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Review

Obesity Pillars roundtable: Excessive weight reduction with highly effective anti-obesity medications (heAOMs)

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ABSTRACT

Background: Historically, many anti-obesity medications (AOMs) were withdrawn from development and/or the market due to safety concerns. Another challenge was that, with some exceptions, most of these AOMs had limited weight reducing efficacy. Approved AOMs often did not meet the weight reduction expectations of either clinicians, or their patients. Currently, newer approved and investigational AOMs achieve greater weight reduction than older AOMs. This has prompted an emerging new challenge of "too much weight loss" with some of these highly effective anti-obesity medications (heAOM) – something many did not think possible prior to year 2020.
Methods: This roundtable review includes perspectives from 3 obesity specialists with experience in the clinical use of AOMs. The intent is to provide perspectives and guidance in managing patients with obesity who experience "too much weight loss" with heAOM.
Results: The panelists generally agreed that before treatment with heAOMs, patients with obesity are best informed about the importance of healthful nutrition, adequate hydration, routine physical activity, behavior modification techniques, goals of treatment, and anticipated changes not only from a medical standpoint, but also from a psychosocial standpoint. Clinicians might best recognize that the definition of "excessive weight reduction" may have both objective and subjective considerations, with body composition analyses often essential to accurately assess adiposity.
Conclusions: The consensus of the panelists is reflected in a proposed structured and algorithmic approach to the patient with excessive weight reduction. Once properly evaluated, if the excessive weight reduction is determined most likely due to the heAOM hyper-responders, then this should prompt the clinician to educate the patient (and possibly family and friends) on the health and psychosocial aspects of weight reduction, and engage in a shared decision-making process that determines if the heAOM is best kept at the same dose, decreased in dose, temporarily held, or rare cases, best discontinued.

1. Introduction of the panelists

Dr. Bays:

Hello. My name is Dr. Harold Bays. I am Editor-in-Chief of Obesity Pillars [official journal of the Obesity Medicine Association (OMA)] and Chief Science Officer of the OMA. I am serving as moderator for this roundtable review regarding: "Excessive Weight Reduction with Highly Effective Anti-Obesity Medications" (i.e., heAOM, defined as defined as achieving 15% or more weight reduction either as mean weight reduction, or achieved in a clinically meaningful percent of clinical trial participants).

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Today I am honored to speak with 3 clinicians having experiences and perspectives regarding the treatment of obesity with anti-obesity medications (AOM). I would like to start by asking each of you to briefly describe your medical practice. Ms. Burridge, please summarize your clinical background and clinical practice setting.

Ms. Burridge:

I am a Physician Assistant (PA) and a Fellow of the Obesity Medicine Association. My education prior to becoming a PA included degrees in psychology and physiology, as well as graduate level education in clinical exercise physiology and health behavior change. I started my work in obesity management as a PA in metabolic and bariatric surgery. Despite my previous education, my work with metabolic and bariatric surgery was the first time that I was exposed to the complexities of the disease of obesity. With that came a curiosity about other treatment options that could help patients living with obesity, especially for those patients who were not surgical candidates.

In 2014, I was introduced to the Obesity Medicine Association, which, at the time was called the American Society of Bariatric Physicians. I eagerly joined as a member. I started a non-surgical obesity management program as an adjunct to our surgical program. Since then, I have developed two other medical obesity programs alongside surgical programs. I strongly believe in having all the treatment options available to patients and meeting them where they are in their journey. I have also worked with other medical obesity management programs within primary care. Most recently, I have joined a program delivering obesity care via telemedicine (Enara Health). Finally, I started my own company, Gaining Health, to provide resources and support for clinicians and organizations who want to start or optimize an obesity management program.

I am passionate about educating clinicians about obesity. I serve as the president of PAs in Obesity Medicine and I am on the Board of the Illinois Obesity Society. It's amazing to see how far this field has come in just a few years, and I look forward to having additional tools for patients with obesity. Mostly, I look forward to the day that obesity will be viewed like any other chronic disease, without the bias and stigma that is, unfortunately, still so common today.

Dr. Bays:

Dr. Richards, please summarize your clinical background and clinical setting.

Dr. Richards:

I am board certified in Internal Medicine. During my training in Internal Medicine at the University of Kansas, I was fortunate to have a clinical mentor who supervised low and very low-calorie diet weight reduction programs. These programs were in collaboration with dieticians and utilized a National Institutes of Health sponsored exercise physiology research laboratory. Initially, I worked as a hospitalist before transitioning to academic faculty in helping to craft the medical obesity program at the University of Oklahoma (OU). I am an advocate for improved primary care treatment of obesity through the American College of Physicians. I am the Director of Obesity Medicine at OU where I founded the Obesity Medicine clinical curriculum. I work with students and residents across primary care. My research interests focus on the neurophysiologic effects of AOMs and new incretin therapies.

Dr. Bays:

Dr. Fitch, please summarize your clinical background and clinical practice setting.

Dr. Fitch:

I completed residency in Internal Medicine and Pediatrics and served as Chief Resident of Internal Medicine at the University of Cincinnati. In 2002, I moved to Minnesota to begin my career as a primary care physician in a large hospital system that was passionate about quality and care innovation. We implemented a team approach towards advancing quality patient care and improving patient outcomes. Given my chemical engineering undergraduate training, and regarding body systems, I was always intrigued by biologic metabolic functions. In the case of obesity, insulin resistance, and diabetes mellitus, I was equally intrigued by the biologic metabolic *dysfunctions* that contributed to these diseases. As the result of my primary care experience in treating type 2 diabetes and metabolic syndrome, I decided to enhance my training in obesity medicine. I became certified in obesity medicine in 2012 with the sitting of the first exam. I subsequently transitioned to full time obesity medicine by leading a multidisciplinary program within an eating disorder institute. Complementary to treating eating disorders, I also established a medical/surgical weight center in Cincinnati Ohio.

I have since moved to Boston Massachusetts to lead the oldest and largest multidisciplinary weight center in the country. At the Massachusetts General Hospital Weight Center, we have 22,000 patient visits a year and we care for both pediatric and adult patients. We employ the

spectrum of treatment options spanning lifestyle intervention, pharmacotherapy, endoscopic treatment, and surgery. Regarding the OMA, I have served as a member since 2010, and I am honored to serve as President of our association today.

