Obesity

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COMMENTARY

TOS/OMA/OAC Expert Guidance Statement on Obesity Pharmacotherapy: A Humbling Call to Action

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In 2013, obesity stepped into a momentous spotlight: the American Medical Association declared obesity a disease, and in the same year, after sponsorship by the National Institutes of Health, multiple professional societies published guidelines on obesity care, a 5-year effort that included recommendations on dietary intervention, lifestyle intervention, and bariatric surgery but was silent on obesity medications due to lack of evidence [1]. Over the subsequent decades, several advancements in the treatment of obesity have shifted public understanding, expectations, and goals. Today, the leading scientific professional organization. The Obesity Society (TOS) and its clinical and patient advocacy partners Obesity Medicine Association (OMA) and Obesity Action Coalition (OAC) share with us an evidence-based overview of obesity pharmacotherapy—its strengths and weaknesses, highlights and blind spots, and current achievements and future potentials [2].

The TOS/OMA/OAC Expert Guidance Statement is distinct in its purpose, with a clear goal of avoiding redundancy with other guidelines and consensus statements [3–6]. The general prescriber will *not* find user-friendly algorithms in this document as such resources have already been expertly developed elsewhere. Instead, this statement approaches the evidence base for obesity pharmacotherapy from a radically different perspective, with the pioneering inclusion of a patient advocacy group, to ask if and how current literature is supporting patients' goals rather than synthesize the literature to reiterate values held by the traditional medical system. This was achieved by partnership with Replica Communications, a strategic research and knowledge mobilization firm. The guidance is also a remarkable achievement in efficiency—it was accomplished in less than a year, thanks to support by Epistemonikos Foundation, a health research methodology nonprofit based in Chile, which used artificial intelligence (AI) to generate the evidence tables that were then reviewed by expert panelists to draft and finalize the recommendations.

With patient-centered outcomes in mind, the committee delineated the priority of outcomes based on patients' inputs and their relative importance (Expert Guidance Statement Table 3). While some outcomes were expectedly highly prioritized (e.g., mortality), others represent a growing understanding of how patient-centered outcomes encompass more than obesity-related complications or diseases (ORCDs): uniquely, quality of life was deemed to be equally important as morbidity and mortality. In contrast to prior guidelines with similar methodology [4], weight loss was not identified as a "critical" outcome, reflecting the evolution of patients' goals to access benefits of obesity treatment beyond weight loss.

Fifteen questions around these outcomes of interest were developed by the panel representing scientists and clinicians from all three organizations and examined with meta-analyses. Epistemonikos conducted systematic reviews using relevant articles sourced from regularly updated databases (e.g., PubMed, Embase), and the authors reviewed and judged two parallel components of each outcome: (1) the magnitude of benefit and harm as well as (2) the certainty of evidence, based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system approach. While the evidence synthesis team provided referential decision thresholds to assess the magnitude of benefits and harms based on "generic threshold indices," little attention was given to how these thresholds may or may not be applicable to the outcomes of interest. The certainty of evidence in the GRADE system is designated as high, moderate, low, or very low, and these thresholds are based on the presence or absence of bias, inconsistent results, imprecision (e.g., small number of studies, small sample sizes, wide confidence intervals),

or indirect evidence. Everyone naturally engages in a similar judgment of "certainty of evidence" when we examine reviews before we buy a product. Just as a lone 5-star review prevents us from strongly recommending a product to a friend, low certainty evidence prevents guideline committees from providing "strong recommendations."

The final recommendations reflect how the modified GRADE system compelled stringent judgment, reinforcing widespread consensus in some cases while raising questions in others (Expert Guidance Statement Table 4). We summarize these and the factors driving strength of the recommendation in Table 1. Several strong recommendations will feel familiar to the broad medical and scientific communities—for example, semaglutide and tirzepatide are strongly recommended for the treatment of overweight/obesity, foreshadowing perhaps their forthcoming designation as first-line therapies. This guidance potentially opens another crucial frontier in its conditional recommendation for GLP-1 or GLP-1/GIP receptor agonists for the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) *or* metabolic dysfunction-associated steatotic hepatitis (MASH). Finally, even a conditional recommendation that *all* obesity medications benefit type 2 diabetes (T2D) is remarkable, as it underpins the widespread consensus to treat obesity as a root cause of T2D while implicitly acknowledging that certain obesity pharmacotherapies are more beneficial than others—an already well-established standard [7].

Other recommendations may be surprising in their conditional statuses. The conditional recommendation for liraglutide, for example, contrasts with the strong recommendation for naltrexone/bupropion and exposes limitations in application or interpretation of the GRADE system (e.g., included studies on bupropion/naltrexone were of 16–56 weeks duration vs. studies on liraglutide were of 6–56 weeks duration, effectively increasing heterogeneity and imprecision of liraglutide's estimated benefit). This provides a lesson for designing methodology for future similar efforts; more thought can be put into defining the criteria for appropriate study selection. A few other points of surprise may be seen in conditional recommendations for GLP-1s in obstructive sleep apnea (OSA) and osteoarthritis, but both analyses were limited by the sparse number of randomized controlled trials (RCTs) eligible for inclusion. Notably, this guidance does not state any recommendations *against* any of the examined interventions, unlike other country-specific guidelines [8]. Even phentermine, which lacks the FDA approval for long-term weight management, was bolstered by enough short-term data (12–28 weeks) to warrant a conditional recommendation.

