AGA CLINICAL PRACTICE GUIDELINE ON PHARMACOLOGICAL INTERVENTIONS FOR MANAGEMENT OF OBESITY

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Abbreviations used in this paper

AGA (American Gastroenterological Association), BMI (body mass index), CI (confidence interval), ER (extended-release), GI (gastrointestinal), GLP-1 (glucagon-like peptide-1), RA (receptor agonist), GRADE (Grading of Recommendations Assessment, Development and Evaluation), FDA (Food and Drug Administration), MD (mean difference), CMS (Center for Medicare and Medicaid Services), PICO (population, intervention, comparison, and outcomes), PPI (proton pump inhibitor), RCT (randomized controlled trial), RR (relative risk), LOCF (last observation carried forward), ITT (intention to treat) SOC (standard of care), SAE (serious adverse event), %TBWL (percent total body weight loss), PPI (proton pump inhibitor), RCT (randomized controlled trial), RR (relative risk), SOC (standard of care, CI (confidence interval), kg (kilogram), SR (systematic review) NMA (network meta-analysis), AOM (anti-obesity medication), HbA1c (Hemoglobin A1c)

ABSTRACT

Background: Obesity has become a worldwide epidemic with deleterious health-related consequences. While lifestyle interventions such as diet and exercise have long been the backbone for the treatment of obesity, the complexity of this disease and limited benefits obtained from behavioral interventions alone has led to the development of new therapies. Interventions such as anti-obesity medications and endo-bariatric and metabolic procedures have become exceedingly popular in recent years. This American Gastroenterological Association (AGA) technical review and guideline aims to examine the long term (≥ 1 year) efficacy and safety of FDA-approved weight loss medications in adults with (Body Mass Index) BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 with weight-related comorbidities, who have had inadequate response to lifestyle interventions.

Methods: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess evidence and make recommendations. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients, conducted an evidence review, and used the Evidence-to-Decision Framework to develop recommendations for the following pharmacological agents: semaglutide, liraglutide, phentermine-topiramate extended release (ER), bupropion-naltrexone sustained release (SR), orlistat, phentermine, diethylpropion, cellulose and citric acid hydrogel (gelesis100).

Results: The guideline panel made nine recommendations. The panel issued one strong recommendation for the use of pharmacotherapy in addition to lifestyle

intervention in adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, who have had inadequate response to lifestyle interventions alone. In addition four conditional recommendations with moderate ceirtanty evidence for the adjunct therapy with semaglutide, liraglutide, phentermine-topiramate ER, and naltrexone-bupropion SR were made. There were two conditional recommendations based on low certainity evidence for phentermine and diethylpropion. The AGA suggested against orlistat with a conditional recommendation, based on moderate certainity evidence. There was a knowledge gap in recommending the use of cellulose and citric acid hydrogel (gelesis100) in the treatment of obesity.

Conclusions: In adults with BMI ≥ 30 kg/m2, or ≥ 27 kg/m2 and weight-related comorbidities, who have had an inadequate response to lifestyle interventions, there are multiple pharmacologic options to add to the physician's armamentarium which are likely more effective than treatment with a lifestyle interventions alone.

INTRODUCTION

This document represents the official recommendations of the American Gastroenterological Association (AGA) and was developed by the AGA Clinical Guideline Committee and approved by the AGA Governing Board. Development of this guideline was fully funded by the AGA Institute with no additional outside funding. According to the Centers for Disease Control and Prevention (CDC), the US obesity prevalence increased dramatically over the past several decades. From 30.5% in the 1999-2000 time period, the prevalence rose to 41.9% between 2017 to March 2020. According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of obesity for young adults increased from 6.2% during the period 1976-1980 to 33% in 2017-2018.[1] Consequently, obesity-related complications such as heart disease, stroke, type 2 diabetes, and certain types of cancer (e.g., colorectal) could be potentially preventable by curving the obesity epidemic. The same CDC report estimated the annual medical cost of obesity in 2019 to be nearly $173 billion dollars, or about a cost of $1,861 higher in people with obesity compared to people with a healthy weight (https://www.cdc.gov/obesity/data/adult.html).[2] COVID-19 has also increased morbidity in people with obesity due to higher disease severity, including increased risk of hospitalizations, intensive care unit stay, and the need for mechanical ventilation.[3, 4] The AGA recently published the Clinical Practice Guidelines on Intragastric Balloons in the Management of Obesity and suggested that individuals with obesity seeking a weight-loss intervention who have failed a trial of conventional weight-loss strategies consider treatment with intragastric balloon (IGB) therapy adjunctively with lifestyle modification over lifestyle modification alone.[5, 6] However, numerous other interventions

have also been developed to treat this chronic disease and the AGA has conducted these clinical practice guidelines to assess the use of pharmacological therapies with Food and Drug Administration (FDA) approved medications for the adjunctive management of obesity.

Objective

The purpose of these guidelines is to provide evidence-based recommendations for the use of pharmacological therapy as an adjunct in treating obesity based on a systematic and comprehensive synthesis of the literature.

Target Audience

The target audience of these guidelines includes health care professionals (gastroenterologists and primary care clinicians), patients, and policy makers. These guidelines are not intended to impose a standard of care rather, they provide the basis for rational, informed decisions for patients and health care professionals. Statements regarding the underlying values and preferences, as well as qualifying remarks or comments accompanying each recommendation, should never be omitted when quoting or translating recommendations from these guidelines. Recommendations provide guidance for typical patients with overweight and obesity; no recommendation can include all the unique individual circumstances that must be considered when making recommendations for individual patients. However, discussions around benefits and harms can be used for shared decision-making, especially for conditional recommendations where patients' values and preferences are important to consider.

These recommendations are summarized in **Table 1** (Executive Summary of Recommendations).

METHODS

Overview

This document represents the official recommendations of the AGA and was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and adheres to best practices in guideline development as outlined by the National Academy of Medicine (formerly Institute of Medicine) using a process outlined previously.[7] Development of this guideline was fully funded by the AGA Institute without additional outside funding.

Panel Composition and Conflict of Interest

Members of the guideline panel were selected based on their clinical and methodological expertise after undergoing a vetting process that required disclosing all conflicts of interest. The evidence review team consisted of two content experts with expertise in obesity medicine (E. G., O. P-B.), gastroenterologists (R. H., O. P-B., R. S., S. Sultan., S. Singh, P. D.), and senior (P. D.) and junior (A. K. C., R. S.) guideline methodologists with expertise in evidence synthesis and GRADE, a registered dietician with expertise in obesity (L. T.) and an adult endocrinologist (T. H.). Panel members disclosed all potential conflicts of interest. Conflicts were managed according to AGA policies, the National Academy of Medicine (formerly Institute of Medicine), and Guidelines International Network (GIN) standards. The guideline methodologists had no

relevant or direct conflicts of interest. All conflict-of-interest disclosures are maintained by the AGA Office.

Formulation of clinical questions and determining outcomes of interest

A protocol was developed a priori to guide the systematic evidence review. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcome(s) for each clinical question. We focused on FDA-approved anti-obesity drugs to treat adults with BMI ≥ 25 kg/m^2 who have had an inadequate response to lifestyle interventions (Supplementary Table 1). Drugs included semaglutide, liraglutide, phentermine-topiramate extended release (ER), bupropion-naltrexone sustained release (SR), orlistat, phentermine, diethylpropion, cellulose and citric acid hydrogel (gelesis100). Although citric acid hydrogel (gelesis100) is considered to be a device by the FDA, the panel included it as an intervention given its ability to be utilized via an oral route similar to a pill. The panel selected desirable (benefits) and undesirable (harms) patient-important outcomes. The outcomes deemed to be critical or important for decision making included: percent total body weight loss (%TBWL), weight loss in kg, proportion of patients achieving ≥5%, ≥10%, and ≥15% TBWL, treatment discontinuation due to adverse event, and serious adverse event (SAE).

Determination of minimally important difference thresholds

A priori, experts on the panel agreed that at least a mean difference (MD) of 3% TBWL when comparing lifestyle intervention alone versus adjunct pharmacotherapy was the minimum threshold in their clinical practice to see patient important benefits. This was further supported by an observational analysis of a multicenter RCT on the the effects of

lifestyle intervention (Look AHEAD Trial) in patients with a BMI ≥25 and diabetes that showed that patients who lost 2-5% TBWL were more likely tohave improvement in blood pressure, gylcemic control, and triglycerides values. Additionally, greater odds of improvement was seen with an increase amount of weight loss. Specifically, meeting the threshold of ≥5% TBWL was associated with significant increased odds in improving cardiovascular risk factors.[8] Moreover, the Center for Medicare and Medicaid Services (CMS) services uses a threshold of 3 kg weight loss at 6 months of intensive behavioral therapy for obesity to cover further face to face visits based on their assessment of the literature (https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=253)[9] A systematic review and meta-analysis of 31 RCT assessing lifestyle intervention versus control showed a pooled estimate of 3.63 kg weight loss at 1 year, 2.45 kg at 3 years and 2.38 kg when less than 28 interventions were included per year.[10] To further confirm the effect of lifestyle intervention the mean of 7 RCTs placebo arm only %TBWL when compared to semaglutide, not including high intensity lifestyle intervention, showed a pooled average of 1.99% TBWL (Supplementary Figure Sem 1 %TBWL). Several publications have discussed the benefit of ≥5% TBWL to achieve clinically meaningful patient benefits in patient's comorbidities and the FDA also uses this threshold to assess pharmacotherapy efficacy for anti-obesity medications.[8, 11-14] Given the average of about 2% TBWL in placebo groups in RCTs, a MD between adjunct pharmacotherapy and lifestyle intervention alone of at least 3% TBWL to achieve the threshold of 5% TBWL was used as the minimum important difference. Additionally, the guideline panel deemed the threshold of crossing 1% for absolute risks for harms to be imprecise.[15]

Search Strategy

We identified a recently published systematic review and network meta-analysis (SRMA NMA) that utilized a comprehensive search strategy (PubMed, Embase, and Cochrane Library [CENTRAL] from inception to March 23, 2021, for randomized controlled trials of weight loss drugs and was conducted by an experienced medical librarian using a combination of controlled vocabulary terms supplemented with keywords.[16] An updated search till the date of January 1st, 2022 using the aid of librarian was performed for all included interventions except for phentermine, diethylproprion and gelesis100. A seperate search from inception to January 1st , 2022 was conducted for these three interventions as they were not included in the SR NMA. The search was limited to English language and human adults. The final strategy is available in Supplement Figure 1. References from included references and prior guidelines were searched to identify any missing relevant studies. Furthermore, content experts aided in the identification of any ongoing studies.

Study Selection, Data Collection and Analysis

The systematic review and meta-analysis informing the guideline was prepared in accordance with the PRISMA guidelines.[17] The inclusion and exclusion criteria were based on the formulated PICO questions. Randomized controlled trials that assessed FDA-approved medications for obesity management in adults were assessed for inclusion. As obesity is a chronic disease, apriori, the panel decided to include studies that had follow up of at least 48 weeks. If 48 weeks outcomes were not available, a follow up period of less than one year was included. The title and abstract of each

identified reference were reviewed by two investigators (one methodology team member: R.S., A.K.C., P.D. and one content expert: O.P.B, E.G). Disagreements were resolved by discussion and if necessary a third member (P.D, R.S) aided in decision making. Each full-text article was evaluated in duplicate (R.S., A.K.C., P.D) and all included full texts were reviewed by all members of the evidence review team; any question or uncertainty was resolved by discussion with this guidelines team. See Supplement Figure 2 for the PRISMA Flow Diagram. Data on the following outcomes was abstracted: baseline body mass index (BMI), weight, waist circumference, age, definition of lifestyle intervention, number of participants in the intervention and comparator group, percent total body weight loss (%TBWL), weight loss in kilograms, proportion of participants who lost ≥ 5% , ≥ 10 % , and ≥ 15% of their body weight, serious adverse events (SAE), discontinuation rate due to side effects, and post-marketing data on SAE from the FDA Adverse Event Reporting System (FAERS). We performed a meta-analysis using Review Manager (Revman), version 5.3, (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), when outcomes were deemed similar enough to be pooled together. In scenarios where 3 or less studies were present, we used a fixed-effects model due to the instability of between-study variance. Otherwise, a random-effects model was utilized.[18, 19] (Higgins 2022, www.training.cochrane.org/handbook). When needed, imputations of SDs were performed using Revman 5.3 calculator. We reported catagorical variables as relative risk (RR) and continuous variables as mean difference (MD) with 95% confidence intervals (CI). For dichotomous outcomes, heterogeneity was assessed using I^2 statistic. We presented data in a narrative fashion when meta-analysis was not feasible.

Certainty of the Evidence

We assessed risk of bias using the Cochrane Risk of Bias Tool for RCTs and the certainty of evidence across outcomes using the GRADE approach.[7, 20, 21] Evidence from observational studies starts as low certainty, while evidence derived from RCTs studies starts as high certainty. The certainity in the evidence conveys our confidence in the estimates of effect. Across each outcome, the evidence is graded into 4 categories (high, moderate, low, or very low) (Table 2) and can be rated down for risk of bias, inconsistency, indirectness, imprecision, and publication bias. For observational studies, the certainity can be rated up in scenarios where there is a large magnitude of effect or dose-response relationship. Using the GRADEpro Guideline Development Tool (https://gradepro.org), evidence profiles were created for each PICO question.