2. Historic perspective of anti-obesity medications (AOMs), weight reduction, and highly effective AOM (heAOM)

Dr. Bays:

Thanks for your introductions. Decades ago, many AOMs had substantial safety findings, resulting in their withdrawal from development and withdrawal from the market [1]. Another challenge with older AOMs was that, other than the topiramate/phentermine combination agent and perhaps liraglutide (https://icer.org/wp-content/uploads/2022/03/ICER_Obesity_Evidence_Report_083122.pdf), it was less common that AOM safely achieved more than 10% weight reduction, which was frequently insufficient to meet the expectations of clinicians and their patients with obesity. However, with the approval of semaglutide in 2021 (and perhaps prior approval of the topiramate/phentermine combination agent) for treatment of obesity, and with the ongoing development of tirzepatide for obesity (as well as research experience regarding other investigational anti-obesity agents) [1], the mean weight reduction is now often 15–20% (See Table 1). Moreover, because the study results are often reported as mean values, some patients experience more profound weight reduction than noted in the overall average clinical trial results (i.e., AOM hyper-responders). Ms. Burridge, please provide your philosophical perspective on what some might characterize as a radical change for many patients regarding the efficacy of highly effective AOMs (heAOM), defined as achieving 15% or more weight reduction either as mean weight reduction or achieved in a clinically meaningful percent of clinical trial participants (See Table 1).

Ms. Burridge:

First, I think it's very exciting to see the kinds of outcomes that we are seeing with these newer agents. While I imagined a time when medical treatment options would start to approach surgical outcomes, I didn't expect it to happen so soon. This gives me great hope for the field of obesity medicine and for patients living with obesity. However, these powerful outcomes can also create challenges, for which clinicians should be prepared to manage.

Second, clinicians should recognize the ways and the degree that substantial weight reduction in patients with obesity can affect a person's life. Most of the weight reduction effects of heAOMs are favorable. But as before, others can create challenges. Just like currently the norm with bariatric surgery, it's important to counsel patients on potential challenges of heAOMs to ensure that patients with obesity have support during potential life changes. Such changes include not only physical changes and health-related changes, but also social and psychological changes.

One of my concerns with the increasing efficacy of newer heAOMs is the potential for nutrient deficiencies due to reduced caloric intake. Bariatric surgery gives us a good roadmap for how we can manage this, although the likelihood of nutrient deficiencies with medical obesity management is much lower than with malabsorptive bariatric surgery procedures. During substantial weight reduction in patients with obesity, I think it is incumbent upon clinicians to counsel patients on sufficient protein intake and recommend resistance training to help limit the almost inevitable lean body mass loss (e.g., muscle mass) that so often accompanies weight reduction. It may also be wise for clinicians to screen for potential vitamin and mineral deficiencies (and perhaps recommend a general multivitamin) and to encourage sufficient fluid intake.

Dr. Bays:

Obesity medicine specialists play a critical role in managing patients with obesity. However, the vast majority of patient with overweight and obesity are managed by primary care clinicians. Currently, only about 2% of patients eligible for AOMs are receiving AOMs [11]. Dr. Richards, how do you believe the emergence of heAOMs might alter how primary care

Table 1
Weight reduction with anti-obesity medications. Shown are estimated degree of mean weight reduction associated with anti-obesity medications, as well as the percent achievement of weight reduction ≥5, ≥10%, ≥15%, and ≥20%. (Adapted with permission from [1].

Anti-obesity medication	Mean percent and categorical percent weight reductions*	Notes	References
Phentermine 15 mg per day (oral)	Overall mean = 7% ≥5% = 46% ≥10% = 21% ≥15% = NA	The placebo group had a 2% mean weight reduction, with 16% and 7% achieving ≥5% and ≥10% weight reduction, respectively	[2,3]
Semaglutide 2.4 mg subcutaneously once weekly	Overall mean = 15% ≥5% = 86% ≥10% = 69% ≥15% = 51% ≥20% = 32%	The placebo group had a 2% mean weight reduction, with 32%, 12%, 5% and 2% achieving ≥5%, ≥10%, ≥15%, and ≥20% categorical weight reduction, respectively	[4]
Liraglutide 3.0 mg subcutaneously once daily	Overall mean = 8% ≥5% = 63% ≥10% = 33% ≥15% = 14%	The placebo group had a 3% mean weight reduction, with 27%, 11%, and 4% achieving ≥5%, ≥10%, and ≥15% categorical weight reduction, respectively	[5]
Phentermine HCl/ Topiramate Extended Release (oral) (top dose = phentermine 15 mg/92 mg topiramate)	**EQUATE 28-week study:** [3] Overall mean = 9% ≥5% = 66% top dose ≥10% = 41% top dose ≥15% = NA **SEQUEL 56-week extension study:** [6] Overall mean = 10% ≥5% = 79% top dose ≥10% = 54% top dose ≥15% = 32% top dose ≥20% = 15% top dose	**EQUATE 28-week study:** [3] The placebo group had a 2% mean weight reduction, with 16% and 7% achieving ≥5% and ≥10% categorical weight reduction respectively **SEQUEL 56-week extension study:** [6] The placebo group had a 2% mean weight reduction, with 30%, 12%, 7%, and 2% achieving ≥5%, ≥10%, ≥15% and ≥20% categorical weight reduction respectively	[3,6]
Naltrexone sustained release (SR) 32 mg/day plus bupropion SR 360 mg/day (oral)	Overall mean = 7% ≥5% = 56% ≥10% = 27% ≥15% = 10%	The placebo group had a 2% mean weight reduction with 18%, 7%, and 2% achieving ≥5%, ≥10%, and ≥15% categorical	[7]

(continued on next page)

Table 1 (*continued*)

