONS

Case 1: An 11-year-old female with ASD (Level 3 support needs) and intellectual disability presented with severe behavioral disturbances coinciding with menstruation. Her aggression, including hitting, head banging, and property destruction, recurred with each menstrual cycle. Baseline R-MOAS score was 30. Despite behavioral therapy and pharmacologic treatment (aripiprazole, clonidine, stimulants), symptoms persisted. Following insurance-related delays, she was initiated on a continuous progestin-only pill (norethindrone 0.35 mg). Within one month, physical aggression ceased, though emotional dysregulation persisted intermittently. By 10 months, menstrual suppression was achieved, and R-MOAS had decreased to 8.

Case 2: A 12-year-old female with ASD and a history of aggression during menstruation was noted to become verbally threatening and physically aggressive during the week preceding menses. Baseline R-MOAS was 23. She had previously been stable on dexmethylphenidate, guanfacine, and hydroxyzine. Hormonal therapy was initiated with norethindrone-ethinyl estradiol (0.4 mg/35 mcg) with quarterly withdrawal bleeding. After 10 months, she showed significant improvement, with verbal threats persisting, but no physical aggression or property destruction. R-MOAS was reduced to 7.

Case 3: A 12-year-old female with ASD and behavioral exacerbations during menstruation exhibited aggression, including punching walls, dangerous outbursts, and auto-aggression. The initial R-MOAS score was 26.

She was first trialed on depot medroxyprogesterone (Depo-Provera®), but it was discontinued due to side effects and lack of amenorrhea. She was then transitioned to a combined oral contraceptive (levonorgestrel-ethinyl estradiol with quarterly placebo dosing). After 10 months, aggression reduced significantly, with only verbal threats and gestures noted. Her R-MOAS score dropped to 7.

Age	ASD Severity	Baseline Aggression Score	Type of Hormonal Contraception	Rx Duration	Follow-up Period	Post-Treatment Aggression Score	Menstruation Suppression (Yes/No)	Adverse Effects
11 y	3	30	norethindrone 0.35 mg oral tablet	12/14/23 to present	12/14/23 to 10/24/24	8	Yes	None
12 y	3	23	norethindrone/ ethinyl estradiol/ ferrous fumarate 0.4-35 mg-MCG oral tablet chewable	02/05/24 to present	02/05/24 to 10/9/24	7	Yes	None
12 y	Not assessed	26	levonorgestrel-ethinyl estradiol (SEASONIQUE) 0.15-0.03/0.01 mg oral tablet	02/05/24 to present	02/05/24 to 10/09/24	7	Yes	None

Summary of Oral Contraception Effect on Menstruation-Related Aggression in the Context of ASD

DISCUSSION

This case report provides preliminary evidence that hormonal contraception may reduce menstruation-related aggression in adolescent females with ASD. MOAS scores of three patients with ASD decreased after the initiation of hormonal therapy, correlating with behavioral improvement and successful menstrual suppression.

Aggression in ASD is a major cause of caregiver burden and increases the risk of psychiatric hospitalization and injury. Existing literature indicates that females with ASD are more prone to PMDD and related behavioral challenges.[1,5,6,9–11] However, the role of hormonal modulation in behavioral symptomatology remains underexplored.

Our findings align with ACOG recommendations supporting menstrual suppression in individuals with disabilities and highlight the need for clinicians to consider hormonal interventions as part of the broader treatment strategy in this population.[7]

Limitations of this report include small sample size, lack of control group design, and reliance on parent-reported outcomes. Variability in hormonal agents used also limits direct comparison across these patients. Nonetheless, the consistent reduction in aggression and absence of adverse effects strengthen the rationale for further investigation.

CONCLUSION

This case report demonstrates that hormonal contraception may reduce perimenstrual aggression in post-menarche adolescents with autism spectrum disorder. Our three patients showed substantial reductions in aggression scores and improved quality of life, with no adverse events reported. These results support the consideration of hormonal therapy as an adjunctive treatment in managing menstruation-related behavioral dysregulation in females with ASD. Larger, controlled studies are needed to validate these findings and inform standardized treatment protocols.

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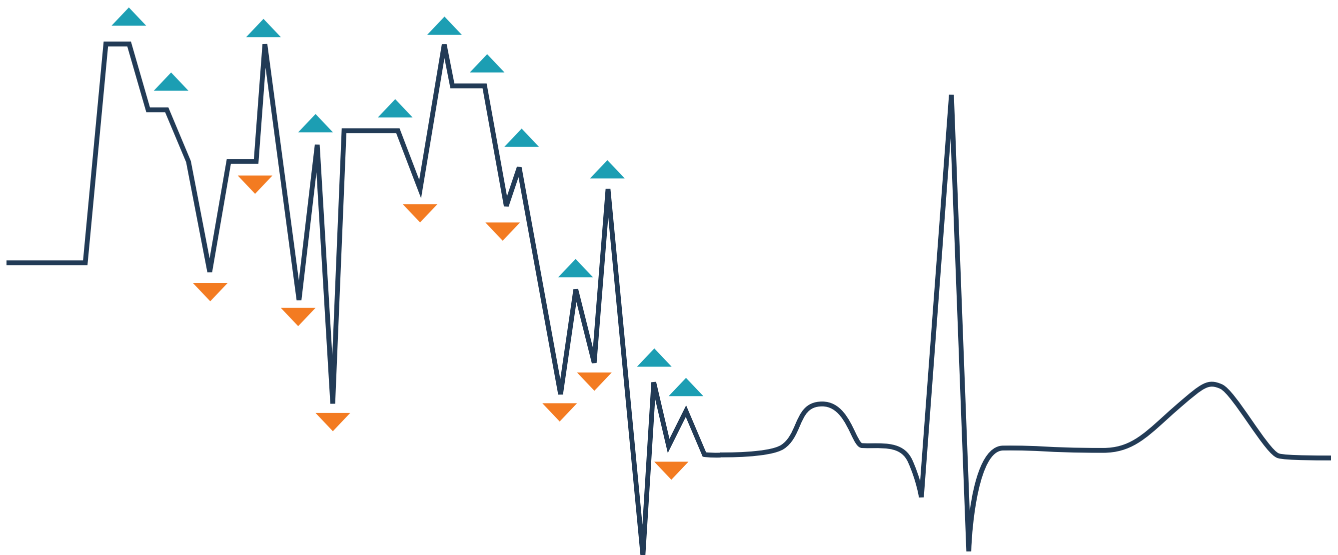

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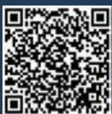

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