National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Pharmacotherapy for Obesity in Children and Adolescents: State of the Science, Research Gaps, and Opportunities

The Bethesdan Hotel
8120 Wisconsin Avenue
Bethesda, MD 20814
and Via Zoom Virtual Platform

November 28–29, 2023

EXECUTIVE SUMMARY

Introduction

The National Institute of Diabetes, and Digestive and Kidney Diseases (NIDDK) sponsored a hybrid, scientific workshop on November 28 and 29, 2023, titled "Pharmacotherapy for Obesity in Children and Adolescents: State of the Science, Research Gaps, and Opportunities." The overarching goal of the workshop was to identify gaps and opportunities to guide research and accelerate progress on the safe, effective, and equitable use of pharmacotherapy for obesity in children and adolescents. The workshop convened leading scientific and clinical experts with expertise in obesity pathophysiology, genetics of obesity, treatment of obesity in children and adolescents including behavioral lifestyle, pharmacotherapy, and metabolic and bariatric surgery (MBS), clinical trial design and management, precision medicine, implementation science, health equity and disparities, and health economics to discuss use of pharmacotherapy in children and adolescents with obesity. Registration was open to the public. Attendance was 71 in person and approximately 100 virtually, and included a diverse audience of scientists, clinicians, and lay persons.

Rationale and Meeting Objectives

Pediatric obesity is highly prevalent and increasing, with approximately 20 percent of children and adolescents living with this chronic, progressive, and relapsing disease. Non-Hispanic Black and Hispanic youth and children experiencing poverty are disproportionately affected. Pediatric obesity has been associated with serious complications and co-morbidities, including type 2 diabetes, metabolic-dysfunction associated steatotic liver disease, dyslipidemia, elevated blood pressure, and mental health problems. The adverse consequences of pediatric obesity threaten the health of tens of millions of Americans and place great strain on the health care system. Obesity and related sequelae can impair a child's well-being and quality of life during a critical time for growth and development. Moreover, most children and adolescents with obesity retain their excess adiposity into adulthood. The frequency of delivery and duration of lifestyle modification therapy needed to meaningfully reduce body mass index (BMI) in children and adolescents is high, often limiting its feasibility in practice. In addition, most behavioral or lifestyle obesity treatment interventions show only modest favorable changes in average BMI; these changes are often not sustained, and a substantial number of children do not experience clinically meaningful improvement.

Since 2020, three anti-obesity medications (AOMs)—liraglutide, semaglutide, and phentermine/topiramate—have been approved by the U.S. Food and Drug Administration for chronic weight management in children ages 12 years and older with non-syndromic obesity. In 2023, the

American Academy of Pediatrics (AAP) released its first clinical practice guideline (CPG) for the evaluation and management of children and adolescents with obesity. The CPG recommended integrating health behavior and lifestyle interventions for weight management with pharmacological treatment or MBS when medically indicated and following current FDA-approved indications.

The availability of AOMs offers an adjunct to lifestyle intervention for children and adolescents at high risk for obesity-related medical and psychosocial complications. NIDDK's leadership recognizes that research is needed to address important knowledge gaps to ensure appropriate, effective, safe, equitable, and successful use of obesity pharmacotherapy in clinical practice, as well as to evaluate the long-term benefits and adverse effects of their use in pediatric populations. Such research will inform optimal and equitable medical management of children and adolescents with obesity.

An organizing committee* worked to develop the meeting agenda and objectives. The objectives of the workshop were to review the rationale for the use of pharmacotherapy for pediatric obesity and to identify gaps and opportunities for future research to guide:

- Best practices for the use of pharmacotherapy for pediatric obesity, including prescriber training, timing of initiation, duration of therapy, combination therapies, and lifestyle support.
- Understanding of contextual factors that influence equitable access to treatment and barriers to care.
- Understanding of unique aspects of the use of pharmacotherapy for obesity in vulnerable populations, including bias and stigma, communication, development of autonomy, spectrum of eating disorders, and growth and development.

Following opening remarks from Dr. Griffin Rodgers, Director of the NIDDK, leading U.S. experts presented their research during five sessions. These sessions encompassed an overview of treatment for pediatric obesity, the science and rationale for pharmacotherapy to treat obesity, the use of evidence-based treatments for pediatric obesity, equity and access to care, and study design and measurements. During moderated discussions, the speakers, panelists, and other participants identified areas for future exploration and opportunities for improved clinical care.