Anti-obesity medication	Mean percent and categorical percent weight reductions*	Notes	References
		weight reduction, respectively	
Orlistat 120 mg three times per day (oral)	Overall mean = 9% ≥5% = 66% ≥10% = 39% ≥15% = NA	The placebo group had a 6% weight reduction with 44% and 25% achieving >5% and >10% categorical weight reduction, respectively	[8]
Non-systemic Oral Hydrogel, three 2.25-g capsules before lunch and dinner (oral)	Overall mean = 6% ≥5% = 59% ≥10% = 27% ≥15% = NA	The placebo group had a 4% mean weight reduction with 42% and 15% achieving ≥5% and ≥10% categorical weight reduction, respectively	[9]
Tirzepatide (subcutaneous once a week) Approved and indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, but investigational for treatment of obesity at the time of publication **	Overall mean = 21% (15 mg) ≥5% = 91% 15mg ≥20% = 57% 15mg	The placebo group had an overall 3% mean weight reduction with 35% and 3% achieving ≥5% and ≥20% categorical weight reduction, respectively	[10]

NA = Not available (data was not found).
*The values in this chart are not intended to represent head-to-head comparisons. Data are derived from different studies. In most cases, the percent weight reductions were dose dependent. Therefore, the listed mean values may be less than the percent weight reduction with the highest doses of anti-obesity medications.

clinicians treat their patients with obesity?

Dr. Richards:

The explosive development of heAOMs parallels the improvements in pharmacotherapy for in diabetes mellitus, hypertension, and hyperlipidemia in the last century. For decades, weight reduction was typified as learned helplessness for primary care clinicians, because the medical treatment options did not produce the weight reduction desired by patients [12]. With the dramatic increase of incretin based and polypeptide therapies in diabetes over the past decade, coupled with their unparalleled efficacy for weight reduction, primary care providers are gaining experience and comfort prescribing heAOMs. Specifically, through the experience of using anti-diabetes medications with similar mechanisms as heAOM, I believe primary care clinicians are becoming more comfortable discussing and prescribing heAOM's used to treat obesity.

The escalation of prescription for semaglutide both on and off label for weight reduction is not primarily driven by specialty obesity medicine clinicians. As primary care clinicians see clinical success with patients in treating diabetes (as well as see potential improvement in non-alcoholic steatohepatitis and cardiovascular disease), they will become eager to learn more and want to offer heAOMs to more patients.

Additionally, as more indications arise for AOMs, then treatment of many metabolic multi-morbidities currently managed by specialists may return to primary care. This change in management paradigm is analogous to how the widespread approval and decreased side effects of selective serotonin reuptake inhibitors (relative to earlier psychiatric medications) empowered primary care clinicians to manage less complicated mental health. The improved efficacy and safety of heAOMs will likely increase the interest and ability of primary care clinicians to manage less complicated cases of obesity, while referring patients with more severe disease to obesity medicine specialists and comprehensive anti-obesity programs.

Dr. Bays:

Dr. Fitch, you are President of the Obesity Medicine Association. How do you believe the emergence of safer heAOMs will affect the way obesity medicine specialists treat their patients with obesity?

Dr. Fitch:

There has been a pivotal shift in obesity care delivery in the past 1–2 years with the launch of heAOMs that are now able to produce a 20% weight reduction in 30–60% of patients. I believe this jump from an average weight reduction in the 5–10% category to the 15–25% category has increased provider, patient, and societal acceptance, as well as the adherence to pharmacotherapy for the disease of obesity. This pivotal shift in categorical weight reduction brings pharmacotherapy closer to the treatment efficacy observed with surgery. Patients will likely perceive that the benefits of a 15–20% weight reduction is more than worth the risk and hassle of taking an heAOM for sustained results. We have encountered a significant increase in referral volume in the past year, with more patients with obesity inquiring about AOM treatment as they hear from friends and family about the favorable results achieved by others. I believe the trend of accepting obesity as a disease that benefits from pharmacotherapeutic intervention has been fueled by the advances in AOM efficacy, safety, and hopefully even cardiovascular benefits. The increased organic awareness of patients should help increase access to treatment as clinicians are increasingly asked by patients for obesity treatment. As noted by Dr. Richards, access to treatment may also be enhanced as clinicians become more comfortable with prescribing heAOMs.

3. Relationship dynamics of substantial weight reduction

Dr. Bays:

Thank you for your perspectives. As a clinical trialist, I can say that within the context of our ongoing clinical research of investigational heAOMs, as well as with the clinical use of approved heAOMs (e.g., topiramate/phentermine combination agent and semaglutide), we are encountering more patients expressing concerns about excessive body weight reduction. While technically still "overweight," [13] when patients experience weight reductions of 15–20% or more and find their body mass index approaching 25 kg/m^2, this not only represents a major change in their health, but a major change in their life relationship dynamics (e.g., interactions with others and their environment). (Fig. 1).

Substantial weight reduction with heAOMs in patients with obesity commonly improves health metrics (e.g., blood glucose, blood pressure, blood lipids, sleep apnea, mobility) and improves body image, mental health, and relationships. However, a substantial number of patients who experience substantial weight reduction (e.g., sometimes 50–100 pounds or more) continue to encounter challenges in relationship life dynamics. Regarding relationship to oneself, weight reduction alone does not always resolve underlying depression, anxiety, or challenges with shame, self-image, or self-worth. Substantial weight reduction may not permanently alter the self-gravitation towards unhealthful eating (e.g., emotional eating, food addition, unhealthful food choices). Equally problematic can be relationships with friends, family, and coworkers. Patients with substantial weight reduction often receive increased attention from family, friends, and coworkers, which while potentially flattering in some cases, can also contribute to uncomfortableness or self-consciousness. Finally, some family and friends are not always understanding or supportive of substantial weight reduction in a patient with obesity because:

- **Jealousy and resentfulness.** Friends, family, and co-workers of patients with obesity experiencing substantial weight reduction may not

