AGA CLINICAL PRACTICE GUIDELINE ON PHARMACOLOGICAL INTERVENTIONS FOR MANAGEMENT OF OBESITY

Supplement Table 1. Problem, Intervention, Comparison, Outcome (PICO) question for this Guideline

Problem	Adults with BMI ≥ 30 kg/m^2, or ≥ 27 kg/m^2 and weight-related comorbidities, who have had inadequate response to lifestyle interventions
Intervention	FDA-approved medications to treat obesity
Comparison	Lifestyle interventions alone
Outcome	Benefits: ✓ % Total Body Weight loss (%TBWL) ✓ >5% Total Body Weight loss ✓ >10% Total Body Weight loss Harms: ✓ Treatment discontinuation due to adverse events ✓ Serious Adverse events Minimal important difference Smallest change in the outcome that would be identified as clinically important was set at -3% TBWL between groups

Abbreviations: Total Body Weight loss (%TBWL)

Supplementary Table 2. Evidence Profile for Semaglutide

Question: Semaglutide plus lifestyle intervention compared to lifestyle intervention alone for management of obesity

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Semaglutide plus lifestyle intervention	lifestyle intervention alone	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Total body weight loss (%TBWL) (assessed with: Percentage %)												
8	randomised trials	not serious	not serious[a, b]	not serious	not serious	none	2658	1694	-	MD **10.76 more (8.73 more to 12.8 more)**	⊕⊕⊕⊕ High	CRITICAL
≥5% TBWL												
6	randomised trials	not serious	not serious[a, c]	not serious	not serious	none	2094/2543 (82.3%)	485/1583 (30.6%)	**RR 2.74 (2.21 to 3.40)**	**533 more per 1,000 (from 371 more to 735 more)**	⊕⊕⊕⊕ High	CRITICAL
≥10% TBWL												
6	randomised trials	not serious	not serious[a, c]	not serious	not serious	none	1651/2543 (64.9%)	195/1583 (12.3%)	**RR 5.25 (3.61 to 7.64)**	**524 more per 1,000 (from 322 more to 818 more)**	⊕⊕⊕⊕ High	CRITICAL
≥15% TBWL												
6	randomised trials	not serious	not serious[a, c]	not serious	not serious	none	1172/2543 (46.1%)	86/1583 (5.4%)	**RR 7.82 (5.19 to 11.76)**	**371 more per 1,000 (from 228 more to 585 more)**	⊕⊕⊕⊕ High	CRITICAL
Weight loss (assessed with kilograms)												
6	randomised	not serious	not serious[a, b]	not serious	not serious	none	2544	1584	-	MD **10.81 higher (8.19 higher to**	⊕⊕⊕⊕	IMPORTANT

	trials									**13.43 higher)**	High	
Serious Adverse Events (SAE)												
8	randomised trials	not serious	not serious	not serious	serious[d]	none	254/2657 (9.6%)	120/1696 (7.1%)	**RR 1.38 (1.10 to 1.73)**	**27 more per 1,000 (from 7 more to 52 more)**	⊕⊕⊕◯ Moderate	CRITICAL
Treatment discontinuation due to adverse events												
8	randomised trials	not serious	not serious	not serious	not serious[e]	none	170/2657 (6.4%)	52/1696 (3.1%)	**RR 2.10 (1.54 to 2.86)**	**34 more per 1,000 (from 17 more to 57 more)**	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. There was inconsistency noted, but it was in the same direction and did not cross the minimally important difference (MID) threshold that we determined apriori at 3%. Thus, we decided to not rate down.
b. The inconsistency can be explained by Davies 2021 including patients with diabetes while Wilding 2021 does not. Thus, the percent total body weight loss appears to be less in patients who have diabetes.
c. The inconsistency can be explained by Wadden 2021 including intensive behavioral therapy and initially low-calorie diet in both arms. Thus, this minimizes the difference between both arms for this dichotomous outcome
d. Absolute risk crosses threshold of 1%, which was the pre-determined MID threshold.
e. Forced titration expected to be captured in this outcome

Supplementary Table 4. Evidence Profile for Liraglutide

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Liraglutide	Control	Relative (95% CI)	Absolute (95% CI)		
Weight loss (follow-up: range 52 weeks to 68 weeks; assessed with: kilograms)												
9	randomized trials	not serious	not serious	not serious	not serious	none	3547	2129	-	MD **5.3 lower (5.9 lower to 4.7 lower)**	⊕⊕⊕⊕ High	IMPORTANT
Percent total body weight loss (follow-up: range 52 weeks to 68 weeks)												
8	randomized trials	not serious	not serious	not serious	not serious	none	3710	2258	-	MD **4.81 higher (4.23 higher to 5.39 higher)**	⊕⊕⊕⊕ High	CRITICAL
Total body weight loss ≥ 5% (follow-up: range 52 weeks to 68 weeks)												