Session 1: Overview of Treatment for Pediatric Obesity

Speakers discussed the current prevalence of childhood obesity and its complications/comorbidities, the consequences later in life, and weight bias and stigma. They also provided an overview of past treatment options and current AAP recommendations for treating childhood obesity. The session included patient and parent panelists who shared their experiences with obesity and obesity care. Key points, themes and research needs identified during this session included:

- The high prevalence of obesity is a complex and systemic problem that is exacerbated by inequality in social drivers of health. The people who most suffer from obesity are the least likely to be able to access care. Treatment should involve an approach that targets the underlying biology of the disease and acknowledges obesity's social and structural drivers.
- Advanced treatments (e.g., MBS, pharmacotherapy) can be given in combination with more foundational treatments (e.g., lifestyle and behavioral interventions) in a manner that is tailored to the patient.
- Clinicians should show humility and respect the lived experience of people living with obesity. Treatment goals should be developed with patient and family participation and should not be limited to BMI stabilization or reduction. Studies should prioritize outcomes that matter to patients and parents.

- Weight bias within the health care system can be tracked and addressed only if it can be reliably measured.
- Priority populations are not well represented in clinical trials. Participants from low- and middle-income backgrounds should be recruited, and such factors as access and affordability should be examined. Other conditions that are under-represented in clinical trials but commonly seen in patients with obesity include mental health disorders, eating disorders, and intellectual and developmental disabilities.
- Children who are being treated for obesity usually present with high psychosocial health risks are likely to discontinue care prematurely and have poor health outcomes. More research is needed to understand psychosocial outcomes in pharmacological trials for obesity.
- Many pediatric patients starting obesity treatment present with disordered eating behaviors. The effects of AOMs on these behaviors should be studied.

Session 2: The Science and Rationale for Pharmacotherapy to Treat Obesity

Speakers discussed the pathophysiology of obesity and the rationale for the use of pharmacotherapy; clinical trial evidence for the safety, efficacy, and tolerability of AOMs; and approved and emerging pharmacotherapies for children with obesity syndromes. Key points, themes and research needs identified during this session included:

- Minimal data are available to guide many aspects of the pharmacological treatment of pediatric obesity—including when to initiate therapy, optimal duration of treatment, strategies to address attrition and sustainability, long-term effectiveness and adverse effects of treatment and indications for discontinuation, heterogeneity of treatment effects and outcomes, management of multiple medications, non-BMI outcomes, cultural consideration in weight management, and telemedicine and electronic and mobile health approaches—and these require in-depth study. Comparative effectiveness trials, as well as trials that implement adaptive Sequential Multiple Assignment Randomized Trial (SMART) research designs, could be used to address these gaps.
- Physiological compensation mechanisms in children and adolescents in response to different types of treatment should be evaluated in greater depth.
- Clinical trials should assess not only whether a treatment is effective but also how it works and for whom it is effective. Establishing patient registries and improving data collection will help generate stronger data sets. Developing informative biomarkers will enhance predictions of treatment response.
- The long-lasting effects of obesity treatments given during certain developmental stages are unclear.
- The preservation of lean muscle and bone mass during weight loss is a priority for patients, families, and clinicians.
- The potential risks and benefits of using AOMs to prevent obesity, especially in high-risk populations, are unknown and require further investigation.
- Patients with genetic obesity syndromes that present in childhood often have severe obesity. Mechanisms that explain this obesity and the effects of pharmacotherapies on syndromic obesities should be determined.