One recommendation should be singled out for comment—the conditional recommendation for semaglutide for adults "with a history of myocardial infarction, stroke, or symptomatic peripheral vascular disease (conditional recommendation for the intervention; low certainty of the evidence)." This rests on the SELECT trial, which demonstrated a 20% relative risk reduction and a 2.5% absolute risk reduction in the composite endpoint of nonfatal heart attack, stroke, or sudden cardiovascular death in individuals with overweight and obesity without diabetes but with established cardiovascular disease (CVD) [9]. Despite participants experiencing weight loss, SELECT was not a dedicated weight loss study. There was no designed weight loss intervention in SELECT. This is important to recognize, because the evidence supports that weight loss was not the primary mediator of the cardiovascular risk reduction in SELECT [10], and it is likely that, going forward, use of semaglutide and other GLP-1 receptor agonists for secondary prevention may not require a body mass index criterion. We question the panelists' reliance on statistical judgment and not applying their own in this instance to produce a statement that is clear in recommending semaglutide for cardiovascular risk reduction and separating this from a weight loss effort. Finally, the designation of "low certainty of evidence" defies logic and again reveals an inherent limitation to the GRADE methodology, in which a large-scale RCT that did not statistically power mortality as its primary endpoint is judged by this metric; to require more than one SELECT, a rigorously designed study executed with precision that included 17,604 participants from > 50 countries, is both impractical and unnecessary. Such statistical methods remind all clinicians to recognize the limits of clinical trials to deliver on these endpoints. Mortality endpoints are very much determined by the population under study. It is meaningless to apply statements about mortality to all patients age 18–100 when we only assess these endpoints in high-risk populations. Because our patients present in any and all stages of health and illness, clinicians are wise to remember how guidance statements provide recommendations or suggestions, not decisions, and the overview of evidence may or may not be applicable to the individual patient in front of them.

While the variability in certainties of evidence gives us pause, it also reminds us that certainty does not necessarily inform effect size. In other words, just because a product has a single 5-star review does not mean it is not a 5-star product; it only means that it has not been reviewed enough. Several recommendations were found to be conditional based on relatively few "reviews" but do not negate the gold-standard evidence that established them as FDA-approved therapies (e.g., tirzepatide for OSA, semaglutide 2.4 mg for CVD). What appears to be a divergence actually reflects how regulatory approval processes, clinical evidence hierarchies, and guidelines recommendations serve fundamentally different purposes. In this respect, clinicians may find that this guidance does not change their current practices but enables them to engage in more nuanced conversations with patients as to where the evidence is secure and where it could be improved.

The TOS/OMA/OAC Expert Guidance Statement is an honest assessment of how patients' goals and scientific evidence are aligned and where opportunities remain. The methodology highlights the professional societies' intentional reprioritization of historical objectives—weight loss is no longer a critically important outcome and has been supplanted by a focus on morbidity, mortality, and quality of life—joining the emerging consensus among international partners [5, 11, 12]. This consensus across leading professional organizations is a powerful message to all health care stakeholders to, simply put, prioritize the patient. By acknowledging the variable certainties of evidence, these recommendations are a directive to expand resources for patient-centered research that incorporates a broad range of health metrics—medical, functional, and psychosocial—on a longitudinal and sustainable scale. They also make the case for continued communication with patients about the limits of clinical research, particularly around mortality and how to

TABLE 1 | A guide to the TOS/OMA/OAC Expert Guidance Statement. [Color table can be viewed at wileyonlinelibrary.com]

	FDA approval(s)	Recommendation	Factors affecting direction of recommendation[a]	Factors affecting strength of recommendation[a]
OMs				
Orlistat	Obesity or overweight with ≥1 ORCD	Conditional recommendation to use OM to treat obesity	Variable value to patients, poor acceptability (e.g., GI side effects), high feasibility	Imprecision; 44 RCTs of 4–156 weeks duration
Bupropion-naltrexone	Obesity or overweight with ≥1 ORCD	Strong recommendation to use OM to treat obesity	Variable value to patients, high feasibility	
Phentermine	Obesity or overweight with ≥1 ORCD for short term	Conditional recommendation to use OM to treat obesity	Moderate acceptability and feasibility as a controlled substance, highly cost-effective	Imprecision, indirect evidence; few 4 RCTs of 12–28 weeks duration
Phentermine-topiramate	Obesity or overweight with ≥1 ORCD	Conditional recommendation to use OM to treat obesity	High value to patients, moderate acceptability and feasibility as a controlled substance	Imprecision; 5 RCTs of heterogeneous populations and of 28–56 weeks duration
Liraglutide	Obesity or overweight with ≥1 ORCD, T2D, CVD and T2D	Conditional recommendation to use OM to treat obesity	Variable value, acceptability, and feasibility to patients; imprecision of RCTs for critical outcomes	Imprecision; 14 RCTs of 6–56 weeks duration, few examining critical outcomes
Semaglutide	Obesity or overweight with ≥1 ORCD, T2D, CVD and T2D, CVD and obesity, MASH	Strong recommendation to use OM to treat obesity	High value to patients, variable acceptability given injectable administration route, moderate feasibility, high resource requirements	
Tirzepatide	Obesity or overweight with ≥1 ORCD, T2D, moderate-to-severe OSA	Strong recommendation to use OM to treat obesity	High value to patients, variable acceptability given injectable administration route, moderate feasibility, high resource requirements	
Setmelanotide	Deficiencies in POMC, PCSK1, LEPR; BBS	Strong recommendation to use OM to treat obesity	Variable value to patients, high acceptability, moderate feasibility, high resource requirements	
Obesity-related complications and diseases				
OSA	Tirzepatide	Conditional recommendation to use GLP-1 or GLP-1/GIP RAs to treat OSA	High value to patients, favorable cost-effectiveness; few and heterogeneous RCTs	Imprecision; few (3) and heterogeneous (2 liraglutide, 1 tirzepatide) RCTs of 24–52 weeks duration
HFpEF	None	Conditional recommendation to use GLP-1 or GLP-1/GIP RAs to treat HFpEF	High value to patients, high acceptability, moderate feasibility	Imprecision; few (3) and heterogeneous (2 semaglutide, 1 tirzepatide) RCTs of 52–236 weeks duration
MASLD or MASH	Semaglutide (MASH only)	Conditional recommendation to use GLP-1 RAs to treat MASLD or MASH	High value to patients, high acceptability, moderate feasibility	Imprecision; 7 RCTs with heterogeneous patient populations

(Continues)

TABLE 1 | (Continued)

Obesity-related complications and diseases				
Osteoarthritis	None	Conditional recommendation to use GLP-1 RAs to treat osteoarthritis	High value to patients, high acceptability, moderate feasibility	Imprecision; few (2) and heterogeneous (1 liraglutide, 1 semaglutide) RCTs
CVD	Liraglutide in T2D Semaglutide in T2D or obesity	Conditional recommendation to use semaglutide to treat CVD	High value to patients, high acceptability, moderate feasibility	Imprecision; 1 RCT; mortality was not powered as primary endpoint
Type 2 diabetes	Liraglutide, semaglutide, tirzepatide	Conditional recommendation to use OMs to treat T2D	High value to patients, high acceptability, variable feasibility	Imprecision; heterogeneous RCTs (11 orlistat, 1 bupropion-naltrexone, 1 phentermine-topiramate, 2 liraglutide, 2 semaglutide, 1 tirzepatide)

Lifestyle intervention and OM			
PICO question	**Recommendation**	**Factors affecting direction of recommendation[a]**	**Factors affecting strength of recommendation[a]**
In adults 18 years of age or older with overweight or obesity who are engaged in medical obesity treatment (OM), should structured physical activity interventions be used compared to self-directed physical activity intervention or usual care?	Insufficient evidence to issue a recommendation		
In adults 18 years of age or older with overweight or obesity who are engaged in medical obesity treatment (OM), should protein intake guided nutritional interventions be used compared to unguided protein intake nutritional interventions to minimize the loss of lean mass relative to fat mass?	Insufficient evidence to issue a recommendation		
In adults 18 years of age or older with overweight or obesity who are engaged in medical obesity treatment using semaglutide or tirzepatide, should concurrent IBT be used compared to no concurrent IBT?	Insufficient evidence to issue a recommendation		

Abbreviations: BBS, Bardet–Biedl Syndrome; CVD, cardiovascular disease; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; HFpEF, heart failure with preserved ejection fracture; IBT, intensive behavioral therapy; LEPR, leptin receptor deficiency; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; OM, obesity medication; ORCD, obesity-related complications and diseases; OSA, obstructive sleep apnea; PCSK1, proprotein convertase subtilisin/kexin type 1; PICO, Patient/Population Intervention Comparison Outcome; POMC, pro-opiomelanocortin; RA, receptor agonist; RCT, randomized controlled trial; T2D, type 2 diabetes.

[a]Factors affecting direction of recommendation include value, acceptability, feasibility, resources required, and cost-effectiveness, and factors affecting strength of recommendation include imprecision, bias, indirect evidence, and inconsistent results; selected factors are highlighted here based on guidance Appendices 1–4.

best interpret clinical research results. Overall, the TOS/OMA/OAC Expert Guidance Statement implores all of us to reexamine goals that are most relevant to patients, aim to fill these literature gaps, and continue truthful and humbling conversations with patients on where the evidence-based medicine is today and where we are aiming for tomorrow.

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Conflicts of Interest

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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