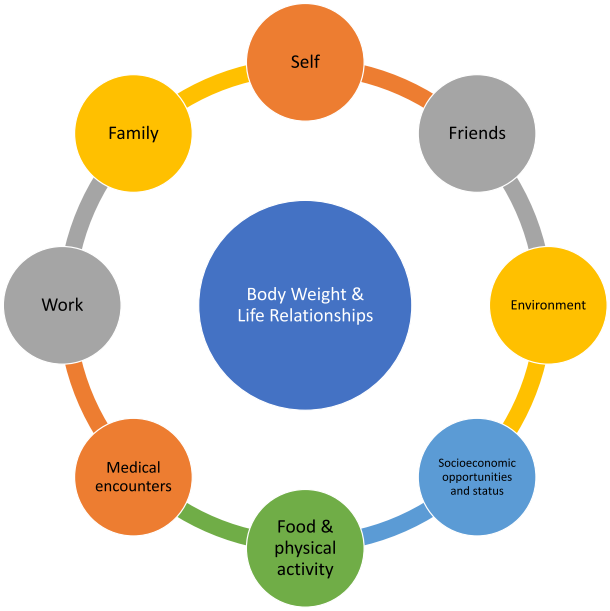

Fig. 1. Illustrative Model of Body Weight Relationships. Changes in body weight can affect relationships, such as relationship to self (i.e., self-worth and self-image), as well as interactions with family, friends, coworkers, and environment. Changes in body weight can also affect relationships respective to medical encounters, socioeconomic opportunities, and socioeconomic status. Finally, changes in body weight can affect the relationship of the patient to food, physical activity, and physical exercise.

understand or be supportive of a patient's commitment to healthful behaviors. ("Now that you are so skinny, we don't know why you can't go with us to eat at the fair. One day of bad food is not going to make any difference. Do you think you are too good for us now?")

- **Change in relationship activities related to nutrition and physical activity.** A patient with obesity with substantial weight reduction may no longer want to eat at fast food restaurants, and instead, may want to spend more time with physical exercise (e.g., at the gym or time walking/running) – which may represent a change in time allocation and potential interactions with friends and family. ("We used to all order fast food for lunch. Now, you spend so much time exercising. Plus, when you bring your own lunch, we feel you are not only judging us, but abandoning us.")
- **Altruistic and not-so-altruistic expressions of concern by family and friends.** In our clinical trials, we are increasingly encountering patients with obesity who achieve substantial weight reduction, accompanied by family members or friends who express more concern about the patient's weight reduction than the patient. Some of these expressed concerns are prompted by a genuine concern that the weight reduction may not be healthful or intentional, but rather due to some undiagnosed serious illness. Sometimes, reassurance is all that is required. Conversely, sometimes family members or friends may express concerns that are self-serving, and reflective of how the weight reduction of the patient has the potential to adversely affect them (i.e., not the patient). In this latter scenario, not only is the patients with obesity battling biologic, behavioral, and personal forces that make attaining and maintaining healthful weight reduction difficult, but are also battling external forces from family and friends as well. Changes in life relationship dynamics can often make weight reduction maintenance even more difficult.

Dr. Fitch, as an obesity medicine specialist, how do you manage patients who are concerned about excessive body weight reduction, and how do you manage their family's and friend's concerns?

Dr. Fitch:

We have been aware of the psychosocial effects of substantial weight reduction for a long time, mainly as it relates to caring for patients after bariatric surgery. I have been fortunate to have worked in collaborative medical/surgical weight centers for most of my obesity career and therefore have seen many patients cope with the issues nicely outlined above. The most important thing I stress is open and honest communication. Also, professional psychological help is often beneficial when encountering body image and acceptance issues. I encourage a focus on health metrics (e.g., body composition) and the health benefits of weight reduction (e.g., blood sugar, blood pressure, blood lipids, sleep apnea, mobility, arthritis), versus sometimes misleading number metrics such as weight or even body mass index. In a shared decision-making fashion, it is also important to talk about expected weight reduction and outcomes as well as potential for personal or external conflicts that may arise. Anticipating and discussing these challenges should be considered not only during treatment, but perhaps even before treatment with some of the more efficacious heAOMs. A continual re-framing the focus on health benefits and quality of life improvement to the patient, family, and perhaps friends is important to maintain obesity treatment success.

Dr. Bays:

Ms. Burridge, the OMA has published an extensive Clinical Practice Statement regarding behavior, motivational interviewing, eating disorders, and obesity management technologies that may help clinicians provide their patients practical coping techniques [14]. Beyond that, please provide a brief overview of how family, friend, and colleague dynamics can influence the treatment outcome of patients with obesity.

Ms. Burridge:

Social support and relationships play an important role in the treatment outcomes for patients with obesity, especially for patients with severe obesity engaged in major changes in behavior, use of heAOMs, and who subsequently undergoing large weight reductions – likely resulting in major changes in the patient's health specifically, and life in general. I believe that attending support groups and the perception of social support are key predictors of improved outcomes after bariatric surgery. This is one of the reasons why bariatric programs are required to offer support groups for their patients to be a "center of excellence." As pharmacologic agents increase in efficacy, social support for patients with obesity treated with these heAOMs may be beneficial as well [15, 16].

As you noted, relationships can have both a positive and potentially a negative impact on a patient's treatment outcomes. I routinely ask patients about their support from family, friends, and colleagues as they start their treatment. Having favorable and healthful support at home or from friends or colleagues is important, even if it is just one important person who will support the patient's healthful lifestyle changes, body changes, and life changes.

But as you also said, relationships can also hinder success. It is not uncommon for a friend or family member to have mixed feeling, or even negative feelings about the person's change in weight and lifestyle, especially if it is impacting the activities they do together or the previous relationship they had. It is important to recognize when this is happening, and to provide support and guidance to the patient on how to manage this. All of this is made more challenging given that food plays a big role in all our lives, beyond providing nutrition. Food is tied to culture, celebration, coping with stress and negative emotions, and so much more [14]. Patients often benefit from guidance when navigating these changes, such that they can still participate in important cultural and family traditions, while at the same time, be mindful of their health. If patients with obesity who have undergone substantial weight reduction with heAOMs are at risk for reverting to food to cope with emotions, then as noted by Dr. Fitch, it may be best for clinicians to anticipate this, and provide alternative, healthful coping mechanisms.

Lastly, a patient's body weight, weight gain, or even weight reduction may be influenced by a history of mental trauma or abuse. The challenge here is that patients may not always report their history of mental trauma or abuse. It may therefore be beneficial to explicitly and compassionately

ask about this, especially if a patient with obesity appears to be self-sabotaging their weight reduction efforts. Referral for counseling may be beneficial.