11	randomized trials	not serious	not serious[a]	not serious	not serious	none	2379/3964 (60.0%)	662/2498 (26.5%)	**RR 2.09 (1.80 to 2.42)**	**289 more per 1,000 (from 212 more to 376 more)**	⊕⊕⊕⊕ High	CRITICAL
Total Body Weight Loss ≥ 10% (follow-up: range 52 weeks to 68 weeks)												
11	randomized trials	not serious	not serious	not serious	not serious	none	1208/3953 (30.6%)	259/2497 (10.4%)	**RR 2.67 (2.14 to 3.34)**	**173 more per 1,000 (from 118 more to 243 more)**	⊕⊕⊕⊕ High	CRITICAL
Total Body Weight Loss ≥ 15% (follow-up: range 52 weeks to 68 weeks)												
6	randomized trials	not serious	not serious	not serious	not serious	none	439/2958 (14.8%)	77/1704 (4.5%)	**RR 3.04 (2.25 to 4.12)**	**92 more per 1,000 (from 56 more to 141 more)**	⊕⊕⊕⊕ High	IMPORTANT
Serious Adverse Events (follow-up: range 52 weeks to 68 weeks)												
11	randomized trials	not serious	not serious	not serious	serious[b]	none	275/3964 (6.9%)	139/2498 (5.6%)	**RR 1.22 (1.00 to 1.50)**	**12 more per 1,000 (from 0 fewer to 28 more)**	⊕⊕⊕◯ Moderate	CRITICAL
Treatment discontinuations due to adverse effects (follow-up: range 52 weeks to 68 weeks)												
10	randomized trials	not serious	not serious	not serious	not serious	none	373/3914 (9.5%)	98/2448 (4.0%)	**RR 2.31 (1.85 to 2.88)**	**52 more per 1,000 (from 34 more to 75 more)**	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. I-squared = 65% and largely influenced by study by Lundgren et al. in which participants had already lost significant body weight during 8-week run-in period, but not rated down as sensitivity analysis by excluding this study did not show significant change in pooled effect size
b. 95% CI extends from no harms to clinically significant SAE

Supplementary Table 6. Evidence Profile for Phentermine-topiramate ER

Question: Phentermine/Topiramate (15/92 mg) plus lifestyle intervention compared to lifestyle intervention alone for management of obesity

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phentermine/Topiramate (15/92 mg) plus lifestyle intervention	lifestyle intervention alone	Relative (95% CI)	Absolute (95% CI)		
Total body weight loss (%TBWL) (assessed with: Percentage %)												
3	randomised trials	not serious	not serious[a]	not serious	not serious	none	1580	1561	-	MD **8.45 % higher (7.89 higher to 9.01 higher)**	⊕⊕⊕⊕ High	CRITICAL
≥5% TBWL												
3	randomised trials	not serious	not serious[a]	not serious	not serious	none	1068/1580 (67.6%)	303/1561 (19.4%)	**RR 3.48 (3.13 to 3.87)**	**481 more per 1,000 (from 413 more to 557 more)**	⊕⊕⊕⊕ High	CRITICAL
≥10% TBWL												

3	randomised trials	not serious	not serious[a]	not serious	not serious	none	730/1580 (46.2%)	114/1561 (7.3%)	**RR 6.33 (5.26 to 7.61)**	**389 more per 1,000 (from 311 more to 483 more)**	⊕⊕⊕⊕ High	CRITICAL
≥15% TBWL												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	161/511 (31.5%)	17/513 (3.3%)	**RR 9.51 (5.86 to 15.44)**	**282 more per 1,000 (from 161 more to 479 more)**	⊕⊕⊕◯ Moderate	CRITICAL
Serious Adverse Events (SAE)												
3	randomised trials	not serious	not serious	not serious	serious[b,c]	none	67/1580 (4.2%)	55/1561 (3.5%)	**RR 1.20 (0.85 to 1.70)**	**7 more per 1,000 (from 5 fewer to 25 more)**	⊕⊕⊕◯ Moderate	CRITICAL
Treatment discontinuation due to adverse events												
3	randomised trials	not serious	not serious	not serious	not serious	none	275/1580 (17.4%)	132/1561 (8.5%)	**RR 2.08 (1.71 to 2.52)**	**91 more per 1,000 (from 60 more to 129 more)**	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Allison 2012; BMI >35
b. Less than 300 events
c. crosses unity

Supplementary Table 8. Evidence Profile for Bupropion-naltrexone SR

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NB32**	**No treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Weight loss in kg												
5	randomised trials	not serious[a,b]	not serious[c]	not serious	serious[d,e]	none	6772	5887	-	MD **3.01 kg fewer (3.39 fewer to 2.62 fewer)**	⊕⊕⊕◯ Moderate	IMPORTANT
%TBWL												
5	randomised trials	not serious[a,b]	not serious[c]	not serious	serious[d,e]	none	6772	5887	-	MD **3.01 % lower (3.54 lower to 2.47 lower)**	⊕⊕⊕◯ Moderate	CRITICAL

TBWL >5%

4	randomised trials	not serious	not serious[f]	not serious	not serious	none	949/2317 (41.0 %)	247/1437 (17.2 %)	**RR 2.18 (1.41 to 3.37)**	**203 more per 1,000 (from 70 more to 407 more)**	⊕⊕ ⊕⊕ High	CRITICAL

TBWL >10%

4	randomised trials	not serious	not serious[f]	not serious	not serious	none	559/2317 (24.1 %)	105/1437 (7.3 %)	**RR 3.04 (1.80 to 5.14)**	**151 more per 1,000 (from 58 more to 303 more)**	⊕⊕ ⊕⊕ High	CRITICAL

TBWL >15%

3	randomised trials	not serious	not serious[f]	not serious	not serious	none	279/2052 (13.6 %)	39/1278 (3.1 %)	**RR 3.88 (2.13 to 7.08)**	**88 more per 1,000 (from 34 more to 186 more)**	⊕⊕ ⊕⊕ High	IMPORTANT

Treatment discontinuation due to AE

5	randomised trials	not serious	not serious[g]	not serious	not serious	none	1798/6947 (25.9 %)	545/5892 (9.2 %)	**RR 2.39 (1.69 to 3.37)**	**129 more per 1,000 (from 64 more to 219 more)**	⊕⊕ ⊕⊕ High	CRITICAL