Evidence To Recommendations

The evidence review team convened virtually on a weekly basis to discuss the evidence and the entire guideline panel met for a virtual meeting to formulate the guideline recommendations on May 7, 2022. In conjunction with the certainity of evidence, the evidence-to-decision framework was utilized and the guideline panel reached consensus to formulate recommendations. We also included a patient representative to assess patients' values and preferences. The guideline panel assessed the magnitude of and balance between benefit and harms, patients' values and preferences, and the domains of feasibility, acceptability, resource requirements and the impact on health equity. Cost and cost effectiveness were important, but did not drive a decision. The

certainty of evidence and the strength of recommendation are provided for each clinical question. According to the GRADE approach, recommendations are labeled as “strong” and utilize the phrasing of “we recommend” or “conditional” and use the wording of “we suggest”. The suggested interpretation per the GRADE approach of strong and conditional recommendations for patients, clinicians, and healthcare policymakers can be found in Table 3.

Review Process

Comments from a 14-day open public comment period, Digestive Disease Week 2022 plenary symposium presentation and independent peer review were all reviewed by the panel. Comments were utilized to revise final documents. All comments were were addressed in an internal response document. This guideline has been approved by the AGA Governing Board.

RECOMMENDATIONS

A summary of all the recommendations is provided in Table 1.

Recommendation 1: In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone (strong recommendation, moderate certainty)

KEY IMPLEMENTATION REMARKS

AOMs generally need to be used chronically and selection of the medication or intervention should be based on the clinical profile and needs of the patient including but not limited to comorbidities, patients' preferences, costs and access to the therapy.

Background

Excess adiposity causes a wide spectrum of chronic illnesses with implications for serious morbidity, mortality, quality of life, and healthcare expenditures.[22-24] Affected individuals are at increased risk of metabolic dysfunction (type 2 diabetes, non-alcoholic fatty liver disease, dyslipidemia), cardiovascular disease (ischemic heart disease, congestive heart failure, arrhythmias, hypertension, stroke) biomechanical disability (osteoarthritis, obstructive sleep apnea, gastroesophageal reflux disease), psychosocial impact (depression, anxiety, absenteeism, presenteeism), and certain cancers (including several gastrointestinal malignancies).[22, 25-29] Weight loss of as little as 3-5% may confer improvement for some weight-related complications, with a higher degree of weight reduction resulting in greater health benefits and even reversal of disease.[30] Treatment goals should be individualized to the particular complications of a patient.

Lifestyle interventions, including nutrition modification, physical activity, stress reduction, and improvement in sleep, are considered the foundation of treatment for overweight and obesity. Unfortunately, for most individuals, significant weight loss is difficult to achieve with lifestyle interventions alone and even harder to maintain long-term.[31] Bariatric surgery is the most effective treatment option for manitude of weight loss, durability, and improvement or remission of many weight-related complications.[32] Despite its proven efficacy, only one percent of potentially eligible patients undergo weight loss procedures in the US, with data demonstrating sociodemographic disparities in bariatric surgery utilization.[33, 34]

Considering the growing number of individuals with obesity, there is a large treatment gap for most people living with excess weight having limited access to qualified clinicians to treat the disease. Moreover, recently approved endoscopic bariatric and metabolic procedures for weight loss are not yet covered by public or private insurance routinely.

In the last ten years, significant advances in the development and marketing of anti-obesity medications (AOMs) have started to bridge the treatment gap in obesity care. In fact, the most recent drugs, and others in the pipeline, are beginning to approach bariatric surgery weight loss outcomes in certain populations. Used adjunctively with lifestyle modification, these agents have been shown to enhance weight reduction and improve many health parameters, such as metabolic biomarkers, blood pressure, and quality of life.[35] Moreover, they appear to be safe with manageable side effects.[36]

Given the high prevalence of patients living with overweight and obesity with related complications, the AGA takes the position that gastroenterologists need up-to-date, evidence-based guidelines to apply contemporary treatments in clinical care, whether it be through direct therapeutic interventions or partnering with a multidisciplinary team. These recommendations, of course, can be used by any healthcare provider involved in the care of patients with obesity.

Summary of the Evidence

Evidence informing the overarching recommendation for use of pharmacotherapy in addition to lifestyle modifications is coming from RCTs. Details on the individual studies along with patient selection, demographics and lifestyle interventions are discussed under each drug separately. FDA approved medications given simultaneously with lifestyle modifications that showed significant weight loss (defined mean difference of 3% and thus, as low as 5% TBWL) were used to informing this PICO. These drugs are: semaglutide, liraglutide, phentarmine/ topiramate and naltrexone/bupropion. In addition, we explored short-term treatment with phentermine and diethylpropion. However, obesity is a chronic condition that warrants long-term management. Although beneficial in certain circumstances we did not include the evidence of short-term treatment in this recommendation.

We identified a total of 27 eligible, well done RCT included in the analysis. These studies were on the adult population with obesity or overweight with weight related comorbidities. Mean age was around 40- 60 years with mean BMI of around 32-36 kg/m^2 and predominantly female population. All trials compared pharmacological

treatment in addition to lifestyle modifications to placebo or usual care and lifestyle modifications. They were all with long-term treatment and follow up > 52 weeks. At the minimum, the lifestyle modifications were hypocaloric diet (500-600 kcal/day deficit) along with 150 minutes of physical activity per week. All of the studies reported on weight loss, tolerability and serious adverse events.

Benefits and Harms

Reported weight loss was substantially higher in the pharmacotherapy group and the MD was ranging between 3%-10.8 % total body weight loss depending on the pharmacotherapy that was used. Treatment discontinuation due to side effects (tolerability) and severe adverse events were higher in the treatment group as well. Treatment discontinuation was ranging from 34 per 1000 to 219 per 1000 more in the treatment group and adverse events rate was low and it was ranging from 7 fewer to 27 more depending on the pharmacotherapy utilized.

Certainty in Evidence of Effects

Across all included drugs for this PICO, the overall certainty in evidence of effects was MODERATE. Please refer to Supplement Table EP Semaglutide, Liraglutide, phen/top and NB 32/360 for the full evidence profiles. The certainty of evidence for all benefits (weight loss outcomes, both continuous and binary) was high. All included studies were well done RCT without risk of bias. There was concern for attrition bias, in some studies, however almost all of them used intention to treat (ITT) analysis, and the total randomized number was used as the last observation carried forward, thus, we did not rate down for risk of bias. Furthermore, there was a serious imprecision only in naltrexone/bupropion for the categorical outcome (%TBWL) because the lower

confidence limit crosses the MID (3%). However, the binary outcomes such as 5%, 10% and 15% weight loss were all precise and therefore the overall certainty for benefits was high. There was Moderate certainty in harms across all drugs due to small event numbers for serious adverse events, with wide confidence intervals that were crossing the 1%, apriori determined minimally important difference threshold for harms leading to serious imprecision. Thus, the overall certainty of evidence mostly driven from the lowest certainty in harm outcomes was deemed to be MODERATE.

Discussion

Judged by the guideline panel, four drugs approved for long-term use were deemed to have moderate or large magnitude of weight loss and small or, not-substantial harms , and hence a balance favoring their utilization. Furthermore, each of the four drugs used adjunctively with lifestyle modifications is likely to result in high proportion of patients achieving 5% or even 10% TBWL. Weight loss of as small as 5% of baseline body weight may confer benefits for some weight-related complications, with a higher degree of weight reduction resulting in greater health benefits and even reversal of the disease.[37-40] Treatment goals should be individualized to the particular complications of a patient.

Cost of AOMs remains a concern for the implementation and access to these therapies, especially among more vulnerable populations. Data regarding the cost-effectiveness of anti-obesity pharmacotherapy is limited.[41, 42] Despite moderate cost of most of the medications examined, the guideline panel considered the benefits of treatment across eligible populations to be greater than economic pressures to the healthcare system

overall. As more AOMs are developed and approved, it is possible that competitive forces may shift the balance of cost and benefit in a more favorable direction. To further explore health equity, we performed a search for articles related to health equity, but no studies were found. Therefore, with moderate certainty of the evidence, the AGA guideline panel made a strong recommendation for use of pharmacotherapy adjuncutively to lifestyle modifications for treatment of obesity.

There are some general good practice statements with all AOMs:

1. AOMs should not be used in pregnant women.
2. For patients with diabetes treated with insulin or insulin secretagogues (e.g. sulfonylureas), they should be counseled on the risk of hypoglycemia, should be properly monitored, and medication doses adjusted as necessary while taking AOMs since serum glucose levels could drop with weight loss and reduced caloric consumption.
3. For patients taking medications that can lower blood pressure, caution is advised when starting AOMs as blood pressure can drop with weight loss.
4. Caution is advised when using AOMs with certain eating disorders. They should not be used in patients with active bulimia nervosa. Patients with binge eating disorder should be monitored closely for decompensation of binge eating behaviors.

Background (Glucagon-like Peptide-1 Receptor Agonists)

Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone produced in response to the intake of nutrients by L cells within the intestinal mucosa. GLP-1 receptors are expressed in multiple organs including pancreas, gastrointestinal tract,

heart, brain, kidney, lung and thyroid. This ubiquitous expression of GLP-1 receptors could be the reason for its pleiotropic benefits for diabetes, weight loss and cardioprotection.[43] GLP-1 has numerous metabolic effects, including but not limited to, glucose-dependent stimulation of insulin secretion, delayed gastric emptying, inhibition of food intake and modulation of beta-cell proliferation.[44] Data from rodents and humans indicate that the reduction of food intake is potentially mediated by the direct anorexigenic effects of GLP-1 in the central nervous system, modulation of homeostatic and hedonic (reward-based behaviors) feeding and inhibition of gastric motility.[44]

Exendin-4, a peptide orginally isolated from the saliva of the Gila monster, a venomous North American lizard, was discovered in the early 1990s, and found to have homology with human GLP-1.[45] Exenatide was the first synthetic GLP-1 RA developed and marketed for the treatment of T2DM.[46] One of the most important features of the naturally occurring exendin-4 that was replicated therapeutically was its resistance to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). In humans, endogenous GLP-1 has a half-life of only minutes. Pharmaceutical companies have developed multiple GLP-1 RA drugs with similar amino acid substitutions to extend their half-lives, thereby achieving supraphysiologic levels to promote glycemic control and weight reduction.

GLP-1 RA agents have been available in the US for the treatment of T2DM for over 15 years.[47] Liraglutide and semaglutide, both originally developed for T2DM, were

approved by the FDA as AOMs in 2015 and 2021, respectively. Having a dose-response effect on weight loss, both agents were studied and approved at doses higher than indicated for diabetes.[48, 49] Moreover, this class of pharmaceuticals may have some advantages over other recently approved AOMs. Aside from possibly a more "physiologic" mechanism of action, they do not have the same neuropsychiatric adverse effects as other FDA-approved drugs on the market.[50, 51] Other benefits include inherent glucoregulatory properties and cardioprotection in select populations.[52, 53] At the time of publication of this report, results from the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial were not yet available, but those results may help inform patients, prescribers, and payors on the cardiovascular benefits of GLP-1 RA drugs – semaglutide specifically – for individuals with excess adiposity but without diabetes.[54]

Recommendation 2. In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, the AGA suggests using semaglutide (2.4 mg SQ weekly) with lifestyle modifications, compared to lifestyle modifications alone (*conditional recommendation, moderate certainty*)

KEY IMPLEMENTATION REMARKS

- Given the magnitude of net benefit, Semaglutide 2.4 mg SQ weekly may be prioritized over currently other AOMs for the long-term treatment of overweight or obesity unless there are contraindications or specific preferences
- In addition to weight loss, it has glucoregulatory benefits

- It is contraindicated in patients with a personal or family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2) based on animal studies
- Monitor for signs and symptoms of acute pancreatitis or gallbladder disease
- Caution is advised in patients with gastroparesis

Summary of the Evidence

A total of 8 RCTs assessing semaglutide 2.4 mg SQ weekly dose was used to inform this PICO.[49, 51, 52, 55-59] We excluded oral semaglutide as it is only FDA approved for treatment of type 2 diabetes but not for weight management. The study by Rubino 2021 et al was excluded during screening process because the study was conducted to examine the maintenance phase of continued semaglutide treatment versus switching to placebo.[60] Thus, the methodology team and technical review experts agreed that this study did not reflect the PICO question. Two studies used a lower threshold for inclusion of BMI was ≥25 kg/m^2 [55, 57], another was ≥30 kg/m^2 [49],while the remaining 5 studies used inclusion BMI ≥27 kg/m^2 with co-morbidity or ≥30 kg/m^2 (Kadowaki et al[56] studying an east Asain population included BMI ≥27 kg/m^2 with 2 co-morbidites or ≥35 kg/m^2 with 1 co-morbidites).[51, 52, 56, 58, 59] At baseline, mean BMI in the intervention arm across studies ranged from 32 to 39.9 kg/m^2, mean weight ranged from 86.9 to 113.2 kg and mean waist circumference ranged from 103.8 to 119 cm. The average age ranged from 46 to 59.5 years old, with the majority of studies including predominately females. Four studies[49, 51, 58, 59] included a population without diabetes, 3 studies[55-57] had a mixed population, and 1 study[52] assessed patients with diabetes. Three studies[49, 55, 57] used

0.4 mg SQ daily, while the remaining studies used 2.4 mg SQ weekly after a protocolized dose escalation. Additionally, the majority of studies incorporated lifestyle intervention of a hypocaloric diet (500 kcal per deficit) along with 150 minutes of physical activity per week. Two studies[55, 57] allowed for diet and exercise counseling, one[55] of which did not include a formal weight loss program. Wadden et al included intensive behavioral therapy and an initial low-calorie diet.[59]