Session 3: Use of Evidence-Based Treatments for Pediatric Obesity

Speakers discussed the clinical use of AOMs and other evidence-based treatments for pediatric obesity, challenges associated with the implementation of treatments in practice, clinical use of AOMs, the intersection of MBS and pharmacotherapy, and mental health considerations. Key points, themes and research needs identified during this session included:

- The intersectionality among racism, socioeconomic status, and weight bias and its effect on the treatment of pediatric obesity should be investigated.
- Implementation barriers are significant for all aspects of obesity treatment in pediatric populations, including inadequate primary care training, capacity/knowledge/bias of prescribers, and low access to lifestyle programs, AOMs and MBS.
- Assessment tools should include comprehensive psychosocial measures; studies are needed to assess psychosocial outcomes.
- Weight regain has been shown to occur in adult populations when AOMs are discontinued. Additional research is needed in pediatric populations and after longer term treatment.
- Health information technology, clinical decision support tools, and shared-care models (e.g., primary and specialty, caregiver and patient) are beneficial approaches that can be implemented in patient care; however, their usefulness in improving outcomes in pediatric patients receiving obesity treatment requires further study.
- Intensive health behavior and lifestyle treatment programs are poorly accessible and difficult to sustain for the healthcare system and patients/families. The role of intensive behavioral and lifestyle modification therapy as standalone treatment or as an adjunct to AOMs should be evaluated.
- MBS is on average the most effective treatment for severe pediatric obesity, but outcomes are heterogeneous, and few response predictors are known. The addition of AOMs to MBS might be helpful in patients with inadequate weight loss or weight regain, but research is needed on identification of appropriate patients, type of medication and dosage, and intervention timing.
- In pediatric patients with severe obesity, a trial of AOMs may enable some to avoid or delay MBS, although investigation is needed.
- Mental health problems (e.g., anxiety, depression, eating disorders, suicidal behaviors) are associated with obesity in children and adolescents. Registry-based studies are needed to evaluate the natural history of mental health problems as well as disordered eating patterns with all modalities of obesity treatment, e.g., IHBLT, AOM, MBS.
- Lessons learned from studies of other obesity treatment modalities should be leveraged in pharmacotherapy trials.

Session 4: Equity and Access to Care

Speakers discussed challenges associated with inequities and access to obesity care, the effects of weight stigma and bias, and tools and approaches to improve access to care. Key points, themes and research needs identified during this session included:

- Many clinicians have explicit or implicit bias related to obesity. The degree to which pervasive weight-related stigma and discrimination in the health care system influences the treatment of pediatric obesity should be further studied.
- Stigma is not an effective tool for motivating people to lose weight or improve health. Rather than using strategic shaming, public health campaigns and health care providers should emphasize the humanity, dignity, and capabilities of people with obesity. Research is needed to identify best strategies to reduce stigma in health care settings and design environments that are inclusive to patients with obesity.
- Medical training should include programs that educate clinicians on how to sensitively and effectively care for patients with obesity.
- Equitable access to broadband internet and related technology is still a challenge and outdated telehealth policies remain. Telemedicine modalities and access policies may reduce health disparities related to access to obesity care.; however, further research is needed in pediatric populations particularly in relation to AOM use.
- Studies should assess the value of telehealth, and ongoing research should evaluate the effectiveness of telemedicine within the full spectrum of obesity care.

Session 5: Design and Measurement

Speakers discussed clinical trial design best practices and future considerations, choosing meaningful outcomes and measures, and cost-effectiveness analyses. Key points, themes and research needs identified during this session included:

- Patient-reported outcomes are critical to consider in study design and should be implemented more broadly in future trials.
- Effective obesity care is not synonymous with weight loss. Treatment outcomes beyond BMI reduction should be recognized, defined, and implemented in future studies.
- Ideal primary endpoints should reflect disease severity and pathology; track with important health outcomes; and be simple, cost-effective, and reproducible. A standardized and robust metric quantifying body fat mass and/or distribution may be an ideal primary efficacy endpoint; however, validation studies will be needed.
- BMI is not ideal as a primary efficacy endpoint, but BMI-related metrics should be reported to allow comparisons across studies.
- Studies should loosen exclusionary criteria to be more representative of real-world populations. For example, including individuals with mental health comorbidities in clinical trials will require additional safety monitoring, but will improve generalizability. Monogenic or syndromic obesity should not automatically be an exclusionary criterion for trials.

- Weight loss that leads to BMI crossing the 50th percentile has been suggested as one potential metric for when an AOM dose should be stabilized, but this requires further study. In addition, research is needed to inform treatment recommendations once the weight goal is achieved.
- Research is needed on the optimal and safe rate of weight loss during treatment and appropriate nutritional and physical activity counseling recommendations. Assessment of disordered eating and eating disorders during treatment is needed to monitor safety.
- Cost-effectiveness analyses help to determine whether an intervention strategy is worth the investment and is one approach to inform health care reimbursement decisions and allocation of resources.