Dr. Bays:

Dr. Richards, from a primary care perspective, how do you manage the concerns of patients with obesity and their family members and friends regarding profound weight reduction?

Dr. Richards:

Concerns from patients seem to fall into several categories. Most patients express concerns about cosmetic changes (i.e., loose skin, loss of muscle tone). Both family members and patients often worry that the excess weight reduction is unhealthy, which I manage by discussing a goal weight and a range of healthy weights for the patient given their height and frame. In addition, patients worry about changes in their relationships with their family, as food and eating are a highly complex social behavior and a large part of how people connect.

Each concern can be addressed early in the process, with the messaging oftentimes more effective when coming from a primary care perspective. Primary care clinicians often have a more intimate, complete understanding of patient family and social dynamics. Additionally, since most patients I see are on treatment for other medical conditions, I frame weight reduction to improve obesity-related medical complications, with the potential to decrease or perhaps even stop medications prescribed for obesity complications (e.g., medications for diabetes, hypertension, dyslipidemia). I also individualize non-scale and body composition related goals. Some older patients may worry about needing a knee replacement. Younger parents may struggle just to play with their little children. Raising the desire for life-altering success in health and mobility as the result of heAOMs often decrease weight reduction trepidations. Finally, addressing the concept as a "new normal" with heAOMs is something I find that helps patients conceptualize large body changes and life transitions. This approach began when I started counseling my bariatric surgery patients about similar changes. During their first visit, I engage my patients with obesity in a discussion of the current social stigma around weight, and how new stigmas may emerge as others interact with them differently at their "new normal" weight. Finally, I also warn patients that self-perception and self-image can lag months behind the actual change in bodyweight. It may take a long time for patients to adjust to their "new normal" body weight.

4. Approach to the patient with obesity experiencing substantial weight reduction with heAOMs

Dr. Bays:

Managing patients with profound weight reduction due to approved or investigational heAOMs presents unique challenges. An initial challenge may be determining what represents "excessive" weight reduction. Some assessments are relatively straight-forward. If a patient being treated for obesity expresses concerns about excessive weight reduction while treated with heAOMs, and their objective achieved body mass index (BMI) is $< 18.5\ kg/m^2$, or if a male has a percent body fat <10%, or if a female has a percent body fat <15%, then this might reasonably represent "excessive weight loss" [13]. Depending on the clinical presentation, BMI and percent body fat above these thresholds may also be reasonably characterized as "excessive." However, "excessive weight reduction" is not always an objective assessment. From a subjective and practical standpoint, "excessive weight reduction" often is defined by whatever the patient, clinician, family, or friends perceive it to mean.

Fig. 2 and the items in Table 2 may help direct the history, physical exam, and diagnostic testing in evaluating possible causes of excessive weight reduction in patients treated with heAOM. An illustrative example at our research site was a woman with past and current cigarette history of smoking and chronic lung disease who entered a long-term anti-obesity trial with a body mass index over $27\ kg/m^2$. Through the course of the study, she achieved a BMI of a little over $19\ kg/m^2$. She was concerned. Her family was concerned. The research coordinator was

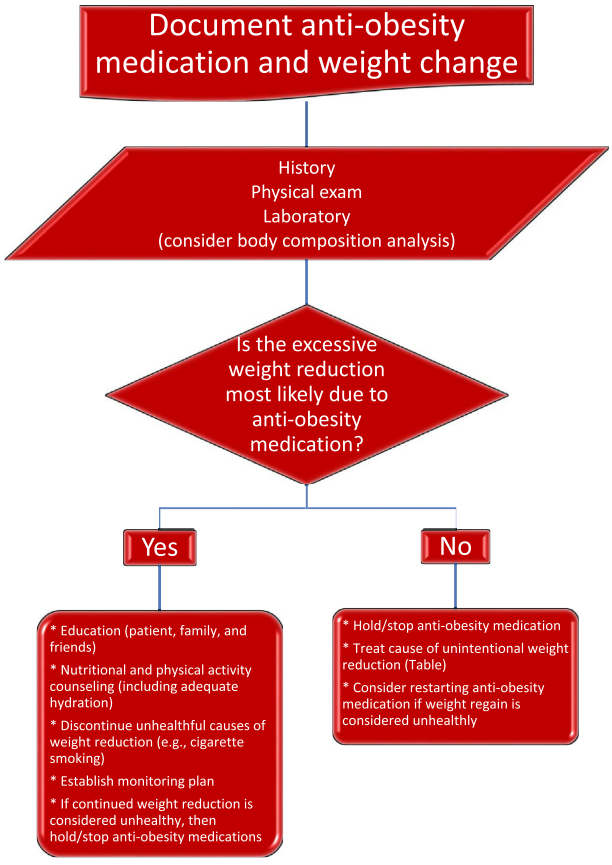

Fig. 2. Algorithmic approach to the patient with excessive weight reduction while treated with anti-obesity medications. Among the most important aspects of managing patients with excessive weight reduction is defining "excessive." Objectively, if a patient has a body mass index (BMI) of $<18.5\ kg/m^2$, then this might reasonably be characterized as achieving "excessive weight reduction." A caveat would be regarding patients with possible sarcopenia. Thus, body composition analyses may be appropriate before definitively diagnosing "excessive weight reduction." If body composition analysis documents a male has a percent body fat <10% or a female with a percent body fat <15%, then this might reasonably represent objective "excessive weight loss" [13]. Depending on the clinical presentation, BMI and percent body fat above these thresholds may also be reasonably characterized as "excessive." Subjectively, "excessive weight reduction" is not always an objective assessment. "Excessive weight reduction" can be defined by whatever the patient, clinician, family, or friends perceive it to mean.

concerned. Truth be told, as the Investigator, I was concerned. Although I have served as an Investigator for over 500 clinical trials spanning 30+ years, I find that I still need to be better acclimated to this new reality. I find I need to better come to grips with the profound efficacy of some of the newer heAOMs. Using the approach in Fig. 2, we knew this patient had a current history of continued cigarette smoking and prior history of obesity, the 2 most common preventable causes of cancer [17]. It was true that she was not technically underweight. It is true we engaged her in a smoking cessation plan. It is also true that a body composition analysis might have documented a higher percent body fat with reduced muscle mass (i.e., sarcopenia) [11]. Nonetheless, we did not know if her weight was going to stabilize or if she was going to continue with weight reduction. Therefore, we decided to (temporarily) hold study drug and asked her to meet with a dietitian. We encouraged her to follow-up with her primary care clinician to determine if further evaluation was indicated for unintentional weight reduction (See Table 2). Her weight seemed to stabilize, and we ultimately did not find any new causes of potential unintentional weight loss (i.e., beyond continued cigarette smoking and lung disease). Another more recent example was a woman

Table 2
Illustrative causes of weight loss [14,17,19,20].

