DCRI **THINK TANKS**

FROM INSIGHT TO ACTION

ANTI-OBESITY PHARMACOTHERAPY: AN URGENT NEED FOR GUIDANCE, ACCESS, AND EQUITY

BACKGROUND/CONTEXT

On October 16-17, 2024, a Duke Clinical Research Institute (DCRI) think tank meeting on "Anti-Obesity Pharmacotherapy: An Urgent Need for Guidance, Access, and Equity" brought together leadership from across the clinical research enterprise to explore access issues related to cost, coverage, and medication shortages; discuss therapeutic targets and clinical practice guidelines to optimize overall health; promote innovation in clinical trial design; and discuss regulatory guidance of anti-obesity therapeutics.

Obesity impacts the lives of ~150 million individuals in the United States (US) and being overweight impacts an additional 105 million, representing approximately 73% of the US population [1]. This affects every facet of the lives of these individuals but also results in a societal cost of ~425 billion USD annually [2]. With recent advances in anti-obesity therapy, the healthcare system finds itself in a situation where a chronic condition that affects a large proportion of the population is now eligible for highly effective, but currently expensive, therapies. How we navigate current and upcoming challenges will shape the field of obesity care for decades to come, highlighting the importance of coordinated, equitable, and efficient actions from multiple stakeholders.

KEY TAKEAWAYS AND THEMES

The field should consider how obesity is measured and defined
Historically, obesity has been defined as a chronic disease characterized by excess body fat accumulation. However, we now understand that excess body fat is simply the end product of a complex neuroendocrine disease. Simplifying obesity to a single anthropometrical measurement is not accurate or comprehensive, does not reflect the degree or impact of adiposity, and does not account for the severity of the disease. A more accurate definition may include anthropometric measures (including, but not limited to BMI), measures of symptoms of obesity (e.g. physical – shortness of breath, low-energy, joint pain; psychological – depression, anxiety), risk assessment measures and obesity-related conditions. While BMI correlates with obesity-related conditions and complications, the use of additional metrics may enable a more accurate capture/characterization of the disease in conjunction with BMI. As novel therapies enter the market, metrics to measure obesity may continue to evolve.

The value, aggregate costs, and individual costs of anti-obesity medications (AOMs)
To be able to provide AOMs to ~12.5 million Medicare beneficiaries would come at a societal cost of an estimated 1.6-7.1 billion USD annually [3]. However, these evaluations do not account for the growing body of evidence highlighting the impact on multiple long-term clinical outcomes.

Ongoing developments, such as the entry of better evidence on the long-term outcomes and prevention of high-cost health events, the improvement in the manufacturing process, and the competition generated by additional agents and generic options will lead to improved cost-effectiveness. However, some of these advances may take over a decade to come to fruition. In the meantime, there is a need to identify solutions that can address equitable access to these medications.

Improving Equity with AOMs
Inequalities exist in both the prevalence and treatment of obesity. Compounding this, there are issues unique to obesity that can impact appropriate care such as societal stigma and health provider biases. As policies and strategies are being developed and implemented, special considerations should be taken to ensure that AOMs improve, rather than exacerbate these inequalities.

Equitable access starts with clinical trials that include representative proportions of under-represented groups. While biologically, there may not be differences in treatment response among various demographics, understanding the impact of lived experiences in the trial setting will improve our ability to implement treatment strategies in the real world. It is also important to recognize that the overall cost of AOM is not the only variable that will result in inequitable use of AOMs. Even among individuals with medication insurance (which is significantly lower in marginalized populations), the co-payment requirement alone may be enough to result in expanding disparities in obesity care.

Long-term Management
There is a paucity of studies examining the long-term management of obesity, with outstanding questions including: At what stage/metric can we consider obesity to be "controlled"? What are treatment targets? What are the optimal therapeutic strategies to maintain these targets long-term? Registry and real-world data represent an opportunity to capture long-term outcomes and guide future studies in this area.

Clinical Trial Design / Ethics / Regulator Considerations
There were mixed opinions on the role of placebo-controlled trials in this rapidly evolving field, requiring the consideration of the risk profile of participants and current level of access of available therapies. Additionally, the availability of approved drugs and generic versions may make the participation in a placebo-controlled trial unappealing. This has direct implications for future trial design and represents additional barriers to the conduct of future trials. As such, both investigator and industry-sponsored trials will undoubtedly explore opportunities to generate data. Independent of the choice of comparator arm, these designs may take the form of platform trials, multi-arm studies, and studies that harness real-world/registry/electronic medical record data. Other concerns in clinical trial design include defining non-inferiority in active comparator trials, establishing what "usual care" means in placebo-controlled trials and ensuring that labelling of products is intentional and patient-centric.

ACTIONABLE ITEMS

1. Develop an Obesity Research Roadmap
With the rapid evolution of the science of obesity, there is an unmet need for stakeholders to identify – in an intentional manner – key challenges and unanswered questions in the field of obesity and prioritize high-quality studies that address these questions. This would harmonize research priorities across all stages of therapy development from pre-clinical studies to post-approval registries.

2. Develop A Consensus Statement on Obesity Measures in Clinical Trials
Our understanding of obesity has drastically improved since the 1970's when BMI categorizations originated. As such, our definition of this complex chronic neuroendocrine disease must also evolve. We need to agree upon standardized measures of obesity and outcomes to apply across clinical trials and real-world registries.

3. Develop systems to ensure equitable access for AOMs (measure/assess)
Routinely assessing equitability of access to AOMs should be a priority to inform initiatives to combat these inequalities. Real-world registries can inform these assessments and the creation of strategies to reduce inequities.

4. Periodically evolve the regulatory and payer framework for evidentiary standards
As cumulative evidence is generated regarding the use and benefits of AOMs, regulatory and payer guidance will need to continue to evolve with the additional inputs. These may include elements of class indications for labelling, ethics of placebo-controlled trials, and reimbursement standards of AOM in special populations.

For more information, please visit https://dcri.org/insights-and-news/insights/dcri-think-tanks.

References:

1. Li M, Gong W, Wang S, Li Z. Trends in body mass index, overweight and obesity among adults in the USA, the NHANES from 2003 to 2018: a repeat cross-sectional survey. BMJ Open. 2022;12(12):e065425. doi: 10.1136/bmjopen-2022-065425.
2. Cecchini M, Vuik S. The heavy burden of obesity. 2019.
3. Office CB. How Would Authorizing Medicare to Cover Anti-Obesity Medications Affect the Federal Budget? 2024.