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Unintended Consequences of Glucagon-like Peptide-1 Receptor Agonists Medications in Children and Adolescents—A Call to Action

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The purpose of this perspective is to highlight potential unintended and adverse consequences of the increasing use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in children and adolescents. We propose a set of activities suited in particular to the NIH National Center for Advancing Translational Science (NCATS) network of Clinical and Translational Science Award (CTSA) hubs to mitigate these possible threats to pediatric health. Our apprehension is heightened, ironically, because recent studies have corroborated in children and adolescents the remarkable effectiveness of the GLP-1RAs in the management of type 2 diabetes and, as satiety enhancing medications, in obesity that had been previously demonstrated in adults. Two studies were published in the impactful *New England Journal of Medicine* (1,2), research motivated, as noted by the authors, in no small measure precisely because the current approved medications for pediatric obesity and type 2 diabetes have proven to be limited in their effectiveness and fraught with adverse events (3). Current administration of the GLP-1RAs is predominantly parenteral, but with the progress in the development of oral formulations (4), their increased use in children and adolescents, unsupervised and/or medically supervised, is inevitable. Little attention has been paid to the possible unintended consequences or adverse impact of these medications on children and adolescents during their critical period of growth and development (**Table**).

A major element of our concern is that unbalanced and inappropriate reductions in caloric (energy) intake could be induced by GLP-1RA in children and adolescents. Energy in children and adolescents is expended not only on physical activity but also, unlike in adults, on growth and development. The balance of energy intake and energy expenditure influences growth and health across the lifespan. For example, with appropriate levels of exercise and diet during adolescence, bone mineralization is increased and the risk of osteoporosis and pathologic fractures much later in life is lessened (5). Almost any deviation from healthy levels of physical activity and diet can adversely impact catabolic and anabolic mediators. Seemingly disparate conditions such as adolescents who are normal-weight but physically inactive (6), those who exercise at excessive levels (7,8), and obese children and adolescents (9), all manifest harmful growth patterns and, often, elevated inflammation associated with increased cardiovascular disease risk.

Rapid development of oral-administration formulations of GLP-1RA and the proclivity among adolescents for risk-taking (10) create a perfect storm for potential abuse. Adolescence

marks a particularly vulnerable period for the development of self-esteem and satisfaction with one's own appearance. Lifetime prevalence data in the United States from 2010 indicated that 2.7% of adolescents manifested eating disorders at some point in their lifetime, with females being more than twice as likely as males (11). Volitional emesis and the use of laxatives or appetite suppressants is not uncommon in youth (12). In recent years, the rapid expansion of social media has resulted in more youth being exposed to body image ideals and diet culture than ever before. Young users of social media have a higher risk of developing eating disorders (13). The potential for GLP-1RA abuse was further enhanced by the shutdowns associated with the COVID-19 pandemic that worsened the intractable epidemics of pediatric obesity and poor cardiorespiratory-metabolic fitness, particularly among minority populations of children and adolescents (14).

Anecdotal clinical experience of our group suggests that there is already widespread knowledge in the pediatric population about the GLP-1RA effectiveness as satiety medications aiding weight loss, not helped by apparent widespread use documented in the popular media (15). Health threats resulting from the explosion of counterfeit drugs are well documented (16), and fueled in part by illegitimate access through the internet (17). We fear that children and adolescents participating in weight-sensitive activities such as wrestling, body building, cheerleading, gymnastics, or dance, might be particularly vulnerable to unsupervised acquisition and use of these medications.

Adding to our concerns about potential abuse and overuse of the new GLP-1RA medications is the increasing medicalization of pediatric conditions (18), many of which result from environmental and societal rather than biological mechanisms, and the lack of progress in particular made in addressing the environmental and lifestyle issues that have contributed immeasurably to the childhood obesity epidemic. The issue of lifestyles was, in fact, highlighted in particular by Weghuber et al. cited above in their publication on semaglutide effectiveness in pediatric obesity (1). The authors carefully adhered to the "lifestyle interventions" mandated by the FDA and its European counterpart for clinical trials of medications for type 2 diabetes and obesity in the pediatric age-range (19,20). However, the lifestyle intervention guidelines date back to 2007-8, do not address the need to precisely measure dose, frequency, and type of physical activity or diet and do not suggest ways (e.g., cardiopulmonary exercise testing) other than self-report to monitor intervention compliance or fidelity.

