Person-centered choice of anti-obesity pharmacotherapy

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Abstract

Several novel drugs are being developed for the management of obesity. While this offers newer opportunities for weight management, it also creates challenges for the treating physician to choose the appropriate drug for a given patient in clinical practice. This communication provides a clinically oriented classification of anti-obesity medications, which will help in person-centered choice of therapy. It lists drugs as calorie restrictors (appetite suppressants), calorie restriction mimetics (absorption inhibitors), calorie substitutes (medical nutrition therapy), and calorie utilizers (energy expenditure enhancers). This novel classification will help provide a patient centered pharmacotherapy in the management of obesity.

Keywords: Bupropion, danuglipron, GLP1RA, liraglutide, naltrexone, orlistat, phenteramine, semaglutide, topiramate, tirzepatide, setmelanotide, TRC 1500194

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Introduction

Obesity has become a major epidemic, with significant ramifications for the affected individual as well as public health. A person-centered approach to pharmacotherapy in patients with obesity is recommended, as is the overall management of obesity.[1] Well defined guidelines are available for the threshold of diagnosis and intervention of obesity.[2] There is no consensus, however, regarding the choice of specific medical therapy for weight control.

We suggest a pragmatic taxonomic rubric of approved as well as in-development medical interventions, and attempt to propose specific patient phenotypes to aid in selection of therapy (Table). This rubric is based upon an understanding of the various facets of barocrinology.[3]

Taxonomic Structure

Obesity is traditionally understood to be a mismatch between energy intake and energy expenditure.[4] Anti-obesity interventions, therefore can be classified as those which limit energy intake, and others which increase energy expenditure. Energy intake can be limited directly (by reducing calorie intake/appetite suppression), indirectly (by mimicking calorie restriction/ absorption inhibition), or by stratagem (by replacing calories with protein-rich medical nutrition therapy). Drugs have been approved, or are being developed, in each of these categories. It is noteworthy that glucagon-like peptide 1 receptor agonists (GLP1RA) and GLP1RA based dual agonists act through multiple mechanisms, and hence find a place in more than one column of the table.[5-7]

The pharmacotherapeutic landscape of obesity has changed frequently over the past few decades, and we have purposefully omitted drugs of historical interest.[8] At the same time, we have added, as a footnote, drugs in advanced stages of development. This will ensure the continued relevance of our taxonomic rubric in the years and decades to come.

Person Centered Choice

The mechanism-based rubric lends itself to rational choice of therapy based on the patient's phenotype. Appetite suppressants should be first line treatment in persons with a voracious appetite, or extreme craving for food. Orlistat, a triglyceride absorption inhibitor, works best in persons on a high fat diet. It must be noted, however, that it is also least tolerated by persons consuming high fat meals. High protein meal replacement, whether partial or complete, helps improve satiety and reduce appetite, especially in persons who find it challenging to wean off from high carbohydrate cuisines and find it difficult to prepare healthy meals.[9]

Energy expenditure enhancement is another way of tackling obesity. While the GLP1RA once daily liraglutide 3.0 mg is already approved by the US FDA, once weekly semaglutide 2.4 mg is in final stages of clinical research.[6,7] Other classes of drugs, such as the GLP1-GIP (gastric inhibitory polypeptide) dual agonist, tirzepatide; imeglimin (reduces mitochondrial reactive oxygen species), amylin analogue (Cagrilintide), amylin-GLP-1 combination (CagriSema) and the iodothyronine analogue, TRC 1500194, are in development as well. Energy expeditive enhancers are indicated in persons who do not respond to conventional dietary or exercise therapy.

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Table: Clinical classification and utility of anti-obesity drugs and medical interventions

Drug class	**Energy intake reducing agents**			**Energy Expenditure Enhancers**
Drug sub-class	Calorie restrictors	Calorie restriction mimics	Calorie replacers	Calorie burners
Synonym	Appetite suppressants	Absorption inhibitors	Calorie substitutes	Energy expenditure utilizers
Examples	Setmelanotide; Phenteramine/ Topiramate; naltrexone/bupropion; GLP1RA*; CagriSema	Orlistat; GLP1RA*	Protein rich meal replacement therapy and /or medical nutrition therapy	GLP1RA*, CagriSema, oxidative phosphorylation blocker (Imeglimin)' Iodothyronine analogue (TRC 1500094)
Preferential indications	Craving for food; excessive activity; associated substance abuse. Setmelanotide for genetic causes of obesity especially MC4R, POMC, LEP, LEPR mutations.(3)	High fat diet	High carbohydrate intake; low satiety levels; exercise regimens	Low energy expenditure; poor response to other interventions
Caveats and concerns	Depression, cardiovascular disease (naltrexone/bupropion)	Gastrointestinal side effects	Gastrointestinal and renal tolerability Hyperuricaemia	Gastrointestinal side effects

*GLP1RA=glucagon-like peptide 1 receptor agonists (liraglutide is approved; semaglutide, tirzepatide, CagriSema, danuglipron under development).

Conclusion

A person centric rubric helps to decide the appropriate anti-obesity agent for the management of obesity. This approach emphasizes on the fact that all patients with obesity do not put on weight because of their fault of eating more and exercising less, but rather reflect an underlying biological urge to do the same that needs to be addressed. In addition to the currently available anti-obesity medications, several newer effective therapeutic targets are in the pipeline. The categorization of both newer and older drugs in 4 classes can help provide effective patient centered obesity management.

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