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EDITORIAL

Current Status and Future Needs: A Pharmacist's Perspective on the Pharmacology of Anti-Obesity Medications

Jennifer Nicole Clements

University of South Carolina College of Pharmacy

Email: jclements1027@outlook.com

Introduction

According to the Obesity Medicine Association, obesity is described as a chronic, neurobehavioral condition caused by a number of factors, and has the potential of relapses.[1] In addition, other characteristics of obesity include an association with an increase in adiposity and presence of physical forces caused by abnormal fat mass.[1] Obesity can result in consequences related to metabolic, biomechanical, and physiological health. This chronic condition is often defined based on body mass index (BMI) which is a calculation of kilograms per meter squared (kg/m^2). Based on BMI, obesity can be categorized as Class I (30 to 34.9 kg/m^2), Class II (35 to 39.9 kg/m^2), and Class III (equal to or above 40 kg/m^2).[2] The higher the BMI, then there is a higher risk of health-related complications including but not limited to diabetes, hypertension, hyperlipidemia, sleep apnea, respiratory conditions, and liver disorders.[2] Overall, BMI is the most reasonable measurement for initial screening of obesity among an individual and is easily calculated within an electronic health record. However, other measurements can be used in

clinical practice by generalists and specialists. These measurements include weight circumference, waist-to-hip ratio, and percent body fat. In contrast, weight is often defined based on weight percentile among children.

Within the United States, there has been an increasing prevalence of obesity from the 1990 to 2020.[3] For worldwide prevalence, approximately 625 million people are living with obesity.[4] People living with obesity can be impacted with higher total health care costs compared to those not living with obesity. It is also predicted that the prevalence will continue to increase by the year 2030. Based on a publication from Ward et al., it is predicted that one in two adults will be living with obesity whereas one in four adults will be living with severe obesity.[5] In addition, high risk populations would include women, African American ethnic group, and those with a lower socioeconomic status.[5] In the United States, Ward et al., projected that the prevalence of obesity will be 50% or higher in 29 states.[5]

The etiology of obesity is complicated and contributed due to many factors related to genetics, the environment, medical care, and organ systems (e.g., immune, endocrine). Table 1 outlines details related to the potential factors associated with obesity.[1,6] Since the etiology is complicated, the general treatment approach for weight management should include lifestyle modifications with anti-obesity medications (AOMs) and/or metabolic surgery. Person-centered interventions can assist in achieving individualized goals, such as reducing obesity-related morbidity, reducing the risk of obesity-related complications, preventing further weight gain, and reducing body weight. One of the most important desired goals for weight management would be achieving weight reduction of 5 to 10% (or more) from baseline over a specific period of time. This percentage of weight loss has been suggested by clinical practice guidelines to improve cardiovascular and metabolic risk factors (e.g., blood pressure, lipid panel, glucose concentrations).[1,7-9] In the presence of certain comorbid conditions, the greater the weight loss would have greater benefit to the individual. The purpose of this editorial was to provide a pharmacist's perspective of the historical, current, and future status on the pharmacology of AOMs in weight management.

Table 1. Potential Factors Associated with Obesity[1,6]

Factor	Details
Genetics	Genetic inheritance Epigenetic inheritance Extragenetic inheritance
Environment	Food supply Physical activity Technology Automation Social network Cultural factors Socioeconomics Religious beliefs
Immune	Acute response (catecholamine) Chronic response (glucocorticoid)
Endocrine	Cardiopulmonary response Metabolic response Hormonal response
Medical	Cushing disease Hypothyroidism Growth hormone deficiency Leptin deficiency Insulinoma Psychiatry disorders Genetic syndromes Medications (e.g., sulfonylureas, insulin therapy, gabapentin)
Neurobehavioral	Motivation Reward Emotion Sensory

Pathophysiology

Energy balance is important as it is related to the laws of thermodynamics. Energy intake must equal energy expenditure plus the change in energy storage.[6,10] However there can be negative energy balance through the degradation of the body's energy stores (e.g., glycogen, fat, protein). A positive energy balance would lead to an increase in body energy stores (e.g., fat). For fat storage, brown adipose tissue can increase insulin sensitivity and thermogenesis which is related to energy expenditure or weight loss. A change in white adipose tissue can lead to inflammation and lipotoxicity and therefore weight gain.[6,10]

For pathophysiology of obesity, the limbic system has a role in appetite. There are multiple neurotransmitters or biogenic amines in which medication could be discovered, developed, and studied for weight loss.[6,10] For example, stimulation of 5-HT_{2C} receptors could lead to a decrease in food intake whereas stimulation of 5-HT_{1A} receptors could increase food intake. As a specific example, lorcaserin was a 5-HT_{2C} receptor agonist, affecting feeding behavior through appetite suppression and ultimately weight reduction.[11] A 5-HT_{1A} receptor agonist would have the potential to suppress appetite based on decrease in the number of meals per day, and therefore, promoting weight loss.[12] Alpha receptors are also associated with the limbic system and could play a role in regulation of feeding behaviors. Stimulation of alpha-1 receptors could decrease food intake whereas stimulation of alpha-2 receptors could increase food intake.[6,10]

