0.70; 95% CI, 0.49–1.00; $P = .047$), and the use of interpreters was independently associated with increased frequency of AOM prescriptions.[152] Because of cost, variable insurance coverage, inconsistent acceptance of some health care professionals to treat 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. Burdensome insurance authorization requirements and visits to monitor for adverse effects may further dissuade some from using these agents. Finally, the participants in the randomized clinical trials reported in this AGA guideline are predominantly non-Hispanic White patients. Future randomized clinical trials addressing the use of AOMs should include a higher proportion of other ethnic groups to assess whether the response to AOM therapy is universal and to further support reimbursement from insurance companies to curb the obesity pandemic.[153]

As obesity is both a disease and a risk factor for other chronic illnesses, it is paramount to continue to assess the effect of weight loss using pharmacological interventions on important outcomes, such as cardiovascular events, nonalcoholic fatty liver disease, mortality, and cancer incidence and treatment response, among others. Although weight and BMI are the measures patients and clinicians use to assess efficacy in the clinical setting, important benefits for health risks, longevity, quality of life, and cost-effectiveness are critical measures with current and emerging treatments. The Look AHEAD trial revealed that intense lifestyle intervention may not be enough to reduce the risk of adverse cardiovascular outcomes.[154] Results of the SELECT Trial will further inform prescribers, patients, and payers regarding cardiovascular benefits of greater weight loss from semaglutide 2.4 mg.[155] Given the challenges of conducting large long-term RCTs to assess important health outcomes, these knowledge gaps will need to be filled by a combination of RCTs, well-designed observational studies, and real-world data.

Likewise, because of a lack of comparative data, prescribers are left to choose among available pharmacological therapies with limited guidance on hierarchical decision making. Head-to-head trials with AOMs are limited to the comparison of liraglutide vs semaglutide.[33] A systematic review suggested superiority of phentermine-topiramate and liraglutide 3.0 mg over other AOMs, but this was before the emergence of more effective therapies now and in the pipelines.[156] Moreover, given the variability in response to any weight loss intervention, establishing response to a given AOM for an individual patient has largely required a trial-and-error approach. Other clinical factors, such as comorbidities, contraindications, historical response, cost, patient preference, and potential drug–drug interactions, are currently the most important contributors to decision making. Phenotype matching to specific agents or class of drugs has shown some promising results.[157] More research is needed to better understand whether and how pharmacogenomic predictors may further enhance weight loss effects beyond current strategies.[158]

Other approaches to optimize weight loss and health outcomes involves combining therapeutic agents and modalities, similar to other conditions, such as cancer, diabetes, or cardiovascular disease. Like other chronic illnesses commonly encountered in the clinic, such as T2DM or hypertension, it would seem logical that a combination of different AOMs may be effective for optimizing outcomes. Although this practice is not uncommon among obesity medicine specialists, the literature is extremely scarce with respect to guidance for the general practitioner beyond the formulated FDA-approved options of phentermine-topiramate ER and naltrexone-bupropion ER.[159,160]

Another common practice is the use of AOMs in patients who have had suboptimal results after bariatric and metabolic surgery. Studies have demonstrated effectiveness for orlistat, phentermine-topiramate ER, topiramate (off-label use), phentermine, naltrexone-bupropion ER, and liraglutide.[161] To date, no large, prospective, long-term RCT has been performed with any AOM specifically in a population with a history of bariatric surgery. There are minimal data on the weight loss effect of combining AOMs with intragastric balloons and other endoscopic bariatric and metabolic therapies. Using liraglutide adjunctively with intragastric balloons may enhance weight loss, but the analyses performed had study designs with a high risk for bias.[162,163] More research is needed to assess the combination of AOMs and various endoscopic bariatric procedures, especially in the era of more effective pharmacotherapy.

Finally, the present review evaluated current FDA-approved AOMs. At the time of publication, tirzepatide, a novel co-agonist of GLP-1 and glucose-dependent insulinotropic polypeptide receptors, was recently approved for the treatment of T2DM, with mean weight loss results of 5.5 kg more than semaglutide 1.0 mg at 40 weeks of treatment in subjects with T2DM.[164] Although not yet approved for the treatment of obesity, results from a phase 3 clinical trial in participants without T2DM, at the highest dose of tirzepatide 15 mg weekly, demonstrated mean weight loss of 21% after 72 weeks of treatment, and nearly 40% of subjects on treatment at the maximum dose demonstrated $\geq$25% TBWL.[165]

What Do Other Guidelines Say?

The present guidelines are similar to recommendations on the management of overweight and obesity published previously. 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, published in 2013 by The Obesity Society with the American College of Cardiology/American Heart Association 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.[166] In 2018, the US Preventive Services Task Force published its most recent Recommendation Statement, "Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and