Energy balance alterations	Changes in diet
	Changes in physical activity
	Cigarette smoking
Cancer	Cancers most described as attributable to obesity [17]:
	• Breast cancer (post-menopausal)
	• Colon and rectal cancer
	• Esophagus adenocarcinoma
	• Gallbladder cancer
	• Kidney cancer
	• Liver cancer
	• Meningioma
	• Multiple myeloma
	• Ovary cancer
	• Pancreas cancer
	• Stomach cancer
	• Thyroid cancer
	• Uterine cancer
	Cancers most common in all patients: *
	• Breast cancer
	• Lung and bronchus cancer
	• Prostate cancer
	• Colon and rectum cancer
	• Melanoma of the skin
	• Bladder cancer
	• Non-Hodgkin lymphoma
	• Kidney and renal pelvis cancer
	• Endometrial cancer
	• Leukemia
	• Pancreatic cancer
	• Thyroid cancer
	• Liver cancer
	Chemotherapy [18]
Hormone dysfunction	Cortisol insufficiency (e.g., Addison's disease, hypopituitarism)
	Diabetes (e.g., poorly controlled)
	Thyroid disease (e.g., hyperthyroidism)
Chronic disease	Heart disease (e.g., heart failure)
	Lung disease
	Renal failure
	Autoimmune disease (e.g., rheumatoid arthritis)
	Debilitation & immobility, contributing to sarcopenia
Gastrointestinal disease	Oral cavity disease (e.g., dental or throat disease)
	Swallowing disorders (e.g., dysphagia, achalasia)
	Celiac disease
	Peptic ulcer disease
	Pancreatic insufficiency
	Gall bladder disease
	Malabsorption due to gastrointestinal surgery or other causes
	Chronic diarrhea
	Crohn's disease
	Ulcerative colitis
	Irritable bowel syndrome
Neurological disease	Dementia
	Parkinson's disease
Infection	Gastroenteritis
	Human immunodeficiency virus infection
	Gastrointestinal parasitic infection
	Tuberculosis
Psychiatric disease	Depression
	Anxiety
	Paranoia
	Psychosis
Eating disorder	Anorexia nervosa
	Bulimia
	Avoidant/restrictive food intake disorder
	Purging disorder
Anti-diabetes medications [19]	Metformin
	Sodium glucose co-transporter 2 Inhibitors
	Alpha glucosidase inhibitors (e.g., acarbose, miglitol)
	Amylin mimetic (pramlintide)
Anti-seizure/migraine medications [19]	Topiramate
	Zonisamide
Anti-depression medications [19]	Bupropion
	Fluoxetine
Other medications, including drugs with abuse potential	Diuretics
	Laxatives
	Stimulants
	Alcoholism
	Opioids
	Hallucinogens
Lack of access to food	Poverty, isolation

https://www.cancer.gov/types/common-cancers#:~:text=The%20most%20common%20type%20of,prostate%20cancer%20and%20lung%20cancer.

who failed to disclose the nausea and vomiting she was experiencing while on a heAOM, despite being directly and routinely asked. She so coveted her substantial weight reduction with the heAOM, that she was fearful that we might stop the heAOM if she "complained" about side effects. As a result, she ultimately ended up in the Emergency Department with lightheadedness, and was hospitalized for 3 days due to dehydration, hypokalemia, and hyponatremia – due to the vomiting from heAOM therapy.

Ms. Burridge, please outline your approach regarding the evaluation and treatment of a patient with excessive weight loss while treated with heAOMs.

Ms. Burridge:

Thank you for sharing those examples. It really illustrates how important it is that clinicians follow up regularly with patients, especially when treated with heAOMs. These medications, and AOMs in general, are not meant to be prescribed and then followed up on in 6 months or a year. Especially when prescribing heAOM, patients require regular follow up, which includes lifestyle counseling as well as monitoring the efficacy and safety of the medications. An illustrative recommendation for patients with obesity treated with AOMs is follow-up is at least monthly for the first 3 months, and then at least every 3 months in all patients using AOMs [21].

When evidence suggests the patient treated with heAOM is losing too much weight, is not obtaining adequate nutrition or hydration, is experiencing excessive muscle mass loss, or if other concerns arise that the patient's health and well-being going in a negative direction with one heAOM, then a clinician may consider adjustment in the medication regimen. This may mean reducing the dose of the heAOM, switching to a less efficacious AOM, or holding heAOMs until greater clinical clarity emerges. This is also a good time to re-evaluate and address any psychological challenges or potential eating disorders, to ensure that patients being treated for obesity are developing and maintaining a healthy relationship with food and with their bodies.

Lastly, patient selection is an important factor to consider for heAOMs. While the BMI cut-offs for these newer heAOM agents are the same as for other AOMs, clinicians may consider whether heAOMs are the best first choice in certain patients, such as those with pre-obesity or class I obesity. It's important to match the anticipated efficacy of the AOM, with the right patient, based upon the severity of the disease of obesity.

Dr. Bays:

We usually think of obesity and depression as bidirectional, with obesity increasing depression, and depression increasing obesity [14]. But sometimes, depression and/or anxiety can also contribute to weight loss. Dr. Richards, how often do you find depression or anxiety as a cause of otherwise unexplained, unintentional excessive weight loss in patients with obesity.

