Obesity Pharmacotherapy: New Era, New Opportunities?

The rapid onset of our current obesity epidemic has caught the public health and medical communities somewhat unaware, with a tripling of obesity prevalence since 1975 such that nearly 40% of adults are obese and ~2/3 are overweight. Given the contribution of obesity to a long, well-known list of co-morbidities, the control of excess adiposity is arguably the public health crisis and challenge of our time. Notably, minority populations are disproportionally affected by this epidemic, further exaggerating existing health disparities and increasing the urgency of successful obesity management**.**

While anti-obesity medicines have been used to some extent since the 1930s, they have not been embraced by the medical community until recently, and only with reluctance in some quarters. This is in large part due to reticence to consider obesity a 'real disease', coupled with stigmatizing those affected with a tinge of moral failure (aka fat-shaming). This tendency to attribute obesity to a simple lack of self-control is sharply contrasted with an eagerness to treat other diseases of lifestyle, such as hypertension and type 2 diabetes, which are often equally treatable with lifestyle modification but do not carry the visible "badge of shame" that characterizes excess adiposity. As an aside, in addition to the well-known changes in our food supply and built environment as well as sleep/circadian disruption and stress that are broadly understood to contribute to obesity, there have also been significant changes to our chemical environment that are not modifiable by individuals; indeed, even wild animals that live adjacent to human communities and highly inbred laboratory mice on highly standardized diets have exhibited a small but measurable increase in adiposity that cannot be attributed to lifestyle.

It's worthwhile to take a quick walk through how we got to our current position in pharmacological management of obesity. Anti-obesity medicines had a rather ignoble start in 1920s and 1930s with the use dinitrophenol (DNP) and its mechanistically predictable side effect of hyperthermia, and the early introduction of amphetamines for weight management in the same era, which then progressed to complex amphetamine-based regimens in the ensuing decades that, while not widely adopted, carried significant risk. Use of, and interest in, anti-obesity therapeutics remained quite limited until two approved drugs of limited utility, the noradrenergic drug phentermine and the serotonergic drug fenfluramine, were found to produce and sustain meaningful weight loss (~10%) when combined in the so called "Fen-Phen" combination in the 1990s. Dexfenfluramine subsequently received approval in 1996, although with lower efficacy than the Fen-Phen combination. Both fenfluramine and dexfenfluramine were withdrawn in 1997 following demonstration of valvular heart disease and of pulmonary hypertension. While phentermine remains on the market, it has limited utility as monotherapy, although does have some utility in combination. Nonetheless, the Fen-Phen combination created a set of expectations of what is achievable with obesity pharmacotherapy; until recently subsequently approved drugs (e.g., Orlistat, Sibutramine, Lorcaserin, Phentermine/Topirimate, Naltrexone/Bupropion) met the efficacy standard for approval, but fell far short of the expectations set by the Fen-Phen consumer experience and were accompanied by significant off-target effects. Two of these (sibutramine and lorcaserin) are no longer on the market for safety reasons.

Largely for these reasons (low efficacy, significant off-target effects leading to poor tolerance, significant safety concerns) the obesity market has until recently been static. With only ~4% of the addressable market treated, obesity represents a substantial unmet medical need and market opportunity. The recent success of GLP-1 agonists in producing more robust weight loss, as discussed below, has clearly signaled strong appetite for a well-tolerated anti-obesity medication with good efficacy, although limited insurance coverage for obesity continues to be a challenge.

Although the GLP-1 agonist liraglutide was approved for treating adult obesity in 2014 and adolescent obesity in 2020, the relatively modest weight loss (~8%) produced was not sufficient to spur substantial uptake. However, the next generation GLP-1 agonist semaglutide produces nearly twice the weight loss (15%) while maintaining a favorable safety and tolerability profile (the typical GI effects that characterize GLP-1 class are generally mild and do not appear to be a major impediment to adoption) such that semaglutide now sets the benchmark for development of anti-obesity medicines. Other GLP-1 agonists and especially incretin-based polyagonists are in development, with several in phases 2 and 3. The most promising approaches to date are polyagonists that target GLP-1 and GIP, such as tirzepatide, those that target GLP-1 and glucagon receptor, and tri-agonists targeting GLP-1, GIP and glucagon receptors. Some, such as tirzepatide, show greater weight loss than semaglutide although they may have greater GI tolerability concerns. Amylin agonists, such as the long-acting amylin analogue cagrilintide, are earlier stage but produce reasonable (~10%) weight loss as monotherapy and impressive weight loss in combination with semaglutide. While these are the most advanced stage therapies, as their development for obesity emerged from diabetes therapeutics, other promising drugs targeting both hunger/satiety pathways and peripheral energy metabolism are in earlier stages of development; these include leptin sensitizers, mitochondrial uncouplers (BAM 15), GDF15 agonists, and PYY agonists. Even with the current and anticipated availability of improved incretin-based anti-obesity therapies, there is ample room and need for these additional therapeutic modalities, especially in light of the heterogeneity of response to any single obesity therapeutic and the incidence of GI intolerance (although predominantly mild) with incretin therapies.

As with any therapeutic indication, translating nonclinical discovery and pharmacology data to clinical efficacy carries significant risk. The good news here, though, is that there is a high degree of correlation between efficacy in the diet-induced mouse model of obesity and subsequent clinical efficacy. The predictive value of these models is strong, but is unfortunately primarily qualitative for a variety of reasons. Firstly, drugs that affect hunger and satiety pathways in mice produce a homogenous response in these highly inbred models, while the clinical response is decidedly heterogeneous. This is, in part, due to the fact that targeting homeostatic eating (hunger and satiety) is more straightforward to model than targeting predominantly hedonic eating patterns that “overrule” homeostatic control. Secondly, significant reductions in food intake in mice has a larger impact on body weight over the relatively short term that these studies are conducted than is generally seen with food intake reductions in humans. Finally, targeting energy expenditure, while qualitatively similar between rodents and humans, is quantitatively different. For example, a drug targeting metabolic uncoupling has the potential to exert a greater effect in mice simply due to the larger relative quantity of brown adipose tissue, as well as the higher metabolic rate per unit mass in mice. While this argues for caution in continuing development of a drug with modest nonclinical effects, mitigating factors include uncertainty surrounding quantitative translational prediction and the opportunity to develop combination products. In short, a negative result in these models is predictive of clinical failure, but a modest result may not be.

Those developing obesity therapeutics should consider early exploration of broader metabolic disease application in light of overlapping mechanisms of action. Semaglutide is a great example here – first developed and approved for diabetes, then for obesity, and now in phase 3 for NASH. Those advancing new obesity medicines would do well to consider broader metabolic indications with high fidelity nonclinical models, recognizing that each indication may require a different dose range. Once in clinic, in addition to early assessment of type 2 diabetes measures as secondary outcomes, exploratory noninvasive NASH biomarkers should be considered as early as possible – certainly in a phase 2a trial, but conceivably as exploratory outcomes in phase 1.

With >95% of obese individuals untreated, the opportunities to develop multiple complementary therapeutics to address this high unmet need is substantial. Heterogeneity of responses to drugs and, indeed, heterogeneity in the underlying causes of the disease, strongly indicate the need for multiple classes of drugs to be used as monotherapy and in as of yet unexplored combinations. The threshold of 10% weight loss considered unattainable a decade ago is now well-surpassed, and we are likely on our way to 20% weight loss and associated opportunity to address a massive burden of medical and psychosocial co-morbidities.

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