Serious adverse events

5	randomised trials	not serious	not serious	not serious	serious[h]	none	67/6947 (1.0 %)	78/5892 (1.3 %)	**RR 0.74 (0.53 to 1.03)**	**3 fewer per 1,000 (from 6 fewer to 0 fewer)**	⊕⊕ ⊕◯ Moderate	CRITICAL

a. Apovian 2013, had imputation in the analysis for week 56. After re-randomization patients receiving higher dose of Naltrexone were excluded from the final analysis and participants receiving FDA approved dose were counted twice "double-weighted". This were not large number of participants and we thought it will not impact the pool estimate.
b. To deal with attrition bias most studies used intention to treat (ITT) and total original number was used as last observation carried forward. However, Hollander, report only on modified ITT analysis and exclude the patients that discontinued the drug within first 4 weeks, majority of this patients were discontinuation due to side effect. We explore this in sensitivity analysis and there was no big difference between the results. Thus, we decided not to rate down for risk of bias
c. Although I2 was high all the studies were showing benefit, so we did not rate down for inconsistency
d. Minimal important difference (MID) or clinically important threshold below which there is no clear benefit of the intervention in discussion with the GL panel and TR team was determined to be 3kg (or ~3%)
e. We noted serious imprecision as the lower confidence limit crosses the minimal important difference (MID), for benefit.
f. Although high I2, all studies showed clear benefit. Furthermore, the Wadden study that was inconsistent with the results from the other studies was with high intensity diet and exercise that may have lead to a ceiling effect, we did sensitivity analysis to explore and the results were not significantly different
g. Although I2 was high all the studies were showing harm, so we did not rate down for inconsistency
h. Low event rate, also CI crossing the line of no effect

Supplementary Table 10. Evidence Profile for Orlistat

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Orlistat	Controls	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Weight loss (follow-up: range 48 weeks to 4 years; assessed with: kilograms)												
23 (24 cohorts)	randomized trials	not serious[a]	not serious	not serious	serious[b]	none	4166	3601	-	MD **2.81 lower (3.45 lower to 2.17 lower)**	⨁⨁⨁◯ Moderate	IMPORTANT
Percent total body weight loss (follow-up: range 48 weeks to 4 years)												
15 (16 cohorts)	randomized trials	not serious[a]	not serious[c]	not serious	serious[b]	none	3514	3004	-	MD **2.78 higher (2.36 higher to 3.2 higher)**	⨁⨁⨁◯ Moderate	CRITICAL
Total body weight loss ≥5% (follow-up: range 48 weeks to 4 years)												
18	randomized trials	not serious	not serious[d]	not serious	not serious	none	3303/5638 (58.6%)	1824/5201 (35.1%)	**RR 1.71 (1.55 to 1.88)**	**249 more per 1,000 (from 193 more to 309 more)**	⨁⨁⨁⨁ High	CRITICAL
Total body weight loss ≥10% (follow-up: range 48 weeks to 4 years)												
15	randomized trials	not serious	not serious[e]	not serious	not serious	none	1577/5083 (31.0%)	715/4652 (15.4%)	**RR 1.94 (1.70 to 2.22)**	**144 more per 1,000 (from 108 more to 188 more)**	⨁⨁⨁⨁ High	CRITICAL
Severe adverse events (follow-up: range 48 weeks to 4 years)												
11	randomized trials	not serious	not serious	not serious	serious[f]	none	362/3542 (10.2%)	329/3545 (9.3%)	**RR 1.04 (0.81 to 1.33)**	**4 more per 1,000**	⨁⨁⨁◯	CRITICAL

										(from 18 fewer to 31 more)	Moderate	
Treatment discontinuations due to adverse events (follow-up: range 48 weeks to 4 years)												
20	randomized trials	not serious	not serious[g]	not serious	not serious	none	339/4252 (8.0%)	195/3804 (5.1%)	**RR 1.51 (1.22 to 1.89)**	**26 more per 1,000 (from 11 more to 46 more)**	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Although most studies did not explain method of randomization or how allocation was concealed, we did not think it would introduce serious RoB as most studies were double blinded and although there was attrition seen in several studies it was usually not disproportionate and LOCF analysis method used for ITT analysis. Thus we did not rate down for Risk of Bias
b. 95% CI includes minimal clinically important difference
c. There was moderate heterogeneity (I-squared = 39%), but not rated down as the inconsistency was largely driven by the magnitude, and not direction of effects
d. There was substantial heterogeneity (I-squared = 73%), but not rated down as the inconsistency was largely driven by the magnitude, and not direction of effects
e. There was moderate heterogeneity (I-squared = 46%), but not rated down as the inconsistency was mostly due to the magnitude and not direction of effects
f. 95% CI is wide and includes 1
g. There was moderate heterogeneity present (I-squared = 30%), but not rated down as the inconsistency was largely driven by the magnitude, and not direction of effects

Supplementary Table 12. Evidence Profile for Phentermine

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Phentermine/ diet/ exercise**	**SOC (diet /exercise)**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Weight loss (kg)												
7	randomised trials	not serious[a]	serious[b,c]	serious[d]	not serious	none	353	343	-	MD **4.74 kg more (5.73 more to 3.75 more)**	⊕⊕◯◯ Low	IMPORTANT
%TBWL												
3	randomised trials	not serious[a]	not serious	serious[d]	serious[b,e]	none	205	202	-	MD **3.63 % more (4.29 more to 2.97 more)**	⊕⊕◯◯ Low	CRITICAL
> 5% TBWL												
5	randomised trials	not serious	not serious	serious[d]	not serious	none	173/322 (53.7%)	40/313 (12.8%)	**RR 4.12 (3.04 to 5.59)**	**399 more per 1,000 (from 261 more to 587 more)**	⊕⊕⊕◯ Moderate	CRITICAL