We recognize the challenges imposed by implementing truly effective lifestyle interventions in children and adolescents who are obese or suffer from frank type 2 diabetes. By the time such children or adolescents gain access to medical intervention (which is currently limited at best) or are eligible for clinical trials, the clinical trialist and primary care provider must overcome the years of poor diet, sedentary behavior, and lack of available, safe, and supportive venues for vigorous play and exercise that for the majority of these children paved the way for their conditions. In the classic 2002 NEJM study designed to prevent the transition of pre-diabetes to frank type 2 diabetes in adults (21), the authors concluded, “Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin.” We speculate that the very fact that the lifestyle interventions in the recent pediatric study had virtually no effect suggests that their ineffectiveness resulted from insufficient implementation and not lack of biologic efficacy.

The pharmacokinetics and pharmacodynamics of certain GLP-1RAs like liraglutide have been studied in both adult and pediatric populations (22); however, children are not miniature adults and as newer formulations emerge it cannot be assumed that pharmacokinetics or adverse effects in adults are the same in children or adolescents (23). We must also consider that pediatric dosage forms may be more expensive than adult formulations (24), there is a potential for lifelong reliance on these medications if started in childhood, and GLP-1RA may require lifestyle interventions (25) to optimize safety, efficacy, and value during growth and development.

The GLP-1RA class of medications will benefit children and adolescents with morbid obesity and type 2 diabetes. We also believe that their overuse and abuse is inevitable. The NCATS emphasis on the science of translation positions the network of CTSA hubs to mitigate these potential threats to child and adolescent health. Attention to real world data, team science, community engagement, implementation and dissemination, and health disparities will be key in formulating research and policy planning. Accordingly, we propose the following elements as a call-to-action for CTSA hubs across the nation:

1. Build and support multidisciplinary teams of frontline clinicians, community partners, physiologists, and behavioral and pharmaceutical scientists to address the knowledge gap in GLP-1RA effects in children and adolescents (see Figure).

2. Address the translational bioethics research (26) issues that will result from approval of pediatric formulations of the GLP-1RA medications in particular and, in general, that have evolved from the medicalization of health conditions like pediatric obesity.
3. Engage and improve the quality and accessibility of relevant real world data such as school based physical fitness testing (SB-PFT), mandated in sixteen states covering ~ 60% of American school children (27). SB-PFT can prove to be an enormously helpful health and fitness metric used to identify regions and communities where poor cardiorespiratory-metabolic fitness and obesity is high, and the possible need for and abuse of GLP-1RA medications are most likely.
4. Work with the FDA and other agencies to update guidelines for lifestyle interventions in pediatric clinical trials that incorporate state-of-the-art approaches to quantifying, monitoring, and evaluating physical activity, adherence to diet, and accurate measurement of body composition beyond the current reliance on the body mass index (BMI), a suboptimal metric of overweight and obesity in adolescents (28).
5. Elevate and enhance training of the clinical trial workforce on state-of-the-art understanding of effective lifestyle interventions. Such training should also target primary care pediatricians whose exposure to exercise and nutritional science is currently quite limited (29).
6. Develop, demonstrate, and disseminate learning modules for school personnel (teachers, coaches), parents, school-aged children, and primary care pediatricians and child mental health professionals about the GLP-1RA medications, their appropriate uses and possible abuse.