Benefits

Eight RCTs informed the outcome of %TBWL with a follow-up period ranging from 52-72 weeks.[49, 51, 52, 55-59] Total of 2,658 participants were in the semaglutide plus lifestyle intervention group and 1,694 in the lifestyle intervention alone group. Mean Difference (MD) for %TBWL was 10.76% TBWL (95% CI 8.73, 12.80) in favor of treatment group (Figure Sem 1 %TBWL). Six RCTs reported weight loss (kg) ranging from 9.7 to 16.8 kg in the semaglutide group versus 1.55 - 6.20 kg in the lifestyle group (MD 10.81; 95 CI 8.19 -13.43).[49, 51, 52, 56, 58, 59] Figure Sem2. Weight loss (kg)

Six RCTs with 2,543 participants in the semaglutide group and 1,583 participants in the placebo group reported for the proportion of participants achieving percent weight loss by thresholds.[49, 51, 52, 56, 58, 59] A pooled analysis showed 82.3% versus 30.6% for ≥5% TBWL (RR 2.74; 95 CI 2.21-3.40), 64.9% versus 12.3% for ≥10% TBWL (RR 5.25; 95 CI 3.61-7.64), and 46.1% versus 5.4% for ≥15% TBWL (RR 7.82; 95 CI 5.19-11.76) in the semaglutide group versus lifestyle intervention group, respectively. **(**Figure Sem3. Pooled analysis TBWL ≥5% **,** Figure Sem4. Pooled analysis TBWL ≥10%)

Special consideration for diabetes

With respect to benefit on glycemic control since semaglutide was originally approved for type 2 diabetes, we also examined glycemic control of semaglutide 2.4 mg dose that approved for weight management. Three studies included a mixed population of patients with and without type 2 diabetes. [55-57] In a phase 2 double-blind clinical trial involving 320 patients who had biopsy-confirmed nonalcoholic steatohepatitis with and without type 2 diabetes, patients with diabetes had a HbA1c reduction by 1.15% in the semaglutide 0.4 mg SQ daily group (49 patients) vs 0.01% in the placebo group (50 patients).[57] Another study reported estimated treatment difference in HbA1c reduction in patients with diabetes and high likelihood of histological fibrosis of 1% in the semaglutide 0.4 mg daily group (28) versus placebo group (21) at week 72.[55] Moreover, a phase 3 double-blinded placebo trial study that examined an east Asian population with overweight/obesity and with or without type 2 diabetes, Kadowaki et al, reported 83% (39/47) of patients with diabetes in the semaglutide 2.4 mg SQ cohort (baseline mean A1c 8.4) and 4% (1/25) in the placebo group (baseline mean A1c 8.1) were able to achieve HbA1c ≤ 6.5 at week 68.[56] Davies et al 2021 assessed the effect of semaglutide 2.4 mg SQ weekly injection in adults with overweight or obesity with type 2 diabetes and found that the mean difference in reduction for HbA1c 1.2% compared to placebo group and the mean difference in %TBWL in the semaglutide group (n=404) versus placebo group (n=403) was 6.22 (5.11-7.33), favoring the semaglutide group.[52]

Harms

A priori treatment discontinuation due to adverse events and serious adverse events (SAEs) were deemed critical outcomes for harm. We pooled 8 RCTs to inform these outcomes with 2,657 participants in the semaglutide group and 1,696 participants in the lifestyle intervention alone group.[49, 51, 52, 55-59] SAEs were defined by the original studies' definition. Pooled estimate for SAEs showed a RR of 1.38 (95%CI 1.10-1.73) when comparing the semaglutide group (254/2657) versus the placebo group (120/1696). Selected examples of SAEs from the largest study[51] included reported rates of abdominal pain (intervention [I]: 3/1306 vs comparison [C]: 0/655), constipation (I: 1/1306 vs C: 0/655), diarrhea (I: 1/1306 vs C: 0/655), nausea (I: 1/1306 vs C: 0/655), vomiting (I: 4/1306 vs C: 0/655), pancreatitis (I: 2/1306 vs C: 0/655), vertigo (I: 3/1306 vs C: 0/655), cholelithiasis I: 12/1306 vs C: 1/655), cholecystitis (I: 4/1306 vs C: 0/655), acute myocardial infarction (I: 2/1306 vs C 1/655), gastroenteritis (I: 5/1306 vs C: 0/655) and suicidal ideation (I: 1/1306 versus C: 0/655).

Treatment discontinuation due to adverse events occurred at a rate of 6.4% (170/2657) in the semaglutide group and 3.1% (52/1696) in the lifestyle intervention group (RR 2.10; 95 CI 1.54-2.86). Additionally, to further support decision making, the FAERS public dashboard was noted to report 131 cases of serious adverse reactions in relation to semaglutide. It was noted that a denominator was not known, but the cases were reported between 2021 and March 2022. Selected examples of these cases include nausea, vomiting, impaired gastric emptying, cholelithiasis, gastrointestinal reflux disease (GERD), constipation, thyroid neoplasia, dyspepsia, hypoglycemia, diarrhea, abdominal pain, electrolyte abnormalities/dehydration, liver function test abnormality, and renal impairment.[61]

Certainty in Evidence of Effects

The overall certainty in the evidence of effects for semaglutide was moderate. See **Supplement Table X** for the full evidence profile. We found inconsistency among the studies for weight loss, but as the effect was in the same direction and did not cross the a priori MID, we decided not to rate down. The inconsistency can be explained by Davies 2021[52] including patient with diabetes while Wilding 2021[51] does not. The percent total body weight loss appears to be less in patients who have diabetes. For the proportion of participant who achieved %TBWL threshold outcomes, we noted inconsistency which could be explained by Wadden 2021[59] because the intensive behavioral therapy and a low-calorie diet were implemented in both arms. Thus, this could minimize the difference between both arms.. For the SAEs, we did find serious imprecision as the 95% CI for the absolute risk crossed 1%.

Discussion

Large magnitude of total body weight lost, was identified with semaglutide treatment. Aso, the portion of subjects achieving 5%, 10% and 15% of TBWL was large. .On the other side, the cumulative treatment discontinuation rate due to adverse events of semaglutide was small when comparing to placebo (6.4% vs. 3.1%).

While the relative risk of serious adverse events (SAEs) was higher in semaglutide compared to placebo (RR 1.38, 95% CI 1.10-1.73), the frequency of each SAE was small. Altogether the panel judged that the undesirable effects from semglutide were

small. Therefore, the balance between desirable and undesirable effects was in favor the use of semaglutide.

However, the guideline panel deemed that there was uncertainty and substaintial difference between individuals in value and preferences between desirable and undesirable effects. In other words, it is not clear that individuals would consistently prioritize the desired outcomes over the potential adverse effects, long-term subcutaneous administration, potential high cost, and challenges associated with insurance approval and reauthorization hassles, which may include more clinic visits, multiple contacts with providers and pharmacies, and burden on healthcare professionals and their staff. There also exists variable response to therapy and potentially inferior weight loss outcomes in people with diabetes.[51, 52] Lastly, some patients may prefer other available non-pharmacologic therapies for the treatment of obesity. Therefore, the panel made a conditional recommendation for the use of semaglutide in individuals with obesity or overweight with weight-related comorbidities given likely variability in values and preferences.

Recommendation 3. In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, the AGA suggests using liraglutide (3.0 mg daily) with lifestyle modifications, compared to lifestyle modifications alone (*conditional recommendation, moderate certainty*)

KEY IMPLEMENTATION REMARKS

- In addition to weight loss, liraglutide 3.0 mg has glucoregulatory benefits

- Liraglutide 3.0 mg is contraindicated in patients with a personal or family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2) based on animal studies
- Monitor for signs and symptoms of adverse events such as acute pancreatitis and gallbladder disease.
- Caution is advised in patients with gastroparesis

Background

Liraglutide is another GLP-1 RA that was originally approved by the US FDA in 2010 for the treatment of T2DM. As an anti-diabetic therapy, it is available up to a dose of 1.8 mg subcuteaneous injection daily. Based on phase 3 clinical trials from the SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence in Nondiabetic and Diabetic Individuals) Program, liraglutide was approved in 2014 for the treatment of obesity up to a dose of 3 mg daily, as an adjunct to lifestyle modification. Similar to semaglutide, liraglutide at 1.8 mg has been shown to reduce morbidity and mortality in people with T2DM at risk for cardiovascular disease.[62]

Summary of the Evidence

Our search identified direct comparative evidence from 11 RCT on liraglutide for the long-term treatment for obesity with a study duration of at least 52 weeks. Of these 11 RCT that met the inclusion criteria, 7 studies were identified from a prior systematic review and network meta-analysis.[16] Our updated search performed till January 1, 2022 further revealed 3 additional studies.[63-65] The technical review team was alerted to the publication of another RCT published after the updated search date, thereby allowing

the addition of one more article to the technical review.[58] In 3 studies, both the liraglutide and placebo groups received adjunct intensive behavioral therapy (IBT) comprised of diet, physical activity, and behavior changecounseling.[65-67] Most studies emphasized a hypocaloric diet with at least 500 kCal energy deficit below their individualized daily total caloric requirements, along with ≥ 150 mins per week of physical activity. Liraglutide or matching placebo was delivered as daily subcutaneous injection, starting at a dose of 0.6mg and weekly dose escalations until the target (i.e. 3.0mg daily) was reached.

Three of the 10 included studies were weight maintenance studies.[63, 64, 67] In all 3 studies, the effect of liraglutide was studied against placebo after a variable-length run-in period wherein patients were asked to follow a calorie-restricted diet. For instance, in 2 studies, patients had to lose at least 5% of their baseline body weight prior to randomization and were put on a very low-calorie diet (800 –1000 kcal diet per day for 8 weeks prior to randomization),[63, 64] whereas in another study, participants had to lose ≥ 5% of their initial body weight during a variable-length (4 –12 week) run-in period during which time they were prescribed a low-calorie diet (1200 – 1400 kcal diet) before they could get randomized.[67] In SCALE-Maintenance, patients lost 6.5kg during the run-in period before randomization,[67] whereas in the other 2 studies patients lost an average of 12.5 – 13.1 kg prior to randomization.[63, 64]

A total of 3964 patients were randomized to liraglutide 3.0 mg whereas 2498 patients were randomized to controls. At baseline, participants had a BMI ≥ 30 kg/m^2, or a BMI ≥27 kg/m^2 in the presence of weight related comorbidities. Baseline demographic

characteristics of the population were similar across the studies with a mean age between 43 and 59 years, predominantly female (~70%) and white (>80%), with an average baseline weight between 100 – 105kg. Two studies included patients with Type 2 diabetes, one of which only included participants on oral antidiabetic medications,[68] while in another, included patients were on basal insulin and were also allowed to be on up to 3 oral antidiabetic medications.[69] In another trial, patients with diabetics were included only if they were on metformin, however, separate outcome data was not provided for diabetic patients in this RCT.[63]

Benefits

Eight studies provided data on % TBWL.[49, 50, 58, 65-69] Pooled analysis of these studies showed a MD of -4.81 (95% CI: -5.39, -4.23) in favor of liraglutide (Figure Lir1. %TBWL). Similarly, patients in the liraglutide group had a higher mean weight loss (kg) when compared to controls (9 studies; MD -5.3 kg [95% CI: -5.9, -4.7])[49, 50, 58, 63, 64, 66-68, 70] Figure Lir2. Weight loss (kg).

Eleven studies were included in TBWL ≥5%.[49, 50, 58, 63-70] Pooled analysis showed that patients on liraglutide were twice as likely to achieve a TBWL ≥5% when compared to controls (RR: 2.09 [95% CI: 1.80, 2.42]) (Figure Lir3. Pooled analysis TBWL ≥5%) Similarly, pooled analysis of 11 studies showed that a significantly higher proportion of patients on liraglutide achieved TBWL ≥10% when compared to controls (RR: 2.67 [95% CI: 2.14, 3.34) (Figure Lir4. Pooled analysis TBWL≥10%). [49, 50, 58, 63-70] About half of all the included studies on liraglutide provided data on ≥15%TBWL.[49, 50, 58, 64-66] Pooled analysis again showed that a significantly greater number of patients on

liraglutide achieved ≥15% TBWL when compared to controls (RR: 3.04 [95% CI: 2.25, 4.12]) (Figure Lir5. Pooled analysis TBWL ≥15%)

Special consideration for diabetes

There were only 2 studies that included patients with type 2 diabetes, namely SCALE Insulin RCT and the SCALE Diabetes RCT.[68, 69] In the SCALE Insulin RCT, participants achieved a modest reduction in HbA1c with liraglutide when compared to placebo (MD: -0.5 [95% CI: -0.8, -0.3]), though it is to be noted that a total of 24 participants who completed the trial (21 on liraglutide and 3 on placebo) were no longer using insulin at the end of the study period.[69] The reduction in HbA1c in the SCALE Diabetes RCT was similarly modest (MD: -0.93 [95% CI: -1.08, -0.78]).[68]

Harms

All 11 studies reported on SAE.[49, 50, 58, 63-70] There was no significant difference between liraglutide and control groups (RR: 1.22 [95% CI: 1.00, 1.50]). (Figure Lir6. Pooled analysis SAE). Most SAE were not from the investigational drug, and they were predominantly GI related side effects.