>10% TBWL

5	randomised trials	not serious	serious[f]	serious[d]	not serious[g]	none	81/322 (25.2%)	15/313 (4.8%)	**RR 5.10 (3.02 to 8.61)**	**196 more per 1,000 (from 97 more to 365 more)**	⨁⨁◯◯ Low	CRITICAL

Treatment discontinuation due to side effects

7	randomised trials	not serious[h]	not serious	serious[d]	not serious	none	257/1274 (20.2%)	76/730 (10.4%)	**RR 1.73 (1.36 to 2.19)**	**76 more per 1,000 (from 37 more to 124 more)**	⨁⨁⨁◯ Moderate	CRITICAL

Severe Adverse Events

5	randomised trials	not serious[h]	not serious	serious[d]	serious[i]	none	11/280 (3.9%)	3/276 (1.1%)	**RR 2.44 (0.60 to 10.03)**	**16 more per 1,000 (from 4 fewer to 98 more)**	⨁⨁◯◯ Low	CRITICAL

a. Although there was a concern for attrition bias, in almost all the studies that have attrition it was very similar between the 2 groups. Thus, we did not rate down for RoB

b. Minimal important difference (MID) or clinically important threshold below which there is no clear benefit of the intervention in discussion with the GL panel and TR team was determined to be 3kg (or ~3%)

c. There is a serious inconsistency between the studies 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

d. Serious indirectness in the intervention duration. Our PICO question is weight loss treatment for a long period of time that most studies define as 1 year. However, the available data is in 3-6 months.

e. Confidence interval is crossing the MID, the lower CI is showing clear benefits while the upper failed to show clear clinical benefit as higher confidence limit is below the MID

f. Serious inconsistency possibly due to different intervention duration and follow up time

g. Concern for serious imprecision due to wade confidence intervals but because most likely is related to the inconsistency and we already rate down for inconsistency decide not to rate down for imprecision

h. Although some smaller and older studies did not blind, overall, there was no concern for serious RoB across the pool of evidence

i. Low event number

Supplementary Table 14. Evidence Profile for Diethylpropion

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diethylpropion + SOC (diet and exercise)	SOC (diet and exercise)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Weight loss (kg)												

6	randomised trials	serious[a]	serious[b,c]	serious[d]	not serious	none	209	199	-	MD **4.74 kg more (6.4 more to 3.08 more)**	⊕◯◯◯ Very low	CRITICAL
% TBWL												
4	randomised trials	serious[a]	not serious	serious[d]	serious[e]	none	119	108	-	MD **5.36 % more (7.23 more to 3.5 more)**	⊕◯◯◯ Very low	CRITICAL
>5% TBWL												
3	randomised trials	not serious	not serious	serious[d]	serious[f]	none	109/143 (76.2%)	26/139 (18.7%)	**RR 3.51 (1.50 to 8.18)**	**469 more per 1,000 (from 94 more to 1,000 more)**	⊕⊕◯◯ Low	CRITICAL
>10% TBWL												
3	randomised trials	not serious	not serious	serious[d]	serious[f]	none	71/143 (49.7%)	3/139 (2.2%)	**RR 14.48 (5.13 to 40.80)**	**291 more per 1,000 (from 89 more to 859 more)**	⊕⊕◯◯ Low	CRITICAL
Treatment discontinuation due to side effects												
5	randomised trials	not serious	not serious	serious[d]	serious[f]	none	10/187 (5.3%)	6/180 (3.3%)	**RR 1.37 (0.51 to 3.66)**	**12 more per 1,000 (from 16 fewer to 89 more)**	⊕⊕◯◯ Low	CRITICAL

a. Majority of the older studies did not do ITT analysis just showed the benefit data from the subjects who completed the study, this probably introduced a RoB and overestimate the effect of the intervention; additionally unclear how the randomization and allocation was done in most of the studies

b. Minimal important difference (MID) or clinically important threshold below which there is no clear benefit of the intervention in discussion with the GL panel and TR team was determined to be 3kg (or ~3%)

c. There is a serious inconsistency between the studies 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

d. Serious indirectness in the intervention duration. Our PICO question is weight loss treatment for a long period of time that most studies define as 1 year. However, the available data is in 3-6 months.

e. Small sample size <400 total

f. Number of events is low <200

Supplementary Table 16. Evidence Profile for Gelesis100

Question: Cellulose and citric acid hydrogel plus lifestyle intervention compared to lifestyle intervention alone for management of obesity

Certainty assessment	№ of patients	Effect	Certainty	

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cellulose and citric acid hydrogel plus lifestyle intervention	lifestyle intervention alone	Relative (95% CI)	Absolute (95% CI)		Importance
Total body weight loss (%) (follow-up: 24 weeks; assessed with: Percentage))												
1	randomised trials	not serious	not serious	not serious	very serious[a,b]	none	223	213	-	MD **2.02 % more (0.96 more to 3.08 more)**	⨁⨁◯◯ Low	
At least 5% TBWL (follow-up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[c]	none	130/223 (58.3%)	90/213 (42.3%)	**RR 1.38 (1.14 to 1.67)**	**161 more per 1,000 (from 59 more to 283 more)**	⨁⨁⨁◯ Moderate	
At least 10% (follow-up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[c]	none	61/223 (27.4%)	32/213 (15.0%)	**RR 1.82 (1.24 to 2.67)**	**123 more per 1,000 (from 36 more to 251 more)**	⨁⨁⨁◯ Moderate	
Treatment discontinuation due to adverse events (follow-up: 24 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[c,d]	none	8/223 (3.6%)	7/213 (3.3%)	**RR 1.09 (0.40 to 2.96)**	**3 more per 1,000 (from 20 fewer to 64 more)**	⨁⨁◯◯ Low	
Serious Adverse Events												
1	randomised trials	not serious	not serious	not serious	very serious[b,c,d]	none	0/223 (0.0%)	1/213 (0.5%)	**RR 0.32 (0.01 to 7.77)**	**3 fewer per 1,000 (from 5 fewer to 32 more)**	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Does not meet minimally important threshold of 3%
b. wide confidence interval
c. Low event rate (<300)
d. crosses unity