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Table 1. Possible unintended consequences of supervised or unsupervised use of oral GLP-1 receptor agonists in children and adolescents

Adverse Effect	Reason for Concern
Long term consequences on growth and development	Balance of energy intake and energy expenditure modulate critical growth hormones such as GH and IGF-1. The appetite suppressant, anti-hedonic, and fatigue effects of the GLP-1RA may alter this balance during critical periods of growth and development.
Abuse among patients with diagnosed eating disorders	Pediatric-aged patients (male and female) with eating disorders are known to abuse appetite suppressants.
Abuse among children and adolescents in certain competitive sports (e.g., wrestling, martial arts, gymnastics, ballet)	Children and adolescents involved in school, club, or community sports like wrestling or gymnastics where body weight is a competitive factor are known to engage in unhealthy behaviors to accelerate weight loss.
Unsupervised use for unwarranted self-perception of obesity and overweight, particularly among female adolescents	Inaccurate perception of being overweight in healthy-weight adolescents result in unnecessary weight control behaviors (30). In children and young adults, supplements sold for weight loss, muscle building, and energy were associated with almost three times the risk for severe medical outcomes compared with vitamins (31).
Excessive or insufficient medical prescription in populations with high prevalence of obesity and poor fitness	Pediatricians have little or no formal training in effective ways to deal with obesity, overweight, or poor physical fitness in their patients. Short-term effectiveness and convenience of drug prescriptions may be well intended but lead to untested effects when used for longer duration during critical periods of growth and development.
Distorted cost-benefit relationship of long-term use in youth	<ul style="list-style-type: none"> • Result in disparities in GLP-1RA availability • Promote counterfeit or drug diversion activity. • Off-label utilization may not be covered by insurers. • Possible lifelong therapy may be cost-prohibitive.

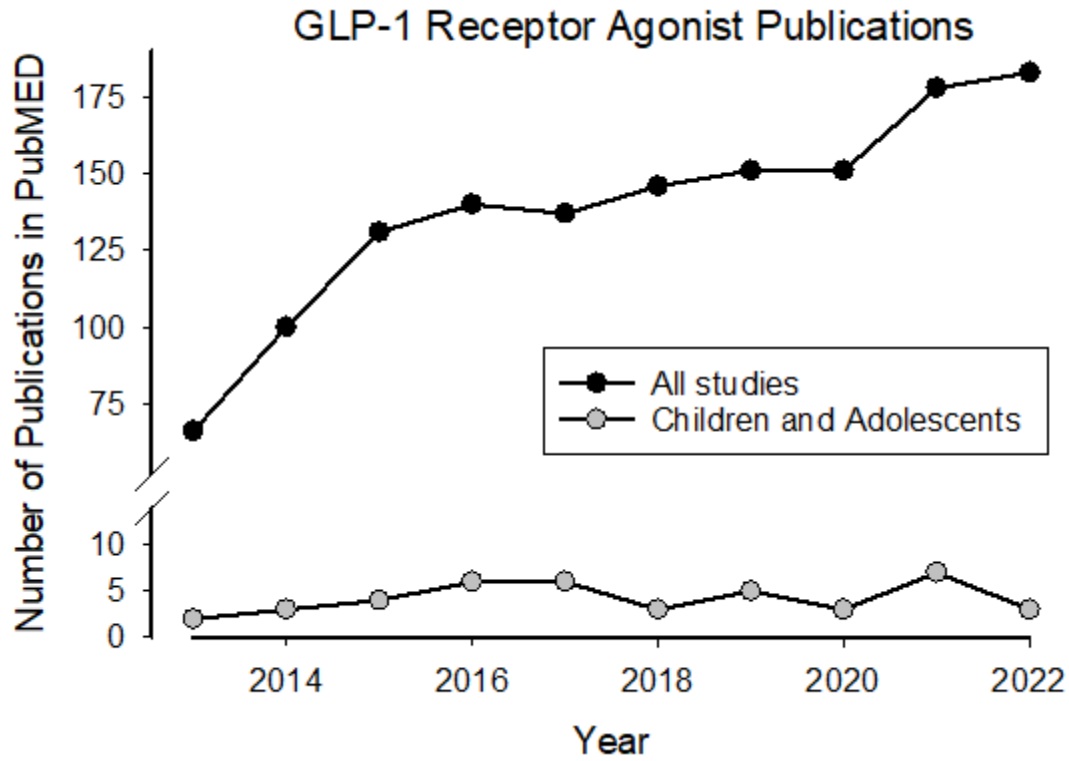


Figure 1. Dearth of research on GLP-1 RAs in children and adolescents. The use of these medications in the pediatric age range is likely to be long term. Little is known about the long-term and lifespan effects of these drugs during critical periods of growth and development.

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