Patient and Parent Perspectives on Their Lived Experience – Panel Discussion

The workshop included parent and patient perspectives during which panelists discussed how they have been affected by obesity and their encounters with obesity care in the United States. Key points, themes and research needs identified during this session included:

- When treating obesity, health care providers must understand that obesity is a chronic health condition and deliver standards of care as they would with any other chronic disease.
- Obesity has serious effects in many areas of patients' lives, but no person is defined by their weight.
- Obesity is a physical, mental, emotional, social, familial, and societal issue and patients with obesity should be treated holistically.
- Because access to obesity specialists is limited by several factors (e.g., lack of providers, insurance coverage, parental and health care provider bias), most parents of children living with obesity will interact primary care providers. Primary care clinicians must be educated about current treatment standards and taught to provide non-stigmatizing care.
- Behavioral and lifestyle interventions are not always effective for treating obesity. Healthcare providers should not prescribe these treatments and then place blame on patients when the treatments do not work.
- Patients and parents expressed their belief that clinical trials of AOMs should no longer be tested against placebos as patients want to be on treatments that have the chance to be effective.
- Treatment goals should go beyond BMI and weight. Measures besides the broad goal of "happiest, healthiest weight" should be determined.
- The patient voice should be included in the study outcomes; however, it is often omitted because Journals do not tend to publish qualitative data.
- Health care providers are also educators and should reassure and empower the patients with an uplifting and positive message.

Summary and Conclusion

Obesity is a complex, heterogeneous, chronic disease that involves multiple organs regulating systemic energy homeostasis and behavior in response to changing environmental conditions. Childhood obesity has become increasingly prevalent; it is exacerbated by societal inequities and disproportionately affects

children from marginalized communities. Recent advances in the pharmacological treatment of pediatric obesity have achieved significant successes, including reductions in BMI and improvements in metabolic health and overall quality of life. However, in some patients, these drugs may have unintended adverse consequences. Furthermore, the persistence of health care inequities results in access to care being a major barrier to the most vulnerable populations. Based on the presentations and discussions, the following key takeaways and research needs were identified.

- Research is needed to determine the screening and selection criteria, monitoring strategy, benefits, and risks of long-term AOM treatment in pediatric populations, including development of standard protocols for monitoring safety in research and in clinical practice.

- Studies of AOMs are needed in more diverse populations including children with mental health diagnoses, disordered eating patterns, intellectual and developmental disabilities, and in priority populations (racial/ethnic diversity and low-income populations).

- Research is needed to determine how to use AOMs with lifestyle and surgical treatments. What should lifestyle look like with AOMs? How intensive does it need to be? Should the content and goals be the same as in stand-alone intensive health behavior and lifestyle treatment?

- Adequately powered studies with AOMs are needed to assess 1) body composition (bone/muscle/fat mass) changes with treatment 2) psychosocial health (disordered eating/eating disorders, depression, anxiety, self- harm, body image, medication use/abuse) and 3) adherence, in both the short and long term.

- Studies should conduct deep phenotyping to better understand heterogeneity in AOM efficacy and adverse effects and to support precision/personalized medicine in practice.

- Appropriate designs, including implementation and dissemination studies, pragmatic trials, SMART designs, adaptive designs, or observational cohorts are needed to assess risks and benefits of AOMs in heterogenous populations, response heterogeneity, best practices in prescribing AOMs' in clinical settings, and to determine treatment strategies, long term safety and to identify approaches that improve health equity and reduce barriers to care.

- Research is needed to identify the optimal timing, age and other patient or family characteristics to initiate AOM treatment and optimal endpoints to adjust dosing of the AOM.

- Research is needed to characterize biopsychosocial mechanisms of weight regain with continuous AOM use to inform durable treatment approaches.

- Research is needed to determine if and when continued high dose (i.e. approved therapeutic dose) AOM is required for sustained weight reduction in all patients or whether lower and/or intermittent doses (or even complete withdrawal of AOM) could be effective in the long-term for some individuals.

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