Dr. Richards:

I agree that oftentimes, obesity can drive depression via physiologic

processes (i.e., increased inflammation) [22] and stigma. Conversely, depression and stress can dramatically affect weight as well. Unfortunately, bereavement is all too common for my patients. I have repeatedly seen patients with severe depression and stress lose their appetite and significantly reduce food intake. Research supports that emotional stress may plan into secretion of both GLP1 and ghrelin which helps account for the mixed phenotype of food response [23].

Around 5% of my patients have comorbid anxiety/depression mood exacerbations that drive significant weight reduction and are the most common sudden weight trajectory modifiers in my clinical experience. One patient became extremely anxious regarding her husband's upcoming heart surgery after starting a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist and began water fasting without discussing it with her clinicians. I discovered it on her follow up visit because she had lost over 20 pounds in 6 weeks. She required extensive counseling on both dietary education, proper hydration, and stress management to help facilitate a healthier weight reduction trajectory.

Dr. Bays:

Dr. Fitch, what is the practical role of the obesity medicine specialist in the evaluation and management of patients with excessive weight reduction when treated with a heAOM ?

Dr. Fitch:

It is important for clinicians treating obesity to address patient concerns around the degree of weight reduction and how that may affect them personally and medically. I don't think the role of the obesity specialist is much different than the primary care clinician or anyone who is coordinating the obesity treatment. The collective efforts of the entire obesity care team might best help identify the causes of excessive weight reduction and determine what is truly "excessive." The definition of "excessive" is personal for each patient. If a healthy body composition is achieved after treatment with heAOM, and fat mass continues to decline, then considerations should include adjustment in dose or a stopping of the heAOM. Clinician can further help by ensuring the patient is receiving adequate nutrition and hydration and is free of symptoms of starvation (i.e., fatigue, malaise, excessive hair loss, bradycardia, and electrolyte imbalance). Clinicians can also help rule out and manage secondary causes for weight reduction (See Fig. 2 and Table 2).

The real question is what body weight is too low. If a patient with obesity is undergoing weight reduction with heAOM and improving their body composition in a healthy fashion, if the patient is consuming enough macronutrients to remain physically active over 150 minutes a week, and if the patient is experiencing psychosocial that favorably effects on their lives, then continued weight reduction below a BMI of 25 kg/m^2 may be appropriate. However, if continued weight reduction is contributing to psychosocial distress, physical symptoms of too little energy intake, and adverse event due to weight loss (i.e., worsening sarcopenia or osteopenia), then guidance regarding weight reduction may differ to prevent worsening quality of life. As obesity medicine specialists, with increased patient access to more effective heAOMs and with more experience in the evaluation and management of patients with excessive weight loss with heAOM, then current guidance (e.g., Fig. 2 and Table 2) may benefit from continued refinement.

5. "Tips" in the evaluation and management of patients with obesity experiencing substantial weight reduction with heAOMs

Dr. Bays:

Dr. Richard, please provide your top 3 "tips" in management patients with excessive weight reduction with heAOMs.

Dr. Richards:

Start with the end in mind.

1. Setting realistic BMI targets from the first session usually means targeting a BMI of 24–26 for patients with severe obesity, as this gives significant wiggle room in terms of excess weight reduction without risk.
2. While it may seem counterintuitive, for anyone on semaglutide or other heAOMs, I have implemented a "minimum intake" guideline and thus I do not typically endorse a Very Low Calorie Diets. My recommendations are, at minimum, an intake of 64 oz of water, 64 g of protein a day (I nicknamed it the "rule of 64"), and no less than 1000 calories daily.
3. Finally, when patients are experiencing excessive weight reduction, or experiencing weight reduction beyond what I would normally expect, I will evaluate for secondary causes (See Fig. 2 and Table 2) and interview them for food aversions/avoidance. If patients treated with heAOM report inability to maintain adequate intake, then I will reduce the dose and assess for any eating disorders (e.g., binge eating disorder developing avoidant or compensatory components). I have observed that heAOM can trigger food aversions, especially in post operative bariatric surgery patients.

Upfront goal setting and clinical monitoring can help guide patients coast towards a healthy stable healthy weight, as opposed to diving past their goal weight and developing sarcopenia or becoming underweight. For patients who struggle with reasonable expectations, we consider body composition analysis, and this has helped inform patients engaged in overly restrictive 400 calories a day while treated with an heAOM. Depending on the results of body composition analyses, this objective data may influence alterations in heAOM dosing, or in extreme cases, potential discontinuation of the heAOM.

Dr. Bays:

Dr. Fitch, please provide your top 3 "tips" in management patients with excessive weight reduction with heAOMs.

Dr. Fitch:

1. Using principles of shared decision making and anticipatory guidance approach, patients with obesity undergoing potential therapy with heAOMs may benefit from weight reduction expectations initiated at the start of treatment. The guidance conversation might best begin with goals of weight reduction (i.e., remission and prevention of the complications of the disease of obesity, and the patient's desire to achieve a certain size or achieve certain physical goals). For example, one may decide to use a generic less effective AOM medication if the patient goal is to achieve a 5–10% weight reduction, vs a heAOM if 15–20% weight reduction might best achieve clinically meaningful improvements in obesity complications (i.e., improvement in diabetes mellitus or perhaps even diabetes remission).
2. Use of body composition as the goal of obesity treatment may better diagnose adiposity and quantify the "cause" and degree of excessive weight reduction. All weight reduction isn't necessarily healthy. Weight reduction leading to excessive reduction in lean body mass may lead to sarcopenia [11]. Finally, shared decision making is especially important in identify weight reduction that is truly excessive. Management of heAOM is best based not only on defined BMI or percent body fat metrics, but also based upon patient medical and psychosocial presentation.
3. Patients benefit from holistic and honest support, open communication about patient body image, and how such perceptions relate to others around them. Patient psychosocial needs can help guide medication doses to meet goals of improved health and quality of life including psychosocial factors.

Dr. Bays:

Ms. Burridge, please provide your top 3 "tips" in management patients with excessive weight reduction with heAOMs.