Neuropeptides can also play a role in the pathophysiology of obesity.[6,10] Orexin increases food intake whereas melanocyte concentrating hormone regulates feeding behavior. Within the brain, leptin is the appetite suppressing hormone to decrease food intake and increase energy expenditure. In contrast, ghrelin is the appetite stimulating hormone within the gastrointestinal tract and appetite would be increased during upregulation. Other gastrointestinal hormones, such as glucagon-like peptide-1 (GLP-1) and peptide YY, can lead to suppressed appetite through episodic signals to the brain. The class of GLP-1 receptor agonists has been expanded since the first approval of exenatide immediate-release in 2005; liraglutide and semaglutide have indications for chronic weight management under different trade names than products for diabetes management.[13,14] Some neuropeptides and gastrointestinal hormones can be in sync together to balance energy through appetite regulation and energy expenditure. Lastly, the pancreas could be involved in episodic appetite signals through the release of co-secreted hormones – amylin and insulin – which can promote satiety within the brain.[6,10]

Historical Perspective

Several medications, originally indicated for weight loss, have been withdrawn from the market due to safety concerns. Sibutramine was taken by many people living with obesity for short- or long-term weight management.[15] It was a serotonin and norepinephrine reuptake inhibitor; due to its effect on norepinephrine, sibutramine had a negative impact on the cardiovascular system by increasing blood pressure and risk of heart failure. It was voluntarily withdrawn in 2010 due to the risk of myocardial infarction, stroke, resuscitated cardiac arrest or death among people who were overweight or had obesity with history of cardiovascular disease and/or type 2 diabetes.[16] Another example is lorcaserin, which became available on the United States market in June 2012. While it had moderate efficacy for weight loss, it was a scheduled medication due to low abuse potential, as the agonism on 5-HT_{2C} receptor could result in euphoria as a possible adverse event. However, it was withdrawn from the United States market in February 2020 due to the trend of increased risk of pancreatic and lung cancers.[17]

Current Perspective

Anti-obesity medications are indicated as adjunct therapy with non-pharmacological strategies, such as reduced daily caloric intake, increased physical activity, and applied behavioral interventions. An AOM is considered for people with a BMI equal to or above 27 kg/m^2 in the presence of a weight-related condition or BMI equal to or above 30 kg/m^2.[1,7-9] The Food and Drug Administration in the United States provided guidance on the clinical design for any new medication to be studied and/or indicated for weight management in order to address some of the limitations from clinical trials.[18,19] This guiding document provides information on methodology, such as inclusion and exclusion criteria, primary and secondary endpoints, and statistical analysis. For results of clinical trials on weight management, a clinically significant outcome would be if the active drug has a placebo-subtracted difference of 5% or more based on weight reduction from baseline. Clinical significance could also be considered when at least 35% of participants in the active medication group lose 5% of body weight from baseline or at least twice as many individuals in the active group lose 5% of body weight compared those in the placebo arm.[18]

Currently, there are medications for short- or long-term weight management, which have

generally promoted weight loss through suppression of appetite, reduction of dietary fat absorption, and reduction in gastric emptying, depending on the specific medication. Phentermine is a sympathomimetic with a mechanism for increasing norepinephrine, and ultimately promoting appetite suppression.[20] However, it cannot be used for long-term weight management due to the impact of norepinephrine on the cardiovascular system as it is structurally similar to amphetamines.[20] Orlistat is a lipase inhibitor and can reduce the 30% of dietary fat absorption; its mechanism may lead to intolerability based on its safety profile.[21] In some instances, combination therapy with two different agents may lead to synergistic effect for appetite suppression. Phentermine and topiramate were approved as a single product for chronic weight management.[22] Its intent was to reduce the dose of phentermine as an immediate-release product and therefore, lower the risk of cardiovascular effect. As an anticonvulsant, topiramate suppresses appetite through unknown mechanisms.