Supplementary Table 3: SAE FAERS for Semaglutide

Table. SAE Semaglutide (WEGOVY)

Contraindications [a]	Serious Adverse Reactions FDA [b]	Selected Serious Adverse Reactions original studies' definitions
1. Personal or family history of medullary thyroid carcinoma or in patients with Multiple	1. 131 cases reported (examples: nausea, vomiting, impaired gastric emptying,	1. Wilding 2021:

Endocrine Neoplasia syndrome type 2 2. Known hypersensitivity to semaglutide or any of the excipients in WEGOVY	cholelithiasis, GERD, constipation, thyroid neoplasia, dyspepsia, hypoglycemia, diarrhea, abdominal pain, electrolyte abnormalities/dehydration, LFT abnormality, renal impairment)[c]	Abdominal pain: I: 3/1306 vs C: 0/655 Constipation: 1/1306 vs 0/655 Diarrhea: 1/1306 vs 0/655 Nausea: 1/1306 vs 0/655 Vomiting: 4/1306 vs 0/655 Pancreatitis: 2/1306 vs 0/655 Vertigo: 3/1306 vs 0/655 Cholelithiasis: 12/1306 vs 1/655 Cholecystitis 4/1306 vs 0/655 Acute MI: 2/1306 vs 1/655 Gastroenteritis: 5/1306 vs 0/655 SI: 1/1306 vs 0/655

a. Product labeling

b. FDA definition: An adverse event when the patient outcome is death, life-threatening, hospitalization, disability of permanent damage Congenital Anomaly/Birth Defect, development of drug dependence or drug abuse (FDA Adverse Event Reporting System Database). See full list on public database.

c. Reported cases are from 2021 to March 31st, 2022. Unknown denominator but is frequently prescribed obesity medication in the United States

Supplementary Table 5. SAE FAERS for Liraglutide

Contraindications [a]	**Serious Adverse Reactions FDA** [b]	**Serious Adverse Reactions original studies' definitions**
1. Pregnancy 2. Patients with a personal or family history of medullary thyroid cancer (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) 3. There was one suicide in the trial in the Saxenda treatment group, so patients should be monitored for depression and suicidal thoughts 4. Should not be used with other GLP-1 RA drugs 5. Should be used with caution with insulin	1. Pancreatitis: 40 required hospitalizations, and 1 was life threatening (out of approximately 29,277 who took Saxenda between 2015 and 2018) – 0.1% 2. No life threatening or fatal breast cancers (between 2015 and 2018) 4. 0 cases of MTC 5. 17 cases of cholelithiasis requiring hospitalization – 0.05% 6. Five cases of renal failure, of which 3 needed hospitalizations, 1 was life threatening, and 1 death occurred – 0.01% 7. 18 cases of dehydration, of which 16 were hospitalized, 1	**Rubino 2022 (STEP 8):** Malignant neoplasms: 3 (including 2 breast cancers) in liraglutide vs. 1 breast cancer in placebo Severe GI adverse events were 3 in liraglutide vs. 3 in placebo 1 acute pancreatitis in liraglutide vs. none in placebo **O'Neil 2018:** 0 acute pancreatitis in liraglutide vs. 1 in placebo 3 neoplasms in liraglutide vs. 4 in placebo, but no pancreatic cancer or breast cancer **Lundgren 2021:**

	life threatening and 1 caused disability – 0.06% 8. Nausea/vomiting: 36 cases required hospitalization, 1 life threatening, and 1 death – 0.1% 9. 1 case of hypoglycemia requiring hospitalization 10. 6 cases of serious suicidal behavior (one completed suicide) while the other 5 needed hospitalization or were life threatening – 0.02%	2/49 severe cases of cholelithiasis in liraglutide group vs. 0 in placebo 1/49 cases of acute pancreatitis vs. 0 in the placebo **Davies 2015:** 1/422 breast cancer in liraglutide vs. 0/212 in placebo Severe hypoglycemia occurred in 3/422 patients taking liraglutide vs. 0/212 patients taking placebo (in those also on sulfonylureas) **Pi-Sunyer 2015:** 1 patient died in the liraglutide group and 2 in the placebo group. 20/2481 patients in the liraglutide group had gallstone that was classified as SAE vs. 5/1242 in the placebo group 1/2481 acute pancreatitis events in liraglutide that was classified as severe 4/2481 breast cancer in liraglutide vs. 1/1242 in placebo (these were advanced node +ve breast malignancies) 6/2481 patients in liraglutide group had active suicidal ideation vs. 3/1242 in the placebo group. **Garvey 2020:** 3/198 severe hypoglycemia with liraglutide vs. 2/198 with placebo

		6/198 malignant neoplasms in liraglutide vs. 2/198 in placebo were considered SAE 0/198 invasive lobular breast cancer in liraglutide vs. 1/198 in placebo **Wadden 2013:** 3/212 had malignant neoplasms (including 2 breast cancers) vs. 2/210 in placebo (neither were breast cancer in placebo group) **Astrup 2012:** 1 SAE related to cholelithiasis + acute pancreatitis in liraglutide vs. 0 in placebo **Gudbergsen 2021:** 1/80 with GI related SAE in liraglutide (ileus) vs. 1/76 GI related SAE in placebo (cholecystitis) **Wadden 2020:** 1 acute cholecystitis, 1 papillary thyroid cancer in liraglutide vs. none in placebo

a. Product labeling
b. FDA definition: An adverse event when the patient outcome is death, life-threatening, hospitalization, disability of permanent damage Congenital Anomaly/Birth Defect, development of drug dependence or drug abuse (FDA Adverse Event Reporting System Database)
c. Reported cases are from 2015 to 2018 in the FAERS database. Unknown denominator but one study reports with 29277 users between 2015-2018 who took Saxenda [ref DOI: 10.1111/dom.14367]