Gastrointestinal side effects, in particular, nausea and vomiting were significantly more common in the liraglutide group when compared to controls. The incidence of nausea in liraglutide was 40% (1578/3884), whereas the incidence of nausea in controls was

14.8% (358/2422). Similarly, the incidence of vomiting in liraglutide group was 16% (636/3884) , whereas the incidence of vomiting in the control group was 4.3% (105/2422) . Extrapolating AE reported to the FAERS, out of approximately 29,277 patients who took liraglutide 3.0 mg between 2015 and 2018,[71] 40 patients developed acute pancreatitis (<0.1%). The FAERS public dashboard did not report any life threatening or fatal breast cancers during this time period. Data from FAERS also showed that during this time period between 2015 and 2018, there were 17 cases of cholelithiasis that necessitated hospitalization (<0.05%). Severe nausea/vomiting requiring hospitalization was reported in 36 patients during this period, corresponding to an incidence of <0.1%.

Ten studies reported on treatment discontinuations due to AE.[49, 50, 58, 63-65, 67-70] Meta-analysis of these 10 studies showed that liraglutide was associated with a significantly higher risk of treatment discontinuations when compared to controls (RR: 2.31 [95% CI: 1.85, 2.88]). (Figure Lir7. Pooled analysis treatment discontinuations due to AE)

Certainty in Evidence of Effects

The overall certainty in the evidence of effects for liraglutide 3.0 mg was MODERATE and was driven mainly by harms. We noted considerable attrition up to 30% in some studies, however, this was similar between intervention and control groups and all studies performed ITT analysis, thus we did not rate down for risk of bias. There was one study with concern with regard to blinding.[70] In this study, a list containing unblinded subject data was sent to 3 trial sites in Europe by accident (22 patients), but the study investigators performed sensitivity analysis for the primary outcome by excluding these

22 patients and found that the study results were not affected by their exclusion from the analysis.[70] Additionally, we performed sensitivity analysis by excluding 3 studies where they instituted a low calorie or very low calorie diet run in period where patients lost significant weight prior to randomization.[63, 64, 67] Sensitivity analysis did not show any meaningful change in the pooled estimate of effect by excluding these articles, and hence we did not rate down for indirectness.

For the ≥ 5% TBWL outcome, there was substantial heterogeneity present in this meta-analysis (I^2 = 68%, but the heterogeneity was largely due to differences in magnitude and not direction of effect estimates, and hence we did not rate down for inconsistency. Finally, for SAE, we rated down for imprecision as the 95% CI extended from no harms to clinically significant SAE.

Discussion

The desirable effect of weight loss (e.g., TBWL of ≥5%, ≥10% or ≥15%) was thought to be of a moderate magnitude, compared to small magniture of harms that mostly included GI adverse evants Studies tried to mitigate gastrointestinal side effects by a slow escalation of liraglutide dosing (increment of 0.6mg weekly) until the target dose (3.0mg) was reached. Nausea and vomiting were mostly transient, with most incidents occurring during the first 4 to 6 weeks of treatment, coinciding with dose escalation of liraglutide. The guideline panel discussed the balance between weight loss and the side effects and decide that would favor the use of liraglutide. Similar to semaglutide, it is not clear that individuals would consistently prioritize the desired outcomes over the

potential adverse effects, long-term subcutaneous administration, potential high cost, and challenges associated with insurance approval and reauthorization hassles, which may include more clinic visits, multiple contacts with providers and pharmacies, and burden on healthcare professionals and their staff. There also exists variable response to therapy and potentially inferior weight loss outcomes in people with clinical insulin resistance.[50, 72] Lastly, some patients may prefer other available non-pharmacologic therapies for the treatment of obesity. Therefore, the panel made a conditional recommendation for the use of liraglutide in individuals with obesity or overweight with weight-related comorbidities.

Special Clinical Considerations: GLP1 RAS

To minimize risk of gastrointestinal adverse effects, dose escalation is recommended starting with semaglutide 0.25 mg weekly for the first 4 weeks, followed by doses of 0.5 mg, 1.0 mg, and 1.7 mg weekly every 4 weeks at each dose until the maintenance dose of 2.4 mg is reached. For liraglutide, it is recommended to start with 0.6 mg daily for the first 7 days, followed by doses of 1.2 mg, 1.8 mg, and 2.4 mg daily every 7 days at each dose until the maintenance dose of 3.0 mg is reached. Clinical judgment is recommended for adjusting the titration schedule as needed for an individual patient's response, tolerance, and adverse effects. Some patients may achieve a strong response at a submaximal dose and could continue that given dose long-term. If more than two consecutive doses are missed clinical judgment is required to decide on subsequent dosing. Based on our expert opinion, if a patient has tolerated the medication well, resuming at the same dose can be considered. Otherwise, prescribers

should consider lowering the next dose. If three or more consecutive doses are missed, restarting the titration schedule should be considered.

Liraglutide and semaglutide should not be used with other GLP-1 RAs or with dipeptidyl-peptidase-4 (DPP4) inhibitors. Given that they can delay gastric emptying, it may impact the absorption of some oral medications that require rapid onset of action. Caution is advised when using liraglutide in combination with insulin or insulin secretagogues (e.g. sulfonylureas). Doses should be adjusted as clinically indicated and patients should be counseled and monitored for hypoglycemia. Otherwise, GLP-1 RAs stimulate insulin secretion from beta cells in a glucose-dependent manner and thus carry a very low risk of hypoglycemia.

GLP1 RAs have been associated with thyroid C-cell tumors in rodents in dose- and treatment duration-dependent fashion.

Recommendation 4. In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, the AGA suggests using phentermine-topiramate ER (15/92 mg daily) with lifestyle modifications, compared to lifestyle modifications alone (*conditional recommendation, moderate certainty*)

KEY IMPLEMENTATION REMARKS

- Phentermine-topiramate ER should be avoided in patients with a history of, or strong risk factors for, cardiovascular disease.
- Topiramate is teratogenic. Women of childbearing potential should be counseled to use effective contraception consistently and monitor with monthly pregnancy tests.

- Blood pressure and heart rate should be monitored periodically while taking medications with phentermine.

Background

After 13 years of no new pharmacologic therapies for obesity in the US, in 2012, the FDA approved the combination of phentermine, a sympathomimetic amine anorectic, and topiramate, an antiepileptic drug, in an extended-release (ER) formulation, as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes, or dyslipidemia. Phentermine is a monoamine anorectic whose mechanism of action is likely mediated through the elevation of norepinephrine in the CNS. Recommendation 7 below describes the history and clarifies common misconceptions regarding phentermine. There is no high quality long-term data on phentermine monotherapy. Although two-year data using phentermine with topiramate in the SEQUEL Trial(22158731) exists[73], it should be noted that the dosing of phentermine (maximum dose of 15 mg) is lower than the dose usually prescribed for monotherapy (37.5 mg) by most clinicians and it is formulated as extended release as opposed to an immediate release product when it is prescribed alone.

Topiramate has been approved for the treatment of epilepsy and migraine headaches for many years. Its effect on weight loss was noted in clinical trials for seizures.[74] (12690085) The exact mechanism of action of topiramate is unknown but reduced energy consumption through modulation of gamma-aminobutyric acid (GABA) receptors

in relevant CNS structures may be involved.[75, 76] In animals topiramate is known to reduce energy intake, an effect that is also observed in humans.[77, 78] Interestingly, topiramate has been shown to increase energy expenditure in rodents by reducing bioenergetic efficiency, but this has not been demonstrated in humans.[78, 79]

Topiramate alone is not FDA approved as an AOM, but many prescribers utilize it for this purpose in off-label fashion. Prospective, randomized, placebo-controlled trials have demonstrated its efficacy in patients with overweight and obesity, but most of them have been less than 12 months in duration.[76, 80-83] Moreover, topiramate has been used in the management of some eating disorders, although most published effects are case series or case reports.[84-86] Nobably, zonisamide, another antiepileptic drug with similar pharmacologic properties as topiramate, is also used off-label by some healthcare professionals that treat obesity. Similarly, although there are published short-term studies, it is not FDA approved as an AOM.[87, 88]

Summary of the Evidence

Three RCTs with a follow up time of 52-56 weeks were included to inform this PICO.[89-91] Allison 2012[90] used inclusion criteria of BMI was ≥35 kg/m^2, while Gadde 2011[91] used BMI 27-45 kg/m^2 with two or more comorbidities and Garvey 2014[89] included BMI of 27-45 kg/m^2 with diabetes. Gadde 2011 also included BMI ≤27 if participants had DM and this lower BMI was 17% of the population.[91] Mean BMI, weight and waist circumference ranges in the intervention arm across studies were as follows: 35.5-41.9 kg/m^2, 94.9-115.1 kg, and 109-120.1 cm respectively. Mean age ranged from 41.9- 51years old, with the majority of patients females. All 3 studies included lifestyle counseling,

including caloric reduction by 500 kcal/day. Garvey 2012[73] was a 52-week extension study of the Gadde 2011 RCT[91] and thus was not included in the meta-analysis for 1-year outcomes.

Benefits

Pooled analysis of 3 RCTs[89-91] with a total of 1580 participants in the phentermine/topiramate 15/92 mg dosing group versus placebo group with 1561 participants resulted in a mean difference of 8.45 (95 CI 7.89- 9.01) %TBWL favoring the intervention (Figure Phentop1. %TBWL). When assessing 7.5/46 mg dosing, Gadde 2011 reported 6.55 (95 CI 5.66 - 7.44) more %TBWL in the phentermine/topiramate group (498 participants) compared to the control group (993 participants).[91]

We pooled the same 3 RCTs for the outcome of (≥5 and ≥10% TBWL Figure Phentop 2. Pooled analysis TBWL ≥5% and Figure Phentop 3. Pooled analysis TBWL ≥10%) which incorporated 1580 participants in the intervention group and 1561 participants in the control group. 67.6% of those who in the phentermine/topiramate 15/92 mg group versus 19.4% of those in the control group were able to achieve ≥5 TBWL (RR 3.48, 95 CI 3.13-3.87). A higher proportion of patients also achieved ≥10% TBWL (46.2% vs 7.3%; RR 6.33, 95 CI 5.26 - 7.61). One RCT (Allison 2012) reported 31.5% (161/511) and 3.3% (17/513) achieved 15% TBWL for phentermine/topiramate 15/92 mg and placebo, respectively (RR 9.51, 95 CI 5.86-15.44).[90]

Special consideration for hypertension

The largest trial assessing phentermine/topiramate used inclusion criteria of blood pressure up to systolic 160/100 or taking two anti-hypertensive drugs. The

phentermine/topiramate 7.5/46 mg group and phentermine/topiramate 15/92 mg group included 52% (261/498 and 520/995, respectively) of participants with hypertension. For the control group 53% (524/994) had hypertension. Reduction in systolic blood pressure in the placebo group, 7.5/46 mg group, and 15/92 mg group was an average of 2.4, 4.7, and 5.6 mm Hg. For diastolic blood pressure, the reduction was 2.7, 3.4, and 3.8 mm Hg. Adverse events leading to discontinuation of 0.5% or more patients due to hypertension was reported as 5 in placebo group, 2 in 7.5/46 mg group, and 3 in the 15/92 mg group.[91]

Harms

Three RCTs were pooled to inform treatment discontinuation due to adverse events.[89-91] This occurred at a rate of 17.4% (275/1580) in the phentermine/topiramate 15/92 mg cohort and 8.5% (132/1561) (RR 2.08, 95 CI 1.71-2.52) (Supplemental Figure: Phentop 5. Pooled analysis treatment discontinuations due to AE)

In regards to SAE, we pooled the same three RCTs with the same number of participants as the outcome of treatment discontinuation due to adverse events. SAE occurred at a rate of 4.2% (67/1580) versus 3.5% (55/1561) in the control group. Selected examples of SAE from the largest study in the meta-analysis (Gadde 2011) included cardiac side effects (5/994 vs 7/993), cholelithiasis (1/994 vs 1/993), syncope/headache/dizziness (1/994 vs 3/993), nephrolithiasis (2/994 vs 0/993) for phentermine 15/92 mg group versus control group[91] (Supplemental Figure Phentop 4. Pooled analysis SAE). To further augment decision making, FAERS was searched for SAE from 2015-2018. Estimates for prescription use was utilized from a recent

publication to allow for approximate calculations for rates. Rates for SAE ranged from 0.3-1% and 7 total deaths were reported.[61, 71] (Supplement table 7: SAE FARES for Phentermine/Topriamate table)

Certainty in Evidence of Effects

The overall certainty in the evidence of effects for phentermine/topiramate 15/92 mg was moderate driven mainly by harms. See Supplement Table Phen/Top EP for the full evidence profile. There was serious risk of bias when assessing Garvey 2014 et al as only completers data from the first 28 week appeared to be reported instead of intention to treat analysis and details describing the first 28 weeks were limited. Additionally, the first 28 weeks phentermine and topiramate were given as individual medications rather than the extended-release version.[89] Sensitivity analysis was performed for the above outcomes, and the effects estimates had trivial differences; thus, Garvey 2014[89] was included in our analysis. As the effect estimates were considered more conservative, we did not rate down for risk of bias or inconsistency. For the outcome of ≥15% TBWL, there was serious concern for imprecision due to low event rate. Additionally, there was serious imprecision for the outcome of serious adverse events due to low event rate and the confidence interval showing both appreciable benefit and harm.

Discussion

The magnitude of weight loss for phentermine-topiramate was judged to be moderate to large. In addition, there was a higher discontinuation rate that was considered to be frequent but not substantial (e.g. paraesthesia, dizziness, dysgeusia, insomnia). Also,

the serious side effects were rare [e.g., cardiac side effects (5/994 vs 7/993)]. Therefore, the balance between desirable and undesirable effects was in favor the use of phentermine/topiramate ER.

Similarly to the other medications there were concerns about the differences in values and preferences and increase in the burden on health monitoring of these patients (e.g. blood pressure and heart rate monitoring, pregnancy tests). All taken in consideration, the panel made a conditional recommendation for the use of phentermine/topiramate ER.