Table 2. Current AOMs for Weight Management[20-25]

Medication	Contraindications	Safety Profile	Dosing
Phentermine	MAOI use within 14 days; pulmonary hypertension; hyperthyroidism; glaucoma; history of substance use; history of cardiovascular disease; pregnancy; breastfeeding	Palpitations, tachycardia, hypertension, xerostomia, constipation, insomnia, valvular heart disease, pulmonary hypertension	15 to 37.5 mg PO QD in 1 or 2 divided doses 25 mg IR PO TID 75 mg SR PO QD
Orlistat	Chronic malabsorption syndrome; cholestasis; pregnancy; breastfeeding; nephrolithiasis	Steatorrhea, flatus (with discharge and/or urgency), bloating, cramping, hepatotoxicity (rare)	60 mg PO TID with meals (OTC) 120 mg PO TID with meals (Rx)
Phentermine + topiramate extended-release	MAOI use within 14 days; pregnancy; breastfeeding; hyperthyroidism; acute angle-closure glaucoma	Phentermine (see above) PLUS paresthesias, xerostomia, constipation, insomnia, pharyngitis, cognitive impairment, dizziness	3.75/23 mg PO QAM x 14 days; then titrated per package insert to max of 15/92 mg, dependent on weight loss
Bupropion + naltrexone extended-release	Chronic opioid agonist or partial agonist use; substance withdrawal; uncontrolled hypertension; seizure disorder; eating disorders; pregnancy; breastfeeding; severe depression; MAOI within 14 days	Nausea, constipation, headache, vomiting, dizziness, insomnia (caution with suicidal behavior and ideation)	90/8 mg PO QAM x 7 days; then titrated weekly to 180/16 mg PO BID (with meals, but not high-fat meals)
Liraglutide	Pregnancy; personal or family history of medullary thyroid cancer; pancreatitis; acute gallbladder disease	Nausea (dose-dependent), vomiting, injection-site reactions	0.6 mg once daily x 1 week (subcutaneously), then titrated weekly to 3 mg once daily (anytime of the day) in 0.6-mg increments
Semaglutide	Pregnancy; personal or family history of medullary thyroid cancer; pancreatitis; acute gallbladder disease	Nausea (dose-dependent), vomiting, injection-site reactions	0.25 mg once weekly x 4 weeks (subcutaneously), then titrated monthly to 2.4 mg once weekly

Abbreviations: BID = twice daily; CNS = central nervous system; D/C = discontinue; IR = immediate release; lbs = pounds; MAOI(s) = monoamine oxidase inhibitor(s); OTC = over-the-counter; PO = orally; QAM = in the morning; QD = daily; Rx = prescription; SNRIs = serotonin-norepinephrine reuptake inhibitors; SR = sustained release; TID = three times per day; XR = extended-release.

While effective, the combination of phentermine and topiramate may have limitations related to contraindications, safety profile, and complex dosing regimen.[22] Another combination product – bupropion and naltrexone – is unique as bupropion can reduce appetite, whereas naltrexone, as an opioid antagonist, can enhance bupropion's effect.[23] There are several contraindications and safety concerns with bupropion and naltrexone, as well as high pill burden (e.g., four pills per day).[23] Liraglutide and semaglutide are both GLP-1 receptor agonists and promote weight loss through slowed gastric emptying and promotion of satiety within the brain.[24,25] Due to the mechanism on gastric emptying, there is caution regarding absorption of oral medications when used concomitantly with liraglutide and semaglutide.[24,25] Table 2 summarizes the contraindications, safety profile, and dosing of current AOMs available in the United States.[20-25]

Future Perspective

There is still a need for new AOMs when reflecting on the pathophysiology of obesity and current landscape of therapeutic options. As an example, there is no AOM as an antagonist to regulate ghrelin as the appetite stimulating hormone. Additional medications that could work on biogenic amines, neuropeptides, and other gastrointestinal hormones are needed to promote weight loss through appetite suppression or another mechanism. The advancement of AOMs can be very challenging due to dedicated time and cost of discovery and development of new therapeutic options. In addition, limitations could include risk of safety events, as seen with historical and current medications. For clinical trials, primary endpoints have been evaluated as the change in weight loss from baseline over one to two years. Clinical trials have also concluded the proportion of participants achieving at least 5% weight loss from baseline to the end of the study. With the recent and future approval of semaglutide and tirzepatide, respectively, for weight management, drug development should focus on larger and sustained weight loss from baseline at doses that can be tolerated by an individual living with obesity. Therefore, the primary endpoint would be adjusted to larger weight loss reductions, such as 10%, 15%, and/or 20% which are comparable reductions as metabolic surgery. Another area for investigation includes combination therapy to achieve a greater weight loss, compared to monotherapy, as two medications with different mechanisms would most likely have an additive or synergistic effect. Regardless of mechanism of weight loss, clinical data should be able to be extrapolated to various populations as there is a lack of diversity within the clinical trials with a large dropout rate.

Conclusion

The prevalence of obesity is expected to increase by the year 2030. Therefore, the landscape of AOMs needs to adapt with increased utilization of current medications and new mechanisms of action in a single pathway or multiple pathways. In addition, clinical data for new agents should validate the efficacy for endpoints of weight loss, as well as a tolerable safety profile for clinical utilization among people living with obesity. Future research in drug discovery and development is necessary to change the clinical management of obesity.

Conflicts of Interest Statement

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