Supplementary Table 7. SAE FAERS for Phentermine-topiramate ER

Table. SAE Phentermine and topiramate extended-release ER (QSYMIA)

Contraindications [a]	Serious Adverse Reactions FDA [b]	Selected Serious Adverse Reactions original studies' definitions
1. Pregnancy 2. Glaucoma	1. Neuro (e.g., blurry vision or vision disturbance, Seizure,	1. Gadde 2011:

3. Hyperthyroidism 4. During or within 14 days of taking monoamine oxidase inhibitors 5. Known hypersensitivity or idiosyncrasy to sympathomimetic amines	CVA, paresthesia, dizziness, LOC, glaucoma, SI, Anxiety, change in HR, attention/thinking disturbance) 105 cases reported (~0.6%) [c] 2. General disorders (nephrolithiasis, arrythmia, vision disturbance, mental disturbance, SI) 79 cases reported (~0.5%) 3. GI (e.g., constipation, abdominal pain, nausea, dry mouth, diarrhea, constipation, change in taste, cholelithiasis, pancreatitis) 51 cases reported (~0.37%) [c] 4. Psychiatric (e.g., anxiety, depression, suicidal ideation, sleep disorder) 74 cases reported (~ 0.39%) [c] 5. 7 deaths	Cardiac (CAD, MI, cardio-respiratory arrest, angina pectoris, ACS, Afib, tachycardia) Intervention 15/92: 5/994; Placebo: 7/993 Cholelithiasis: I: 1/994 and C: 1/993 Syncope/Headache/Dizziness: I: 1/994 vs C: 3/993 Nephrolithiasis: I: 2/994 vs C: 0/993

a. Product labeling

b. FDA definition: An adverse event when the patient outcome is death, life-threatening, hospitalization, disability of permanent damage Congenital Anomaly/Birth Defect, development of drug dependence or drug abuse (FDA Adverse Event Reporting System Database). See full list on public database.

c. Reported cases are from 2012 to March 31st, 2022. Unknown denominator but is frequently prescribed obesity medication in the United States, one study reports with 11,513 users between 2015-2018 that would account for an indirect estimate of 0.3- 1 % SAE [ref DOI: 10.1111/dom.14367]

Supplementary Table 9. SAE FAERS for Bupropion-naltrexone SR

Contraindications [a]	Serious Adverse Reactions FDA [b]	Serious Adverse Reactions original studies' definitions [e]
1. Chronic opioid, opiate agonist (e.g., methadone) or partial agonist (e.g., buprenorphine) use 2. Acute opioid withdrawal 3. Uncontrolled hypertension 4. seizure disorder or a history of seizures 5. abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiseizure drugs [d]	1. Neuro (e.g., dizziness, Seizure, CVA, headache) 93 cases reported (~0.1%) [c] 2. GI (e.g., nausea, vomiting, diarrhea, constipation, cholecystitis) 103 cases reported (~0.1%) [c] 3. Psychiatric (e.g., anxiety, depression, suicidal ideation) 75 cases reported (> 0.1%) [c]	**1. Apovian 2013** 1/992 (0.1%)passive suicidal ideation, 1/992 (0.1%) seizure 2. **Wadden 2010** 2/ 584 (0.3%) cholecystitis 3. **Nissen 2016** CV events: all death, nonfatal stroke, MI: 40/4455 (0.9%) vs. 62/4450 (1.4%) in placebo 4. **Greenway 2010** 2/ 573 (0.3%) Cardiac (1 HF 1 MI) 0/573 stroke 5. **SR MA** Seizure - 0.1% vs 0% in placebo Suicidal ideation was 1/ 3,239 (0.03%)vs 3/1,515 (0.20%) in placebo

6. Use during or within 14 days following MAO inhibitor 7. in a patient receiving linezolid or IV methylene blue		

a. Product labeling
b. FDA definition: An adverse event when the patient outcome is death, life-threatening, hospitalization, disability of permanent damage Congenital Anomaly/Birth Defect, development of drug dependence or drug abuse (FDA Adverse Event Reporting System Database)
c. Reported cases are from 2014 to Dec 31st, 2021. Unknown denominator but is frequently prescribed obesity medication in the United States, one study reports with 42 138 users between 2015-2018 that would account for 0.5- 1 % all SAE [ref DOI: 10.1111/dom.14367]
d. A small number of children, teenagers, and young adults (up to 24 years of age) who took antidepressants such as bupropion during clinical studies became suicidal
e. Nissen: CV events: all death, nonfatal stroke, or nonfatal MI infarction and hospitalization, Greenway: by good clinical practice (same as FDA)