Special Clinical Considerations

Phentermine-topiramate ER is available in capsules with doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg. It is recommended to start with the starter dose of 3.75 mg/23 mg taken once daily for 14 days, followed by a maintenance dose of 7.5 mg/46 mg daily. After 12 weeks, if the patient has not lost at least 3% of their body weight, consider discontinuation or dose escalation. For escalating the dose, titrate up to 11.25 mg/69 mg daily for 14 days, followed by the maintenance maximum dose of 15 mg/92 mg daily. If the patient has not lost 5% or more of their weight after 12 weeks on the maximum dose, discontinue the medication by taking one capsule every other day for one week, then stopping, to minimize the risk of precipitating a seizure. Because of potential benefits for patients who suffer from significant migraine headaches, phentermine-topiramate ER should be considered in patients with excess weight and migraines.

One of the most important concerns among prescribers surrounds the cardiovascular safety of phentermine. Perceptions regarding cardiotoxicity with sympathomimetic

AOMs can be categorized into two different pathphysiologic domains. The first, regarding serotonergic stimulation of myocardial tissues (pulmonary hypertension, valvulopathies), is addressed below in recommendation 7 for phentermine monotherapy. The second domain reflects adrenergic hemodynamic effects (heart rate, blood pressure) and the potential for adverse cardiovascular outcomes. In pivotal clinical trials for phentermine-topiramate ER, blood pressure generally declined, and there was a very modest increase in heart rate, usually at higher doses.[73, 90, 91] Observational data from phentermine monotherapy does not seem to be associated with significant increases in blood pressure or heart rate in treated individuals.[92-94] Currently, there are no large cardiovascular outcome trial data for long-term use of phentermine-topriamate ER. Caution is therefore advised and it should be avoided in patients with a history of cardiovascular disease or uncontrolled hypertension. Subjects in phase 3 trials enrolled subjects up to the age of 70 years, but there is no high quality data to guide the use of phentermine-topiramate ER in the geriatric population. It should be avoided in patients treated with, or within 14 days, of monoamine oxidase inhibitors. Due to concerns for arrhythmias and seizures, medications with phentermine should not be used in patients with untreated hyperthyroidism.

Fetal exposure to topiramate during the first trimester is associated with an increased risk of oral clefts.[95] Female patients with child-bearing potential should be counseled on the risks of teratogenicity and consistent use of reliable contraception while using phentermine-topiramate ER. Monitoring with monthly pregnancy tests is advised. Topiramate has carbonic anhydrase inhibitor properties and can induce metabolic acidosis and elevated urine pH with hypercalciuria and hypocitraturia.[96] With higher

doses and prolonged exposure, there may be in increased risk of kidney stones. Caution is advised in patients with a history of significant nephrolithiasis. Consideration should be given to periodic monitoring of serum bicarbonate levels in patients treated with phentermine-topiramate ER long-term.

Due to potential for insomnia, it is recommended that phentermine-topiramate ER be taken early in the day. Other commonly reports side effects include cognitive impairment, constipation, dry mouth, palpitations, paresthesias, dysgeusia, and irritability.[73, 90, 91]

Recommendation 5. In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, the AGA suggests using Naltrexone-Bupropion ER (32/360 mg)with lifestyle modifications, compared to lifestyle modifications alone (conditional recommendation, moderate certainty)

KEY IMPLEMENTATION REMARKS

- Naltrexone-bupropion ER may be considered for the treatment of overweight or obesity in patients who are attempting smoking cessation
- Naltrexone-bupropion ER may be considered for the treatment of overweight or obesity in patients with depression to minimize polypharmacy.
- Naltrexone-bupropion ER should not be used in patiens with epilepsy or at high risk of seizures.
- Naltrexone-bupropion ER cannot be used concomitantly with opiate medications.

- Blood pressure and heart rate should be monitored periodically while taking naltrexone-bupropion ER, especially in the first 12 weeks of treatment.

Background

The FDA approved the combination of naltrexone, an opioid antagonist, and bupropion, a dopamine and norepinephrine reuptake inhibitor class of antidepressant, in 2014 as an adjunctive therapy to a lifestyle modification for chronic weight management in adults with BMI 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200063s000lbl.pdf). This combination likely has dual mechanisms of action, both by modulating hedonic eating and anorexigenic effects. The former phenomenon is likely driven by increased dopamine levels and antagonism of opioid receptors by bupropion (11210998,8725871) and naltrexone (12479844), respectively in mesolimbic structures.[97-99] Anorexigenic effects and modulation of energy homeostatis with naltrexone-bupropion ER likely occur in the hypothalamus. The arcuate nucleus (ARC), located in the ventromedial hypothalamus, integrates multiple systemic signals and plays a critical role in the regulation of energy balance.[100] (25258511) Two major neurons in the ARC exert opposing downstream effects on both energy consumption and energy expenditure. The neurons that express pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), designated POMC/CART, are characterized as anorexigenic since they inhibit energy consumption when activated. Conversely, neurons that secrete neuropeptide Y (NPY) and agouti-releated protein (AgRP), designated NPY/AgRP, are orexigenic because when activated they promote energy

consumption. When stimulated, the POMC/CART neurons release α-melanocyte stimulating hormone (α-MSH) and ß-endorphin. α-MSH is a neurotransmitter that serves as an agonist for downstream receptors that exert anorexigenic actions in multiple brain areas. Bupropion can activate POMC/CART neurons, but ß-endorphin has auto-inhibitory effects on these cells, hence the weak anorectic effects of bupropion monotherapy. Naltrexone therefore, by antagonizing this inhibition, is the rationale for combining the two agents as an AOM.

Summary of the Evidence

Our search identified direct comparative evidence from RCT reporting on bupropion/naltrexone vs. placebo in long term treatment for obesity (all studies were with follow-up time of 56 weeks). All 5 studies were on patients with BMI more than 30 kg/m^2, or a BMI ≥27 kg/m^2 and the presence of obesity-related comorbidities.[101-105] They all used a dose-escalation that occurred during the first 4 weeks of treatment, beginning with 1 tablet daily during the first week, increasing to 2 tablets during week 2, 3 tablets during week 3, and 4 tablets daily during week 4 and thereafter. Each active tablet contained an extended-release formulation of 8 mg of naltrexone and 90 mg of bupropion or placebo. Target maintenance dose was 32 mg of naltrexone and 360 mg of bupropion (NB 32/360).

Demographics and baseline characteristics of the population were similar across the studies. Mean age ranged between 43 to 61 years, predominantly females, with baseline weight of around 100kg, BMI of around 36 kg/m^2, and weight circumference of around 110-120 cm. Furthermore, 3 studies included patients without diabetes and with

controlled hypertension and/or dyslipidemia.[103-105]The other 2 studies included patients with diabetes and/or hypertension/dyslipidemia.[101, 102]

Lastly, all the studies encouraged hypocaloric diet (500 kcal/day deficit) and increased exercise by walking 30 min most days of the week in addition to the study medication, except for the Wadden et al. study[103] where naltrexone SR/bupropion SR or placebo, was combined with an intensive program of diet, exercise, and behavior therapy.

Benefits

All 5 studies[101-105] report on % TBWL and weight loss in kilograms (kg), while one study[102], did not report on the 5%,10% and 15% TBWL and another study[101] just did not report on 15% TBWL.

In pooled quantitative meta-analysis for categorical outcomes, there were total of 6,772 subjects that received NB 32/360 and 5,887 in the placebo group. Mean Difference (MD) for %TBWL was -3.01% TBWL (95% CI: -3.54, -2.47) in favor of treatment group (Supplementary Figure Bup1 %TBWL). Similarly, there was more weight loss in the treatment group compared to placebo MD -3.01 kg (95% CI: -3.39, -2.62) (Figure Bup2. Weight loss (kg))

Four studies[103-106] were included in TBWL >5% and 10 % and the total number of patients in the pooled meta-analysis was 2,317 for the NB 32/360 and 1,437 for the placebo. There were more patients that achieved TBWL >5% and TBWL >10% (Figure Bup3. 5% TBWL and Figure Bup4. 10% TBWL) in the treatment group when compared

to placebo with RR 2.18 (95% CI: 1.41, 3.37) and RR 3.04 (95% CI: 1.80, 5.14) respectively.

Three studies[103-105] reported on TBWL >15% and the total number of patients analyzed was 2,052 in treatment and 1,278 in placebo group. Significantly more people in the treatment group had >15% TBWL when compared to the placebo group (RR 3.88, 95% CI: 2.13, 7.08) (Supplementary Figure Bup 5. Pooled analysis TBWL >15%).

All the presented analysis was done by using ITT method when available with the last observed weight included. There was a significant number of patients that were lost in follow up and mostly due to intolerability of the treatment. For patients that were able to tolerate the drug and complete treatment the %TBWL was up to 6.8% more in the treatment group.[104]

Special consideration for comorbidities

Psychiatric disorders

All the above mentioned studies investigated psychiatric disorders such as anxiety and depression as a comorbidity and as a side effects. In both scenarios, there was no significant difference between the groups. At the end of the study, anxiety was reported to occur from 0.6% - 5.4% in the intervention group and 0.2%- 4.3% in the placebo group. Depression occurance ranged from 0.1% -1.3% in the intervention group and from 0.2% -1.6% in the placebo.

Diabetes mellitus and hypertension

Two studies that include patients with diabetes, reported improvement in Hg A1C that was favoring the treatment group. This change was reported to be around -0.6 % for the treatment and 0.1% for the placebo group.[101, 102] Similarly, of the studies reporting on hypertension, there was no significant difference for blood pressure with a usual pattern of mild increase in blood pressure by week 8 and then back to baseline blood pressure for the intervention group.

Harms

All 5 studies reported harms on all patients that were randomized. All studies reported on discontinuation due to side effects and serious adverse events outcomes. They all reported on the frequency of the specific side effects too.[101-105]

The total number of patients included in the analysis was 6,947 in the treatment group and 5,892 for the placebo. There were significantly more patients that discontinued the treatment due to side effects in the treatment group compared to the placebo (RR 2.39, 95% CI: 1.69, 3.37) (Supplemental Figure Bup 7. Pooled analysis AE). The discontinuation rate for the NB 32/360 was around 25% ranging between 16.1% and 29.4% for the intervention group and around 10% ranging between 3.5% and 15.4% for placebo group. The most common reason for discontinuation of the study drug was nausea ranging between 4.6% and 9.6%, vomiting from 0.7-2%, headache 0.9 -1.8%, dizziness 0.7-1.4 % and depression 0.2 -0.6%.

The total number included in the analysis for SAE was the same as in the discontinuation due to side effects. However, there was no difference between the treatment and placebo group, (RR 0.74, 95% CI: 0.53, 1.03) (Supplemental Figure Bup

6. Pooled analysis SAE). Most reported serious adverse events were not typically from the investigated drug and were predominantly cardiovascular, gastrointestinal or psychiatric (e.g., Apovian et al. reported 1 MI, 1 passive suicidal ideation, 1 seizure in intervention group and 0 in the placebo[104]; Greenway et al. reported 1 heart failure and 1 MI in intervention group and 1 pericardial effusion in the placebo group[105]; Nissen et al. reported 40/4455 (0.9%) major CV events all death, nonfatal stroke, or nonfatal MI infarction in the treatment and 62/4450 (1.4%) in the placebo group[102]; and Wadden et al. reported 2 cases of cholecystitis that were judged to be potentially related to study drug[103]).

Certainty in Evidence of Effects

The overall certainty in evidence of effects for NB 32/360 was moderate. See Supplement Table EP NB 32/360 for the full evidence profile. There was a concern for attrition bias in the Apovian 2013 study[104], since there was an imputation in the analysis for week 56. After re-randomization, patients receiving a higher dose of Naltrexone were excluded from the final analysis and participants receiving FDA-approved doses were counted twice and "double-weighted". This was not a large number of participants, and we thought it would not impact the pooled estimate. Also, to deal with attrition bias, most studies used intention to treat (ITT) analysis, and the total original number was used as the last observation carried forward. However, Hollander et al[101], reported only a modified ITT analysis and excluded the patients that discontinued the drug within the first four weeks. The majority of these patients discontinued due to side effects. We

explored this in sensitivity analysis and there was no difference between the results. Thus, we decided not to rate down for risk of bias. Although I^2 was high for most pooled estimates, all the studies showed clear benefit or harm, so we did not rate down for inconsistency. Furthermore, the minimal important difference (MID) or clinically important threshold was pre-determined to be 3kg (or ~3%). For the categorical outcomes (%TBWL and weight loss in kg) the lower confidence limit crossed the MID, for benefit; thus, we rated down for imprecision. Similarly, wide CI and small event numbers for serious adverse events were noted, leading to serious imprecision. Lastly, the results of the Wadden et al. study[103] were inconsistent from the other studies. This was most likely due to the high-intensity diet and exercise co-intervention that may have led to a ceiling effect. Therefore, we did sensitivity analysis to explore, and the results were not significantly different, so we did not rate down for inconsistency.

Discussion

The guideline panel explored the evidence for the magnitude of the desirable and undesirable effects of the Naltrexone/Bupropion ER used along with lifestyle interventions in individuals with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities. The desirable effect is weight loss presented as a percentage of total body weight loss or a portion of subjects achieving 5%, 10% or 15% as detailed above. The desirable effect was thought to be of moderate magnitude. The undesirable effects represented by tolerability or treatment discontinuation that was for 132 per 1000 more individuals in the intervention group compared to no treatment and serious adverse events such as nausea, vomiting, diarrhea, constipation, cholecystitis, headache, and

anxiety all in rate of less than 1 in 1000. The magnitude of the undesirable effects was judged to be small effect. Therefore, the balance between desirable and undesirable effects would probably favor the use of NB.