Ms. Burridge:

1. Monitor patients closely and adjust heAOM as needed

2. Assess the patient's nutrition and their relationship with food at every visit
3. Monitor body composition, with special attention to muscle mass; counsel patients on adequate protein consumption and resistance training to prevent excessive muscle mass reduction

6. Conclusion

Many thanks to you as excellent panelists for this most unique review of the emerging issue of excessive weight reduction with heAOM. As clinicians gain more experience with these agents, and as more heAOM are developed and approved, then this review may be a good starting point for guidance in patient management. My 3 takeaways from this discussion includes:

1. Before treatment with heAOM, patients with obesity might best be informed about appropriate nutrition, hydration, goals of treatment, and anticipated changes in body weight, not only from a medical standpoint, but also from a psychosocial standpoint. Even if patients are pleased with the degree of weight reduction, patients should continue to notify their clinicians of side effects of the heAOM, and not withhold this information for fear the medication will be discontinued. Patients may benefit if obesity medicine specialists and/or other clinicians who prescribe heAOM have sufficient resources for close follow-up of patients, with special attention given to patients experiencing rapid weight reduction, patients at risk for withholding reports of side side effects of the heAOM, and patients who may be experiencing both medical and psychosocial consequences of excessive weight reduction.
2. Clinicians should recognize that the definition of “excessive weight reduction” may have variable objective and subjective considerations. Objectively, it is often wise to obtain body composition analyses to assess percent body fat, prior to assuming a lower BMI means low body fat. Patients with “normal” BMI can often have increased percent body fat and reduced muscle mass (sarcopenia).
3. Evaluation of excessive weight reduction with heAOM might benefit from a structured approach (Fig. 2 and Table 2). Once properly evaluated, management of excessive weight reduction with heAOM should prompt the clinician to educate the patient (and possibly family and friends) on the likely cause, likely health effects, through shared decision making, how the heAOM is best managed (e.g., kept at the same dose, decreased in dose, temporarily held, or rarely, possibly discontinued).

Author contribution

HEB conceptualized the submission, wrote/sent questions to the other authors, and assisted with editing the manuscript. KB, JR, and AF responded to their assigned questions, reviewed their sections for accuracy, and gave final approval of their contribution.

Ethical review

This Obesity Medicine Association Roundtable represents original works, with work and/or words of others appropriately cited or quoted in the submission. This submission did not involve human test subjects or volunteers. HEB was not involved in the peer review process, nor the acceptance/rejection of this submission. Responsibility for the editorial process for this article was delegated to an independent Editor and/or Associate Editor.

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References

[1] Bays HE, Fitch A, Christensen S, Burridge K, Tondt J. Anti-obesity medications and investigational agents: an obesity medicine association (OMA) clinical practice statement (CPS) 2022. Obesity Pillars 2022:100018.
[2] Hollander P, Bays HE, Rosenstock J, Frustaci ME, Fung A, Vercruysse F, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: a randomized clinical trial. Diabetes Care 2017;40:632–9.
[3] Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Obesity 2013;21:2163–71.
[4] Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989.
[5] Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;373:11–22.
[6] Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012;95:297–308.
[7] Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, et al. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity 2013;21:935–43.
[8] Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, et al. Weight control and risk factor reduction in obese subjects treated for 2 Years with OrlistatA randomized controlled trial. JAMA, J Am Med Assoc 1999;281:235–42.
[9] Greenway FL, Aronne LJ, Raben A, Astrup A, Apovian CM, Hill JO, et al. A randomized, double-blind, placebo-controlled study of Gelesis100: a novel nonsystemic oral hydrogel for weight loss. Obesity 2019;27:205–16.
[10] Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16.
[11] Bays HE, Golden A, Tondt J. Thirty obesity myths, misunderstandings, and/or oversimplifications: an obesity medicine association (OMA) clinical practice statement (CPS) 2022. Obesity Pillars 2022;3:100034.
[12] DeJesus RS, Bauer KW, Bradley DP, Haller I, Bradley SM, Schroeder DR, et al. Experience and expectations of patients on weight loss: the learning health system network experience. Obesity Science & Practice 2019;5:479–86.
[13] Fitch AK, Bays HE. Obesity definition, diagnosis, bias, standard operating procedures (SOPs), and telehealth: an Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022. Obesity Pillars 2022;1:100004.
[14] Freshwater M, Christensen S, Oshman L, Bays HE. Behavior, motivational interviewing, eating disorders, and obesity management technologies: an Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022. Obesity Pillars 2022;2:100014.
[15] Song Z, Reinhardt K, Buzdon M, Liao P. Association between support group attendance and weight loss after Roux-en-Y gastric bypass. Surg Obes Relat Dis 2008;4:100–3.
[16] Kaiser KA, Franks SF, Smith AB. Positive relationship between support group attendance and one-year postoperative weight loss in gastric banding patients. Surg Obes Relat Dis : official journal of the American Society for Bariatric Surgery 2011;7 1:89–93.
[17] Lazarus E, Bays HE. Cancer and obesity: an obesity medicine association (OMA) clinical practice statement (CPS) 2022. Obesity Pillars 2022;3:100026.
[18] Álvaro Sanz E, Abilés J, Garrido Siles M, Pérez Ruíz E, Alcaide García J, Rueda Domínguez A. Impact of weight loss on cancer patients' quality of life at the beginning of the chemotherapy. Support Care Cancer 2021;29:627–34.
[19] Tondt J, Bays HE. Concomitant medications, functional foods, and supplements: an obesity medicine association (OMA) clinical practice statement (CPS) 2022. Obesity Pillars 2022;2:100017.
[20] Alibhai SM, Greenwood C, Payette H. An approach to the management of unintentional weight loss in elderly people. CMAJ (Can Med Assoc J) : Canadian Medical Association journal = journal de l'Association medicale canadienne 2005;172:773–80.

[21] Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342–62.
[22] Shelton RC, Miller AH. Inflammation in depression: is adiposity a cause? Dialogues Clin Neurosci 2011;13:41–53.
[23] McKay NJ, Giorgianni NR, Czajka KE, Brzyski MG, Lewandowski CL, Hales ML, et al. Plasma levels of ghrelin and GLP-1, but not leptin or amylin, respond to a psychosocial stressor in women and men. Horm Behav 2021;134:105017.