Supplementary Table 11. SAE FAERS for Orlistat

Contraindications [a]	**FAERS data on Orlistat from 2015 to 2018** [b]	**Serious Adverse Events (SAE) original studies' definitions**
1. Pregnancy 2. Patients with chronic malabsorption syndrome 3. Patients with cholestasis 4. Patients are strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because Orlistat has been shown to reduce the absorption of fat-soluble vitamins and beta-carotene	1. Liver failure: 12 foreign cases with Orlistat 120mg and 1 case in the USA with Orlistat 60mg reported between April 1999 and August 2009 out of an estimated 40 million people worldwide who have used either of these medications 2. There were 4 cases of pancreatic cancer, of which 2 died 3. 4 cases of renal failure reported among 1341 patients (only in year 2017 in FAERS).	Davidson 1999: no major SAE in either Orlistat or placebo groups. Broom 2002 (one of the larger studies with 265 patients in orlistat and 266 in placebo – none of the SAE were thought to be attributable to Orlistat. Sjöström 1998: SAE were reported by 25 out of 345 patients on Orlistat vs. 24 out of 343 patients on placebo in year 1, of which only one SAE was judged by the investigators to be related to treatment. Similarly, 2 SAE were judged by the investigators to be possibly related to treatment during year 2. Torgerson (XENDOS) 2004: Over the 4-year study period, a

		similar proportion of Orlistat and placebo-treated patients had at least one SAE (15 vs. 13%) Lindgärde 2000: A total of 19 patients out of 190 in the orlistat group and 5 patients out of 186 in the placebo group experienced SAE, none of which were deemed by the investigators to have a causal relationship with the study medication.

a. Product labeling
b. FDA definition: An adverse event when the patient outcome is death, life-threatening, hospitalization, disability of permanent damage Congenital Anomaly/Birth Defect, development of drug dependence or drug abuse (FDA Adverse Event Reporting System Database)
c. Reported cases are from 2015 to 2018. Unknown denominator but is frequently prescribed obesity medication in the United States, one study reports that approximately 1341 patients were on orlistat [ref DOI: 10.1111/dom.14367]

Supplementary Table 13. SAE FAERS for Phentermine

Contraindications [a]	Serious Adverse Reactions FDA [b, c]	Serious Adverse Reactions original studies' definitions [e]
1. History of cardiac dz (arrhythmias, heart failure, CAD, stroke, uncontrolled hypertension) 2. Hyperthyroidism 3. Glaucoma 4. Agitated states 5. History of drug abuse 6. Use during or within 14 days following MAO inhibitor 7. Pregnancy and/ or breast-feeding	1. Cardiac disorders (e.g., valve disease, MI, Arrythmias CHF, palpitations, tachycardia) 2,554 cases reported (~ 0.05% incidence) 2. Primary pulmonary hypertension - 672 case reported [d] (> 0.0008%) 3. CNS effects (e.g., delirium, mania, psychosis, insomnia, irritability, and anxiety) 1,434 cases (~0.01%) 4. Neuro (dizziness, headache, Amnesia, syncope CVA) 1,394 cases reported (~0.01%)	**Aronne 2013** 1/109 (1%) chest pain **Kim 2006** 3/28 (10%) Severe HA and nausea 1/28 (3%) dry mouth **Tsai 2012** 3/ 23 (13%) clinically significant BP elevation 1/ 23 (4%) HR elevation

a. Product labeling
b. FDA definition: An adverse event when the patient outcome is death, life-threatening, hospitalization, disability of permanent damage Congenital Anomaly/Birth Defect, development of drug dependence or drug abuse (FDA Adverse Event Reporting System Database)
c. All SAE reported cases are from 1975 to 2021. Unknown denominator but is widely prescribed obesity medication in the United States, with 116 435 users between 2015-2018 [doi.org/10.1111/dom.14367]
d. Appears to be associated with longer use
e. No definitions were provided for SAE in any of the studies

Supplement Figure 1. Search strategy for the Guideline

PICO 1-6

((("Obesity"[Mesh] OR "Weight Loss"[Mesh] OR "Overweight"[Mesh] OR obes*[tw] OR "body mass ind*"[tw] OR adiposity[tw] OR overweight[tw] OR "over weight"[tw] OR "overload syndrome*"[tw] OR "over eat*"[tw] OR overfeed*[tw] OR "over feed*"[tw] OR overfed[tw] OR "over fed"[tw] OR "weight cycling"[tw] OR "skinfold thickness"[tw] OR antiobesity[tw] OR "anti-obesity"[tw] OR obesitas[tw] OR bodyweight[tw] OR "body weight"[tw] OR adipositas[tw] OR BMI[tw]) AND (alli[tw] OR orlipastat[tw] OR orlistat[tw] OR "ro 18 0647"[tw] OR "ro 180647"[tw] OR ro180647[tw] OR tetrahydrolipstatin[tw] OR Xenical[tw] OR (phentermine[tw] AND topiramate[tw]) OR "phentermine topiramate"[tw] OR phenterminetopiramate[tw] OR qnexa[tw] OR qsiva[tw] OR Qsymia[tw] OR topiramatephentermine[tw] OR "phentermine-topiramate"[tw] OR (amfebutamone[tw] AND naltrexone[tw]) OR (bupropion[tw] AND naltrexone[tw]) OR Contrave[tw] OR mysimba[tw] OR "nb 32"[tw] OR nb32[tw] OR "bupropion-naltrexone"[tw] OR liraglutide[tw] OR "nn 2211"[tw] OR nn2211[tw] OR "nnc 90 1170"[tw] OR "nnc90 1170"[tw] OR Saxenda[tw] OR Victoza[tw] OR semaglutide[tw] OR nn9535[tw] OR "nn 9535"[tw] OR ozempic[tw] OR rybelsus[tw] OR "Orlistat"[Mesh] OR "Liraglutide"[Mesh] OR "semaglutide" [Supplementary Concept] OR "bupropion hydrochloride, naltrexone hydrochoride drug combination" [Supplementary Concept])) NOT (("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tw] OR randomised[tw] OR placebo[tw] OR "drug therapy"[sh] OR randomly[tw] OR trial[tw] OR groups[tw]) NOT ("Animals"[sh] NOT "Humans"[sh]) AND ("2021/01/01"[Date - Publication] : "3000"[Date - Publication])