Furthermore, the panel explored the possibility of an important uncertainty and variability about how much different individuals will value the desirable vs. undesirable outcomes. In addition, the intervention was thought to have moderate cost and unknown incremental net benefit but was considered to be feasible as an oral prescription without any complex treatment approach and just some minimal administrative work.

Taking all this into consideration, in addition to the moderate certainty in the overall evidence, the panel made a conditional recommendation for the use of NB in individuals with obesity or overweight with weight-related comorbidities. Lastly, we explored specific populations with comorbidities such as diabetes, hypertension, and psychiatric comorbidities. However, there was no substantial added benefit.

Special Clinical Considerations

Naltrexone-bupropion ER is available in tablets each containing 8 mg of naltrexone and 90 mg of bupropion in a sustained release formulation. The recommended titration schedule begins with one tablet daily in the morning, followed by weekly escalation to one tablet twice a day, then two tablets in the morning and one in the afternoon, until the maintenance dose of two tablets twice a day is reached. The second dose should not be taken late in the day to minimize the risk for insomnia. In patients with moderate to severe renal impairment, the total daily dose should be reduced by half (ie, one tablet twice a day), and should be avoided in end-stage renal disease. In patients with moderate to severe hepatic impairment, the total daily dose should not exceed one

tablet daily. After 12 weeks of therapy on the maintenance dose, if the patient has not lost 5% of their total body weight, the medication should be discontinued as they are likely a poor responder.

Because of the opioid antagonism from the naltrexone component, it should not be used in patients that require short-term or long-term opiate therapy since naltrexone-bupropion ER could reduce the efficacy of the analgesic or precipitate a withdrawal reaction, respectively.

Bupropion may lower the seizure threshold and naltrexone-bupropion ER should be avoided in patients with epilepsy, history of seizures, or with any clinical factors that may increase the risk of seizures.[107]

In phase 3 clinical trials for naltrexone-bupropion ER, subjects in the treatment groups demonstrated less improvement in placebo subtracted changes of blood pressure and modest increases in heart rate. Vital signs should be monitored in patients treated with naltrexone-bupropion ER, and should be avoided in patients with uncontrolled hypertension. It should also be avoided in patients treated with, or within 14 days of, monoamine oxidase inhibitors. Currently, there are no large cardiovascular outcome data for the long-term use of naltrexone-bupropion ER.

Since bupropion is also an antidepressant, patients should be observed for neuropsychiatric adverse effects, including suicidal thoughts and behaviors, especially in individuals younger than age 24. Patients and their families should be counseled for the emergence of these reactions.

Recommendation 6. In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, AGA suggests against the use of Orlistat (*conditional recommendation, moderate certainty*)

Implementation remark: Patients who put high value on the potential small weight loss benefit and low value on GI side effects would reasonably choose treatment with Orlistat.

IMPLEMENTATION REMARKS

- Orlistat should be taken two hours apart from other medications.
- Patients using orlistat should take two multivitamins daily.

Background

Orlistat, a locally- acting, irreversible inhibitor of gastrointestinal lipase, was approved in 1999 by the FDA for the treatment of obesity. The drug is indicated for the induction of and maintenance of weight loss in conjunction with a reduced-calorie diet (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020766s029lbl.pdf). Orlistat exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze approximately 30% of ingested dietary fat from triglycerides into absorbable free fatty acids and monoglycerides.The undigested triglycerides are not absorbed, resulting in a caloric deficit and subsequent weight loss.

Summary of the Evidence

Our search identified 28 RCT comprising 6455 cases and 5893 controls providing direct comparative evidence for orlistat vs. usual care in the long term treatment of obesity. Studies varied in duration between 48 weeks to 4 years. Most studies encouraged a hypocaloric diet (500 - 800 kcal/day deficit) with particular emphasis on low fat diet (30% energy from fats) and increased physical activity. Dose of orlistat was 120 mg three times a day with meals. All 28 RCT were on patients with who were obese (BMI ≥ 30) or overweight (BMI ≥ 27) with one or more weight-related comorbidities. The patient population was mostly female (55 - 85%), with an age range between 42 and 58 years. Average weight of patients in the trials was between 95 to 112kg, with an average BMI between 33 to 36 kg/m^2. Average waist cirumcumference was between 105 and 115 cm. An over-the-counter formulation of Orlistat which is available in a 60mg dose was not examined in this systematic review and guideline given the paucity of long term study data on the 60mg dose.

Benefits

A total of 23 RCT with 24 cohorts comparing orlistat to controls provided data for mean weight loss (kg).[108-130] Meta-analysis showed that orlistat produced a mean weight loss of 2.81 kg (95% CI: -3.45 to –2.17) (Supplementary Figure Orl2. Weight loss kg). Similarly, a total of 15 RCT comprising 16 cohorts provided data for %TBWL.[109, 110, 115-121, 125, 127, 129, 131-133] Pooled analysis of these RCT showed that patients on orlistat lost 2.78% (95% CI: 2.36 to 3.20) Supplementary Figure Orl1. %TBWL) of their total body weight when compared to controls. Eighteen RCT provided data on ≥ 5% TBWL.[70, 108-

[110, 115-121, 125, 126, 128, 129, 131, 133, 134] Meta-analysis of these studies showed that more patients on orlistat achieved ≥ 5% TBWL when compared to controls (RR: 1.71, 95% CI: 1.55 to 1.88). Similarly, meta-analysis of 15 studies showed that more patients on orlistat achieved ≥ 10% TBWL (RR: 1.94, 95% CI: 1.70 to 2.22).[70, 109, 110, 115, 117-121, 125, 128, 129, 131, 133, 134] No RCT provided data on ≥ 15% TBWL for orlistat. (Supplementary Figure Orl3 and Orl 4. Pooled analysis TBWL ≥5% and ≥10%, respectively)

Harms

Only 11 of 28 included studies on orlistat provided data on SAE.[70, 108, 109, 112, 120, 121, 128, 130, 132-134] Pooled analysis showed that there were no significant differences in the incidence of SAE between orlistat and control groups (RR: 1.04, 95% CI: 0.81 to 1.33) (Supplementary Figure Orl5. Pooled analysis SAE). On the other hand, meta-analysis of 20 studies demonstrated that patients on orlistat had a higher incidence of treatment discontinuations when compared to controls (RR: 1.51, 95% CI: 1.22 to 1.89) (Figure Orl6. Pooled analysis treatment discontinuations due to AE).[70, 108-112, 115-121, 125, 128-133] Most treatment discontinuations of orlistat were due to transient GI side effects such as flatulence, oily spotting/stools, fecal urgency and fecal incontinence. Meta-analysis of 12 studies showed that the risk of treatment discontinuations due to GI side effects were significantly higher in orlistat when compared to controls (RR: 2.86, 95% CI: 1.91 to 4.30).[108-110, 115-118, 121, 126, 129, 130, 133]

Per the FDA, there have been 12 cases of liver failure occurring in countries outside the USA in patients on Orlistat 120mg and 1 case of liver failure in a patient on Orlistat

60mg in the USA that have been reported between April 1999 and August 2009 out of an estimated 40 million patients who have used these medications. While a cause and effect relationship has not been established, the FDA has added a label warning about the potential for serious liver injury due to Orlistat. The FAERS public dashboard also reported 4 cases of pancreatic adenocarcinoma(Supplementary Table 11. SAE FAERS for Orlistat).

Certainty in Evidence of Effects

The overall certainty in evidence of the effects of orlistat was moderate. See Supplement Table 10 Orlistat for the full evidence profile. We rated down the quality of evidence for imprecision for the two continuous outcomes, namely weight loss in kilograms and %TBWL as the 95% CI for the pooled effect size for both of these outcomes included the MID. Studies were also scant in their reporting of allocation concealment. However, we did not rate down for risk of bias as a majority of studies were reported as double-blinded. Additionally, although there was significant attrition (25 to 56%) seen in most studies, it was usually not disproportionate between groups and studies used ITT analysis with LOCF, hence the technical review team felt comfortable not to rate down the quality of evidence for risk of bias. The quality of evidence for ≥5% TBWL and ≥10% TBWL outcomes were both rated as high despite substantial heterogeneity (I^2 = 73% in the former and I^2 = 46% in the latter), and not rated down as the inconsistency was largely driven by the magnitude and not the direction of the effect estimates. In terms of SAE, we rated down for imprecision because the 95% CI extended from no harms to clinically significant SAE based on *a*

priori criteria.

Discussion

The weight loss for orlistat was thought to be of a small magnitude - 2.78%, with the 95% CI including the MID (2.36 to 3.20). In contrast, the magnitude of the harms was judged to be moderate because the treatment discontinuation rate due to adverse events maily GI related effects such as oily stools, diarrhea and stool incontinence were signficantly higher in orlistat group and were also considered to be bothersome. Thus, the balance between desirable and undesirable effects would probably not favor the use of orlistat.

The panel recognized that different individuals may value the weight loss and side effects difrently. Furthermore, compared to some of the newer agents, the cost of the orlistat is lower making it attractive for some patients and since orlistat is not a centrally acting agent, some individuals may favor the low potential for neuropsychiatric side effects too.Allthogether, the guideline panel made a conditional recommendation against the use of orlistat for individuals with obesity or overweight with weight-related comorbidities. However, the panel recognized that a small, but meaningful minority of patients who place a higher value on the small amount of weight loss and lower value on the possibility of GI adverse effects such as oily stools, diarrhea and stool incontinence would reasonably choose treatment with orlistat.

Special Clinical Considerations

Orlistat is available in 60 mg or 120 mg capsules. It is recommended to take within one hour before meals as an adjunct to a calorie reduced diet and physical activity. If a meal

is very low in fat, the corresponding dose can be omitted. Because the mechanism of action involves fat malabsorption, patients are at risk of deficiencies of fat soluble vitamins, and it is recommended to supplement with daily multivitamins to be taken at least two hours apart from orlistat. Certain medications, such as cyclosporine, levothyroxine, and warfarin, may require longer intervals between doses of orlistat and may require closer monitoring. Patients with chronic malabsorption from conditions such as chronic diarrhea, celiac disease, inflammatory bowel disease, or a history of bariatric surgery may not be ideal candidates for long-term orlistat therapy.

There have been rare reports of acute hepatic failure in patients treated with orlistat but if causally related, they are thought to be rare idiosyncratic reactions.[135, 136] Weight loss as a result of orlistat treatment may also be accompanied by a small risk of cholelithiasis.

Recommendation 7. In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, the AGA suggests using Phentermine with lifestyle modifications, compared to lifestyle modifications alone (*conditional recommendation, low certainty*)

KEY IMPLEMENTATION REMARKS

- Phentermine monotherapy is approved by the FDA for short-term use (12 weeks)
- Given the chronic nature of weight management, many practitioners use phentermine longer than 12 weeks in an off-label fashion.
- Phentermine should be avoided in patients with a history of, or strong risk factors for, cardiovascular disease.

- Blood pressure and heart rate should be monitored periodically while taking phentermine.

Background

Phentermine was approved in 1959 by the FDA to treat obesity. It is a sympathomimetic amine anorectic approved for short-term (12 weeks) use adjunctively with lifestyle intervention in adults with a BMI 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202088s005lbl.pdf). As a sympathomimetic agent, phentermine has pharmacologic activity similar to amphetamine. Although it has been available for decades and there is vast clinical experience with its therapeutic use, there exist no large high quality studies surrounding its long-term efficacy and safety for monotherapy. Nevertheless, it has remained the most commonly prescribed AOM in the United States.[137, 138]

On the other hand, many healthcare professionals fear using phentermine due to its history associated with fenfluramine. Popular in the 1990s, phentermine with fenfluramine, commonly known as “fen-phen”, was being prescribed to millions of patients in the United States.[139] In 1997, the first report of valvular heart disease and pulmonary hypertension associated with this combination drug was published.[140] Phentermine’s therapeutic effect is mediated through increased levels of norepinephrine and dopamine in the CNS, while fenfluramine is thought to increase central serotonin

levels, hence exerting their anorexigenic effects synergistically in relevant brain structures. It was initially thought that valvulopathies associated with fenfluramine were also a result of increased serotonin levels in cardiac tissues, but studies later demonstrated that fenfluramine metabolites activated serotonin receptors directly with more affinity than serotonin itself.[141] The serotonin receptor, 5-hydroxytryptamine type 2B (5-HT_{2B}), (26132939*) is prominent in human cardiovascular tissue and may be responsible for the cardiotoxicity seen with fenfluramine-phentermine.[142] In the context of millions of patient-years of clinical experience with phentermine, there is no high quality data demonstrating an association between phentermine monotherapy and cardiac valvulopathies or pulmonary hypertension. One report demonstrated a case of pulmonary hypertension in a patient using phentermine.[143] However, a prospective analysis performed from a large database of patients with pulmonary hypertension in North America implicated fenfluramine, but not phentermine, as a risk factor for pulmonary hypertension.[144]

Summary of the Evidence

We identified 8 RCT that were reporting on Phentermine vs. placebo in treatment for obesity.[106, 145-151] There were no studies with long term treatment and follow up > 52 weeks. All identified studies were with short-term treatment such as 12 weeks of phentermine in doses between 15-37.5mg daily vs. placebo, except two studies[106, 145] that used Phentermine 15 mg daily for 26-28 weeks. Almost all studies included patients with BMI more than 30 kg/m^2, except for the studies from Asia-Pacific region, which used BMI of 25 kg/m^2 or higher as a cutoff point for obesity. In regards to metabolic

comorbidities (hypertension, diabetes or dyslipidemia), all studies either included subjects without comorbidities or with well-controlled comorbidities: (1) hypertension by taking anti-hypertensive treatment except MAO inhibitors (systolic blood pressure under 140 mmHg and diastolic pressure under 90 mmHg), (2) dyslipidemia, mostly included subjects that had controlled lipids with lifestyle modifications, and (3) diabetes if A1C <7.5.

Demographics and baseline characteristics of the population were similar across the studies. Mean age was ranging between 34 and 46 years, predominantly females, with baseline weight of around 80-110kg, and BMI of around 29-38 kg/m2. Lastly, all the studies encouraged lifestyle interventions that were either a hypocaloric diet (500 kcal/day deficit) and increase exercise by walking 30 min most days of the week in addition to the study medication, or hypocaloric diet with total 1200- 1800 kcal per day along with increase physical activity except one study[147] which included weight watcher intensive program as a lifestyle intervention.

Benefits

Seven[106, 145-147, 149-151] out of eight studies reported weight loss in kilograms (kg) as a continuous outcome, and 3 studies[106, 145, 147] reported on %TBWL. Furthermore, 5 studies[106, 145, 146, 149, 151] reported on the 5%, and 10% TBWL thresholds and no studies reported on 15% TBWL.

In pooled quantitative meta-analysis for %TBWL categorical outcome, there were total of 205 subjects that received phentermine and 202 in the placebo group and 353 subjects receiving phentermine and 343 in the placebo group for weight loss (kg) outcome. Mean Difference (MD) for %TBWL was 3.63% TBWL (95% CI: 4.29, 2.97) in favor of phentermine (Supplementary Figure Phen1. %TBWL). Similarly, there was more weight loss in the treatment group compared to placebo MD 4.74 kg (95% CI: 5.73, 3.75) [Supplementary Figure Phen2. Weight loss (kg)].

As outlined above 5 out of 8 studies were included in TBWL >5% and 10 % and the total number of patients in the pooled meta-analysis was 322 for the phentermine and 313 for the placebo. There were more patients that achieved TBWL >5% and TBWL >10% in the treatment group when compared to placebo (RR 4.12, 95% CI: 3.04, 5.59 and RR 5.10, 95% CI: 3.02, 8.61, respectively) [Supplementary Figure Phen 3. Pooled analysis TBWL ≥5% and Figure Phen 4. Pooled analysis TBWL ≥10%]

Harms

Seven[106, 145-150] out of eight studies reported on discontinuation due to side effects outcome and 5[106, 145-147, 149] of 8 reported on serious adverse events outcome. They all reported on the frequency of the specific side effects too. Given the small sample size and side effects event rate, we look into FAERS report as indirect evidence because in this database the reports are only on harms, but there is no data on how many individuals received the drug. For this purpose, we used a population-based cohort

study using claims data from commercial health insurance in the United States to estimate a denominator.[71`]

The total number of subjects included in the analysis was 1274 in the treatment group and 730 for the placebo. More subjects discontinued the treatment because of side effects in the treatment group compared to the placebo (RR 1.73, 95% CI: 1.36, 2.19) [Supplementary Figure Phen 6. Pooled analysis treatment discontinuations due to AE**]**. The discontinuation rate in the phentermine group was 257/1274 (20%) and 76/730 (10%) for placebo. The most common reason for discontinuation of the study drug was insomnia, irritability, anxiety, headache, nausea and increase in blood pressure and heart rate.

None of the studies described clear definitions for serious adverse events. Two hundred and eighty subjects were included in the analysis for serious side effects that received phentermine and 276 in the placebo group. There were more serious side effects reported in the intervention group, total of 11/280 (4%) events and 3/276 (1%) in the placebo group for RR of 2.44 (95% CI: 0.6, 10.03) [Figure Phen 5. Pooled analysis SAE]. For example: Aronne et al.[145] study reported 1/109 (1%) chest pain. Kim et al. reported 3/28 (10%) severe headache and nausea. In the same study there were 1/28 (3%) dry mouth reports. Lasty in Tsai 2012 study[147] there were 3/ 23 (13%) clinically significant BP elevation events and 1/ 23 (4%) HR elevation events.

When explored the FAERS, the rate of serious adverse events was significantly lower, all the reported side effects were less than 1 in 1000 (Supplementary Table 13. SAE FAERS for Phentermine)

Certainty in Evidence of Effects

The overall certainty in evidence of effects for phentermine were low. See **Supplement Table EP Phentermine for WL** for the full evidence profile. Although there was a concern for attrition bias, in almost all the studies with attrition, it was very similar between the 2 groups. Thus, we did not rate down for risk of bias. In addition, some smaller and older studies did not use blinding, but given the small number of events and since these studies did not contribute much to the overall pooled estimate, we were not concerned about serious risk of bias across the pool of evidence. Additionally, for the categorical outcome (%TBWL) the lower confidence limit crossed the pre-determined threshold of (3Kg or ~3%) MID, for benefit; thus, we rated down for imprecision. Similarly, wide CI and small event numbers for serious adverse events were noted, leading to serious imprecision. Also, there is a serious inconsistency between the studies in the weight loss (kg) outcome, because some studies are showing clear benefits with both upper and lower confidence interval being above the MID, while other studies failed to show clear clinical benefit as the point estimate and the lower confidence limit are below the MID. Serious inconsistency was considered in the >10% TBWL outcome and was possibly due to different intervention duration and follow up time. Therefore, we did sensitivity analysis to explore this and confirmed that the inconsistency is likely due to the difference in intervention duration. Lastly, there was serious indirectness detected in all the outcomes because of the intervention duration. Our PICO question is weight loss treatment for chronic management of which we apriori determined to at least 48 weeks. However, the available data is in 3-6 months. Certainty of evidence for benefits is moderate, because of the highest certainity among benefit

outcomes, but because the certainty for harms was low, the overall certainty of evidence for phentermine is low.

Discussion

Using the evidence to decision framework, the panel examined the evidence for the magnitude of phentermine's desirable and undesirable effects in individuals with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities. Obesity is a chronic condition that warrants long-term management and phentermine's trials were no longer than approximately 3-6 months; hence the low certainity of evidence for the recommendation given that data on long-term use for phentermine monotherapy is lacking (note that phentermine at 7.5-15 mg is approved for long-term use when combined with topiramate in the FDA approved extended release combination). The desirable effect is weight loss presented as a percentage of total body weight loss or a proportion of subjects achieving 5%, 10% or 15% as detailed above. The desirable effect was thought to be of moderate magnitude [-3.63% TBWL (95% CI: -4.29, -2.97) phentermine vs. placebo) crossing the limit of MID. The cumulative treatment discontinuation rate due to adverse events was much higher in the phentermine group compared to the control group (20% vs. 10%: phentermine vs. placebo), mainly because of significant CNS effects (e.g. insomnia, irritability). Serious side effects were rare (1 in 1000 using the FDA Adverse Event Reporting System Database). Altogether the panel judged that the undesirable effects from phentermine were frequent, but not serious and, therefore, the balance between desirable and undesirable effects would probably favor the use of phentermine.

The panel also examined uncertainty and variability about how much different individuals will value desirable and undesirable effects.

The major issue was the trials' duration which extended to 3-6 months and we were unable to extrapolate its use beyond that duration. The long-term safety of phentermine monotherapy is uncertain although as noted previously, it has been studied up to two years in phase 3 clinical trials when combined with topiramate in extended release formulation. There are some observational studies that may be informative regarding long-term safety. One retrospective observational study in approximately 270 patients treated with phentermine continuously for an average of seven years did not show worsening of hemodynamic measures such as blood pressure or heart rate when compared to a group that lost weight without AOMs.[94] Another study using a retrospective review of electronic health record data in nearly 14,000 patients showed superior weight loss and no increased cardiovascular events with long-term use compared to short-term treatment.[93] Due to the lack of high quality data for the efficacy and safety of long-term monotherapy, the panel made a conditional recommendation for the use of phentermine for individuals with obesity or overweight with weight-related comorbidities. It should be noted however, that because of the current understanding of obesity as a chronic metabolic disease and biological realities of weight regulation, many experienced clinicians use phentermine for longer than three months in off-label fashion.[152] Prescribers are advised to confirm with their respective state licensure authorities regarding local laws and regulation. It is advised that if a healthcare professional deems the benefits of long-term use are warranted, they document the

specific benefits, tolerance and side effects, and that the patient is advised regarding off-label use and lack of data supporting this approach.

Special Clinical Considerations

Phentermine hydrochloride is available in capsules at doses of 15 mg, 30 mg, and 37.5 mg, and in tablet formulation at 8 mg and 37.5 mg. The recommended dose is to be taken once daily up to 37.5 mg, preferably earlier in the day to minimize risk of insomnia. In 2016, phentermine 8 mg was approved in the US for dosing up to three times a day, approximately 30 minutes before meals. These tablets are scored so that dosing can be achieved as low as 4 mg. Some have used these low doses on an “as needed basis” before situations with high risk of hedonic food consumption (expert opinion).

One of the most important concerns among prescribers surrounds the cardiovascular safety of phentermine. Perceptions regarding cardiotoxicity with sympathomimetic AOMs can be categorized into two different pathphysiologic domains. The first, relating serotonergic stimulation of myocardial tissues (pulmonary hypertension, valvulopathies), which was addressed above. The second domain reflects adrenergic hemodynamic effects (heart rate, blood pressure) and the potential for adverse cardiovascular outcomes. In pivotal clinical trials for phentermine-topiramate ER, blood pressure generally declined, and there was a very small increase in heart rate, usually at higher doses.[73, 90, 91] (22051941, 21481449, 22158731) Observational data from phentermine monotherapy does not show significant increases in blood pressure or heart rate in treated individuals.[92-94] (34236303, 30900410, 21527891) Currently, there are no large cardiovascular outcome trial data for long-term use of phentermine-topriamate ER or

phentermine monotherapy. Caution is therefore advised and it should be avoided in patients with a history of cardiovascular disease or uncontrolled hypertension. Subjects in phase 3 trials for phentermine-topiramate ER enrolled subjects up to the age of 70 years, but there do not exist high quality data to guide the use of phentermine-topiramate ER in the geriatric population. It should be avoided in patients treated with, or within 14 days, of monoamine oxidase inhibitors.

Due to concerns for arrhythmias and seizures, phentermine should not be used in patients with untreated hyperthyroidism. Commonly reported side effects include constipation, dry mouth, palpitations, insomnia, and irritability.[152](29156182)

Recommendation 8. In adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, the AGA suggests using Diethylpropion (75 mg daily) with lifestyle modifications, compared to lifestyle modifications alone (*conditional recommendation, low certainty*)

KEY IMPLEMENTATION REMARKS

- Diethylpropion monotherapy is approved by the FDA for short-term use (12 weeks)
- Given the chronic nature of weight management, many practitioners use diethylpropion longer than 12 weeks in an off-label fashion.
- Diethylpropion should be avoided in patients with a history of, or strong risk factors for, cardiovascular disease.
- Blood pressure and heart rate should be monitored periodically while taking diethylpropion.

Background

The FDA approved diethylpropion in 1959 for the treatment of obesity adjunctively with caloric restriction and increased physical activity.[153] It is approved for short-term use in patients that have not responded adequately to lifestyle interventions alone. Similar to other sympathomimetic amines, it has potential for central nervous system stimulation, but it is chemically modified to limit these symptoms as well as other adrenergic effects.[141] Like other amphetamine derivative AOMs, diethylpropion was approved by the FDA when obesity was considered a curable condition. In other words, it was

thought that weight loss was sustainable in the absence of continued treatment and studies evaluating their efficacy and safety were designed based on this paradigm.

Summary of the Evidence

We identified 6 RCT[154-159] that were reporting on diethylpropion vs. placebo in treatment for obesity. There was just one study[156] with long-term treatment and follow up > 52 weeks, 2 studies[154, 157] used diethylpropion 75 mg divided in 3 doses for 24 weeks and all other identified studies[155, 158, 159] were with short-term treatment, 12 weeks of diethylpropion in 3 doses of 25mg vs. placebo. Older studies did not report on the BMI as a inclusion criterion, however, the 3 newer studies[154, 156, 157] included subjects with BMI more than 30 kg/m2. None of the studies included subjects with diabetes, or dyslipidemia, and some studies have included well-controlled hypertension (blood pressure <160/100 mmHg).

Demographics and baseline characteristics of the population were similar across the studies. Mean age was ranging between 34 and 38 years, predominantly females, with baseline weight of around 80-95kg, and BMI of around 34 kg/m2. Lastly, all the studies encouraged lifestyle interventions that were either hypocaloric diet (500-600 kcal/day deficit) and increase exercise by walking 30 min most days of the week in addition to the study medication, or hypocaloric diet with total 1000- 1200 kcal per day along with increase physical activity.

Benefits

All 6 studies[154-159] reported on weight loss in kilograms (kg) as a continuous outcome, and 4[154-156, 159] of them reported on %TBWL. Furthermore, 3 studies[154, 156, 157] reported on the 5%, and 10% TBWL and no studies reported on 15% TBWL.

In pooled quantitative meta-analysis for %TBWL categorical outcome, there were total of 119 subjects that received diethylpropion and 108 in the placebo group. For weight loss (kg) outcome there were 209 subjects receiving diethylpropion and 199 in the placebo group. Mean Difference (MD) for %TBWL was 5.36% TBWL (95% CI: 7.23, 3.50) in favor of diethylpropion [Figure Die1. %TBWL]. Similarly, there was more weight loss in kg in the treatment group compared to placebo group: MD -4.74 kg (95% CI: -6.40, -3.08) [Figure Die2. Weight loss (kg)].

Three studies that reported on TBWL >5% and 10 % included total of 143 subjects for the diethylpropion and 139 for the placebo group. There were more patients that achieve TBWL >5% and TBWL >10% in the treatment group when compared to placebo: RR 3.51 (95% CI: 1.50, 8.18) (Supplementary Figure Die 3. Pooled analysis TBWL ≥5%) and RR 14.48 (95% CI: 5.13, 40.87) [Figure Die 4. Pooled analysis TBWL ≥10%] respectively.

Harms

Five[154, 156-159] out of six studies reported on harms and those studies only reported on discontinuation due to adverse events outcome and there were no SAE reported in any of the studies. Given the small sample size and side effects event rate, we queried the large FAERS database[61] as indirect evidence as the reports are only on harms and there is no data on how many individuals receive the drug. For the purpose of this we used a population-based cohort study using claims data from commercial health insurances in the United States.[71]

The total number of subjects included in analysis for treatment discontinuation due to adverse events was 187 in the treatment group and 180 for the placebo. More subjects discontinued the treatment because of adverse events in the treatment group compared to the placebo: RR 1.37 (95% CI: 0.51, 3.66) [Figure Die 5. Pooled analysis treatment discontinuations due to AE]. The discontinuation rate in the diethylpropion group was 10/187 (5%) and 6/180 (3%) for placebo. The most common reason for discontinuation of the study drug was insomnia, irritability, or anxiety.

None of the studies described clear definitions for serious adverse events nor reported any SAE. Some studies reported on all adverse events, for example: Suplicy et al.[156], reported on most common side effects in the intervention group were constipation (21.4%), insomnia (7.1%), anxiety (32.1%) and irritability (28.6 %).

When exploring the FDA Adverse Event Reporting System Database the rate of serious adverse events was significantly lower, all rates of the reported side effects were same with the phentermine SAE and all less than 1 in 1000[61, 71].

Certainty in Evidence of Effects

The overall certainty in evidence of effects for diethylpropion was low. See Supplementary Table 14. Evidence Profile for Diethylpropion. There was some concern for serious risk of bias because most of the older studies did not perform ITT analysis by using last observation carried forward (LOCF) for continuous outcomes. Benefits data was derived from the subjects who completed the study, and this probably introduced bias and overestimated the effect of the intervention. Additionally, it is unclear how the randomization and allocation was done in most of the studies. Thus, we decided to rate down once for risk of bias for continuous outcomes. Furthermore, the minimal important difference (MID) or clinically important threshold as discussed before was determined to be 3kg (or ~3%). For the categorical outcome, weight loss (kg), there was serious inconsistency because some studies showed clear benefits with both upper and lower confidence intervals being above the MID, while other studies failed to show clear clinical benefit as the point estimate and the lower confidence limit were below the MID. In regard to imprecision, almost all the outcomes were imprecise due to small sample size and very small number of events. Lastly, we found serious indirectness in all the outcomes because of the intervention duration. Our PICO question is weight loss treatment for a chronic disease, which was determined to have a minimum treatment duration of 48 weeks, apriori. However, the available data is mostly 3-6 months. In summary, the certainty of the evidence for benefits is low as determined by the highest certainty among benefits, and certainty for harms was low as well, thus, the overall certainty of evidence for diethylpropion was low.

Discussion

For the intervention of diethylpropion, the desirable and undesirable effects in individuals with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities was discussed with the entire guideline panel. Given that obesity is a chronic condition that warrants long-term management, and trials were conducted for only 3-12 months, the evidence for the recommendation was deemed low due to lack of long-term data. The desirable effect was thought to be of moderate magnitude [5.36% TBWL (95% CI: 7.23, 3.50) in favor of diethylpropion vs. placebo]. The cumulative treatment discontinuation rate due to adverse events was higher in the diethylpropion group (5% vs. 3% in the placebo group), mainly because of significant CNS effects (e.g. insomnia, irritability). Serious adverse events were rare (1 in 1000 using the FDA Adverse Event Reporting System Database). Altogether the panel judged that the undesirable effects from diethylpropion were infrequent, not serious and therefore, the balance between desirable and undesirable effects would probably favor the use of diethylpropion.
The panel also examined uncertainty and variability about how much different individuals will value desirable and undesirable effects.
The major issue was trial duration of only 3-6 months and we were unable to extrapolate its use beyond that period. Therefore, the panel made a conditional recommendation for the use of diethylpropion in individuals with obesity or overweight with weight-related comorbidities.

Like phentermine and other amphetamine derivatives, there was concern in the literature for risk of pulmonary hypertension with diethylpropion exposure. Although a

case-control study suggested a higher incidence of pulmonary hypertension associated with diethylpropion use , most of these affected patients also used other anorectics, including fenfluramine.[160] Similar to phentermine, there are concerns regarding stimulant properties, cardiotoxicity, and potential for abuse and dependence. However, as previously described, a chemical modification of the active molecule results in less potential for CNS stimulation and blood pressure elevation.[141]

Diethylpropion is classified as a schedule IV controlled substance by the DEA based on concerns for abuse and dependence. Many prescribers who use AOMs off-label use diethylpropion longer than 12 weeks as well.[161]

Special Clinical Considerations

Diethylpropion is available in doses of 25 mg immediate release tablets or 75 mg ER tablets, to use three times a day before meals or once in the morning daily, respectively. Due to concerns for arrhythmias and seizures, phentermine should not be used in patients with untreated hyperthyroidism. Commonly reported side effects include constipation, dry mouth, insomnia, headache, and irritability.[154]

Recommendation 9. In adults with BMI between 25 to 40 kg/m^2, the AGA recommends using Gelesis100 Oral Superabsorbent Hydrogel only in the context of a clinical trial (*knowledge gap*)

Background

In contrast to the prior pharmacological agents, FDA identifies Gelesis100 as a generic type of device similar toingestible balloons that are delivered iin the form of a “pill.” Gelesis-100 is a capsule containing absorbant hydrogel spheres (made of modified celluose and citric acid) that once ingested create a transient space occupying three dimensional matrix (composed of cellulose, citric acid, water and food material) in the stomach, as compared to intragastric ballons which remain in the stomach until removal. The three dimensional matrix passes through the luminal gastrointestinal tract until reaching the colon where it is degraded. The water component of the matrix is reabsorbed, while other components are excreted in the stool. The mechanism of action is enhanced satiety and reduced caloric intake resulting from increased gastric volume generated from the three-dimensional matrix. Gelesis100 is approved for weight management in adults with overweight and obesity with a BMI of 25 - 40 kg/m^2 , in conjunction with a calorie reduced diet and physical exercise. The recommended dosing is three (3) capsules (2.25 g/dose) with water before both lunch and dinner. (https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN180060.pdf)

Summary of the Evidence

One multicenter, double blind RCT with 24 weeks of follow up was found to inform this PICO and recommendation.[162] Mean BMI, weight, waist circumference and age were similar between both groups and in the intervention arm was 33.5 kg/m2, 97.6 kg, 108.3 cm, and 48.2 years old. Lifestyle intervention included 300 kcal per day reduction and daily moderate intensity exercise.

Benefits

A total of 223 participants in the intervention group versus 213 participants in the lifestyle intervention alone group informed this recommendation. The intervention group had a MD 2.02% more %TBWL (95 CI 0.96 to 3.08) than the control group. Higher proportion of patients were able to achieve 5% TBWL (58.3% vs 42.3%; RR 1.38, 95 CI 1.14-1.67) and 10% (27.4% vs 15%; RR 1.82; 95 CI 1.24-2.67) TBWL in the intervention group.

Harms

The treatment discontinuation rate was 3.6% vs 3.3% in the intervention arm and control arm, respectively (RR 1.09, 95 CI 0.40-2.96). Only one serious adverse event was reported in the lifestyle intervention group (0/223 vs 1/213; RR 0.32, 95 CI 0.01-7.77).

Certainty in Evidence of Effects

The overall certainty in evidence of effects for carboxymethylcellulose and citric acid hydrogel was low. See Supplementary Table 16. Evidence Profile for Gelesis100 for the full evidence profile. We found very serious imprecision for the harm outcomes mainly due to low event rate and confidence interval crossing unity. Dichotomous weight loss outcomes were found to have serious imprecision due to low event rate. Moreover, we noted very serious imprecision for the outcome of %TBWL as the pooled estimate did

not meet the pre-determined minimally important threshold of 3% and wide confidence interval.

Discussion

The panel was not able to make a recommendation for the use of Gelesis100 oral superabsorbent hydrogel in adults with BMI between 25 to 40 kg/m^2 because there was only a single RCT. The study had a small weight loss (only 2.02% placebo subtracted mean weight loss) over 24 weeks without a 1 year follow up duration.[162] One interesting finding was that in categorical analyses of weight loss, subjects with evidence of insulin resistance (prediabetes or T2DM) seemed to have a more robust response to treatment compared to those with normoglycemia at baseline. Since this observation is contrary to most studies with other interventions, showing inferior weight loss in individuals with diabetes, it merits further confirmation and investigation. Given the scarcity of the data, the panel recommended to use this adjunct therapy for the treatment of obesity only in the context of a randomized clinical trial.

LIMITATIONS and EVIDENCE GAPS

Effective pharmacological interventions for obesity have historically been challenging to achieve. The reasons are complex and include both behavioral and biologic factors, which are difficult to separate from each other. Physiologically, metabolic adaptations in response to energy deficits and weight reduction defend against sustained loss of fat mass. In the CNS, there are redundant pathways that seem to favor a state of anabolic and orexigenic balance. Hence, efforts to develop pharmaceutical agents that can

overcome these strong neurobiologic defenses while limiting adverse side effects has proven to be somewhat elusive. Our systematic review and meta-analysis showed that, even with the best current therapies has a % TBWL (in addition to lifestyle intervention) of about 15% (semaglutide).

While these results are considered quite successful, one major challenge remains bridging the gap between evidence-based expectations and patients' desired weight loss outcomes. Foster et al.[163] reported that patients may consider success only if their weight loss approaches that of bariatric surgery results. Prescribers will therefore not only need to have an understanding of these realities, but be prepared to properly counsel patients to maintain adherence to various treatments, including pharmacotherapy. Healthcare professionals should help the patient focus on health related improvements and quality of life benefits, rather than the absolute number on the scale.

Another major obstacle to large scale implementation of available therapies is access. Because of cost, variable insurance coverage, inconsistent acceptance by some healthcare professionals to treating obesity as a biologic disease, and racial and minority disparities, many individuals who may benefit from treatment may never have the opportunity to receive adequate therapy. Healthcare disparities are compounded by the fact that groups of lower socioeconomic status tend to have higher prevalence of obesity and chronic disease. Burdensome insurance authorization requirements and

visits to monitor for adverse effects may further dissuade some to utilize some of these agents.

WHAT DO OTHER GUIDELINES SAY?

The present guidelines are similar with previous published recommendations on the management of overweight and obesity. Naturally, given the rapid advances in this field, particularly with anti-obesity pharmacotherapy, this report bridges some gaps in the contemporary literature. “Guidelines for Managing Overweight and Obesity in Adults”, supported by the National Heart, Lung, and Blood Institute (NHLBI), published in 2013 by The Obesity Society (TOS) with the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines addressed lifestyle intervention and bariatric surgery, without much guidance for use of AOMs, due to the fact that most of the newer FDA-approved medications had not come to market yet.[30] The United States Preventive Services Task Force (USPSTF) published in 2018 its most recent Recommendation Statement, “Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults”, but focused on guidance for intense lifestyle interventions.[164] In 2013, the American Academy of Family Physicians produced a document titled “Diagnosis and Management of Obesity”, which touched on the use of the most recent agents, phentermine-topiramate ER and lorcaserin, which has since been withdrawn from the market[165] (AAFP et al.). Naltrexone-bupropion ER and GLP1 receptor agonists had not yet been approved for obesity. Likewise, over the past decade, the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), the Obesity Medicine Association (OMA), the Endocrine Society, and Obesity Canada with The Canadian Association of Bariatric

Physicians and Surgeons have all provided guidance to healthcare professionals for many aspects of obesity care, including pharmacotherapy.[166-168] The American Gastroenterological Association (AGA) now further advances evidence-based recommendations with this guideline based on a systematic review and meta-analysis using GRADE methodology of currently available AOMs to help the millions of people suffering with obesity and its complications. Since the field is rapidly evolving with newer and more effective agents just around the corner, the authors look forward to updating this document as more data comes to light.

IMPLEMENTATION CONSIDERATIONS

This guidelines is intended for the Gastroenterology community to be familiar and implement pharmacological therapies in people with obesity. Without minimizing the key role of lifestyle interventions (diet, exercise, cognitive-behavioral therapy), these medications will expand the toolkit for the practicing gastroenterologist to address the obesity pandemic. Considering out-of-pocket expenses for patients, insurance plans, side effect profiles and patient's preferences (e.g. oral vs. Injectable), treatment of obesity highlights the paramount importance of the patient–physician relationship, in particular when the expected weight-loss is not achieved. To help the Gastroenterological community the guideline and clinical decision support tool are available on the AGA website (www.gastro.org) free of cost

PLANS FOR UPDATING THIS GUIDELINE

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. This document will be updated when major new research is published. The need for update will be determined no later than Summer of 2025 and, if appropriate, we will provide rapid Guidance updates to incoporate updated recommendations as new evidence without duplicating or created a new full guideline.

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