PICO 7 and 8

("Obesity"[Mesh] OR "Weight Loss"[Mesh] OR "Overweight"[Mesh] OR obes*[tw] OR "body mass ind*"[tw] OR adiposity[tw] OR overweight[tw] OR "over weight"[tw] OR "overload

syndrome*"[tw] OR "over eat*"[tw] OR overfeed*[tw] OR "over feed*"[tw] OR overfed[tw] OR "over fed"[tw] OR "weight cycling"[tw] OR "skinfold thickness"[tw] OR antiobesity[tw] OR "anti-obesity"[tw] OR obesitas[tw] OR bodyweight[tw] OR "body weight"[tw] OR adipositas[tw] OR BMI[tw]) AND ("Phentermine"[Mesh] OR phentermine[tw] OR 0k2i505otv[tw] OR "1197-21-3 (hcl)"[tw] OR "122-09-8 (phentermine)"[tw] OR "adipex p"[tw] OR "adipex-p"[tw] OR adipexp[tw] OR c045tql4wp[tw] OR duromine[tw] OR ionamine[tw] OR "1,1 dimethyl 2 phenylethylamine"[tw] OR "2 benzyl 2 propylamine"[tw] OR "alpha,alpha dimethylphenethylamine"[tw] OR "beta aminoisopropylbenzene"[tw] OR "beta phenyltert.butylamine"[tw] OR dimethylphenethylamine[tw] OR dimethylphenetylamine[tw] OR "ex adipos"[tw] OR exadipos[tw] OR fastin[tw] OR lomaira[tw] OR "minobese−forte"[tw] OR "obermine black and yellow"[tw] OR "obestin-30"[tw] OR "oby-cap"[tw] OR "oby-trim"[tw] OR "ona-mast"[tw] OR panbesy[tw] OR "panbesyl nyscaps"[tw] OR phentercot[tw] OR phentermide[tw] OR phentermin[tw] OR phentrol[tw] OR "pro-fast"[tw] OR reducyl[tw] OR redusa[tw] OR suprenza[tw] OR "t-diet"[tw] OR terbutylamine[tw] OR umine[tw] OR wilpo[tw] OR zantryl[tw] OR "Diethylpropion"[Mesh] OR 19v2pl39ng[tw] OR "2-diethylaminopropiophenone"[tw] OR "90-84-6 (diethylpropion)"[tw] OR amfepramon[tw] OR amfepramone[tw] OR anorex[tw] OR delgamer[tw] OR diethylpropion[tw] OR "dietil retard"[tw] OR "dietil-retard"[tw] OR dietilretard[tw] OR "ifa norex"[tw] OR lipomin[tw] OR maruate[tw] OR moderatan[tw] OR neobes[tw] OR nobesine[tw] OR phepranon[tw] OR prefamone[tw] OR propion[tw] OR q94yyu22b8[tw] OR regenon[tw] OR regibon[tw] OR tenuate[tw] OR tepanil[tw] OR "1 benzoyltriethylamine"[tw] OR "2 diethylaminopropiophenone"[tw] OR adiposon[tw] OR alipid[tw] OR "alpha benzoyltriethylamine hydrochloride"[tw] OR "alpha diethylaminopropiophenone"[tw] OR amphepramon[tw] OR anorexil[tw] OR apisate[tw] OR atractil[tw] OR derfon[tw] OR diepropon[tw] OR "diethyl propion"[tw] OR diethylaminopropiophenone[tw] OR diethylpropion[tw] OR diethylpropione[tw] OR dobesin[tw] OR dualid[tw] OR elontril[tw] OR "linea magerion"[tw] OR magrene[tw] OR moludar[tw] OR obesitex[tw] OR prothin[tw] OR sacin[tw] OR "t 712"[tw] OR tylinal[tw] OR

voxra[tw] OR zyntabac[tw]) NOT (("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tw] OR randomised[tw] OR placebo[tw] OR "drug therapy"[sh] OR randomly[tw] OR trial[tw] OR groups[tw]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

PICO 9

("Obesity"[Mesh] OR "Weight Loss"[Mesh] OR "Overweight"[Mesh] OR obes*[tw] OR "body mass ind*"[tw] OR adiposity[tw] OR overweight[tw] OR "over weight"[tw] OR "overload syndrome*"[tw] OR "over eat*"[tw] OR overfeed*[tw] OR "over feed*"[tw] OR overfed[tw] OR "over fed"[tw] OR "weight cycling"[tw] OR "skinfold thickness"[tw] OR antiobesity[tw] OR "anti-obesity"[tw] OR obesitas[tw] OR bodyweight[tw] OR "body weight"[tw] OR adipositas[tw] OR BMI[tw]) AND (((plenity[tw] OR gelesis100[tw] OR "gelesis 100"[tw] OR "gelesis-100"[tw] OR gs100[tw] OR "gs 100"[tw] OR "gs-100"[tw] OR (superabsorbent[tw] AND hydrogel*[tw]) OR (oral[tw] AND hydrogel*[tw]) OR OSH[tw] OR "carboxymethylcellulose-citric"[tw] OR (carboxymethylcellulose[tw] AND citric[tw]) OR (carboxymethyl[tw] AND cellulose[tw] AND citric[tw]))) OR ((oral[tw] OR superabsorbent[tw]) AND "Hydrogels"[Mesh])) NOT (("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh]) NOT "Adult"[Mesh]) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tw] OR randomised[tw] OR placebo[tw] OR "drug therapy"[sh] OR randomly[tw] OR trial[tw] OR groups[tw]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

Supplementary Figure 2. PRISMA Flow Diagram

PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources