Mini-CAT Draft – RT 5 PICO 2 **Name: Jay Kolasinac**

51-year-old, obese, male, with PMH of metabolic syndrome and HLD presents to the office today for his routine check up. He recently heard about the drug semaglutide and its possible effects on weight loss in patients who suffer from obesity. He wants to know how effective this drug is and if it could help him or not.

Search Question: In obese adult patients, how effective is semaglutide in reducing weight loss?

Question Type: What kind of question is this? (boxes now checkable in Word)

☐Prevalence ☐Screening ☐Diagnosis
☐Prognosis ☒Treatment ☐Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?
Please explain your choices.

Randomized control trials will be studies I will be searching for because my question is all about treatment and the efficacy of the intervention [semaglutide]. Prospective cohort studies could also be included because these studies track patients over a period of time to see how they respond although their quality of evidence is not as high as the RCTs.

PICO search terms:

P	**I**	**C**	**O**
Obese	Semaglutide	Placebo	Reduced weight loss
Overweight		None	Reduced body fat
Adults			Reduced appetite

Search tools and strategy used:

Database	Terms	Filter	# of Articles
PubMed	Semaglutide obesity weight loss	Medline, last 5 years	488
ScienceDirect	Semaglutide obesity weight loss	Last 5 years, research articles	134
MEDLINE Complete	Semaglutide obesity weight loss	last 10 years	20

I narrowed down my search results to articles that were published within 5 years and that were Medline. Many articles were focused on the different trials that were going on for the past few years researching semaglutide and its effects on weight loss. I needed the actual published version rather than a trial overview so that was what I was looking for.

Results found:

Article 1

Citation:

Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.

https://pubmed.ncbi.nlm.nih.gov/33567185/

Article Type:

Randomized Control Trial

Abstract:

Background: Obesity is a global health challenge with few pharmacologic options. Whether adults with obesity can achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention has not been confirmed.

Methods: In this double-blind trial, we enrolled 1961 adults with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand (a precise description of the treatment effect reflecting the objective of the clinical trial) assessed effects regardless of treatment discontinuation or rescue interventions.

Results: The mean change in body weight from baseline to week 68 was -14.9% in the semaglutide group as compared with -2.4% with placebo, for an estimated treatment difference of -12.4 percentage points (95% confidence interval [CI], -13.4 to -11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was -15.3 kg in the semaglutide group as compared with -2.6 kg in the placebo group (estimated treatment difference, -12.7 kg; 95% CI, -13.7 to -11.7). Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in participant-reported physical functioning from baseline than those who received placebo. Nausea and diarrhea were the most common adverse events with semaglutide; they were typically transient and mild-to-moderate in severity and subsided with time. More participants in the semaglutide group than in the placebo group discontinued treatment owing to gastrointestinal events (59 [4.5%] vs. 5 [0.8%]).

Conclusions: In participants with overweight or obesity, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight. (Funded by Novo Nordisk; STEP 1 ClinicalTrials.gov number, NCT03548935).

Article 2

Citation:

Friedrichsen, M, Breitschaft, A, Tadayon, S, Wizert, A, Skovgaard, D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes Metab*. 2021; 23: 754– 762. https://doi.org/10.1111/dom.14280

https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.14280

Article Type:

Randomized Control Trial

Abstract:

Aim

To investigate the effects of once-weekly subcutaneous (s.c.) semaglutide 2.4 mg on gastric emptying, appetite, and energy intake in adults with obesity.

Materials and Methods

A double-blind, parallel-group trial was conducted in 72 adults with obesity, randomized to once-weekly s.c. semaglutide (dose-escalated to 2.4 mg) or placebo for 20 weeks. Gastric emptying was assessed using paracetamol absorption following a standardized breakfast. Participant-reported appetite ratings and Control of Eating Questionnaire (CoEQ) responses were assessed, and energy intake was measured during ad libitum lunch.

Results

The area under the concentration–time curve (AUC) for paracetamol 0 to 5 hours after a standardized meal ($AUC_{0–5h,para}$; primary endpoint) was increased by 8% ($P = 0.005$) with semaglutide 2.4 mg versus placebo at week 20 (non-significant when corrected for week 20 body weight; $P = 0.12$). No effect was seen on $AUC_{0–1h,para}$, maximum observed paracetamol concentration, or time to maximum observed paracetamol concentration. Ad libitum energy intake was 35% lower with semaglutide versus placebo (1736 versus 2676 kJ; estimated treatment difference −940 kJ; $P < 0.0001$). Semaglutide reduced hunger and prospective food consumption, and increased fullness and satiety when compared with placebo (all $P < 0.02$). The CoEQ indicated better control of eating and fewer/weaker food cravings with semaglutide versus placebo ($P < 0.05$). Body weight was reduced by 9.9% with semaglutide and 0.4% with placebo. Safety was consistent with the known profile of semaglutide.

Conclusions

In adults with obesity, once-weekly s.c. semaglutide 2.4 mg suppressed appetite, improved control of eating, and reduced food cravings, ad libitum energy intake and body weight versus placebo. There was no evidence of delayed gastric emptying at week 20, assessed indirectly via paracetamol absorption.

Article 3

Citation:

O'Neil, P. M., Birkenfeld, A. L., McGowan, B., Mosenzon, O., Pedersen, S. D., Wharton, S., … Wilding, J. P. H. (2018). *Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. The Lancet.* doi:10.1016/s0140-6736(18)31773-2

https://pubmed.ncbi.nlm.nih.gov/30122305/

Article Type:
Randomized control trial

Abstract:

Background: Obesity is a major public health issue, and new pharmaceuticals for weight management are needed. Therefore, we evaluated the efficacy and safety of the glucagon-like peptide-1 (GLP-1) analogue semaglutide in comparison with liraglutide and a placebo in promoting weight loss.

Methods: We did a randomised, double-blind, placebo and active controlled, multicentre, dose-ranging, phase 2 trial. The study was done in eight countries involving 71 clinical sites. Eligible participants were adults (≥18 years) without diabetes and with a body-mass index (BMI) of 30 kg/m^2 or more. We randomly assigned participants (6:1) to each active treatment group (ie, semaglutide [0·05 mg, 0·1 mg, 0·2 mg, 0·3 mg, or 0·4 mg; initiated at 0·05 mg per day and incrementally escalated every 4 weeks] or liraglutide [3·0 mg; initiated at 0·6 mg per day and escalated by 0·6 mg per week]) or matching placebo group (equal injection volume and escalation schedule to active treatment group) using a block size of 56. All treatment doses were delivered once-daily via subcutaneous injections. Participants and investigators were masked to the assigned study treatment but not the target dose. The primary endpoint was percentage weight loss at week 52. The primary analysis was done using intention-to-treat ANCOVA estimation with missing data derived from the placebo pool. This study is registered with ClinicalTrials.gov, number NCT02453711.

Findings: Between Oct 1, 2015, and Feb 11, 2016, 957 individuals were randomly assigned (102-103 participants per active treatment group and 136 in the pooled placebo group). Mean baseline characteristics included age 47 years, bodyweight 111·5 kg, and BMI 39·3 kg/m^2. Bodyweight data were available for 891 (93%) of 957 participants at week 52. Estimated mean weight loss was -2·3% for the placebo group versus -6·0% (0·05 mg), -8·6% (0·1 mg), -11·6% (0·2 mg), -11·2% (0·3 mg), and -13·8% (0·4 mg) for the semaglutide groups. All semaglutide groups versus placebo were significant (unadjusted p≤0·0010), and remained significant after adjustment for multiple testing (p≤0·0055). Mean bodyweight reductions for 0·2 mg or more of semaglutide versus liraglutide were all significant (-13·8% to -11·2% vs -7·8%). Estimated weight loss of 10% or more occurred in 10% of participants receiving placebo compared with 37-65% receiving 0·1 mg or more of semaglutide (p<0·0001 vs placebo). All semaglutide doses were generally well tolerated, with no new safety concerns. The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, as seen previously with GLP-1 receptor agonists.

Interpretation: In combination with dietary and physical activity counselling, semaglutide was well tolerated over 52 weeks and showed clinically relevant weight loss compared with placebo at all doses.

Article 4

Citation:

Blundell, J., Finlayson, G., Axelsen, M., Flint, A., Gibbons, C., Kvist, T., & Hjerpsted, J. B. (2017). *Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes, Obesity and Metabolism, 19(9), 1242–1251.* doi:10.1111/dom.12932

https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.12932

Article type:

Randomized control trial

Abstract:

Aim

The aim of this trial was to investigate the mechanism of action for body weight loss with semaglutide.

Materials and methods

This randomised, double-blind, placebo-controlled, two-period crossover trial investigated the effects of 12 weeks of treatment with once-weekly subcutaneous semaglutide, dose-escalated to 1.0 mg, in 30 subjects with obesity. *Ad libitum* energy intake, ratings of appetite, thirst, nausea and well-being, control of eating, food preference, resting metabolic rate, body weight and body composition were assessed.

Results

After a standardised breakfast, semaglutide, compared with placebo, led to a lower *ad libitum* energy intake during lunch (−1255 kJ; $P < .0001$) and during the subsequent evening meal ($P = .0401$) and snacks ($P = .0034$), resulting in a 24% reduction in total energy intake across all *ad libitum* meals throughout the day (−3036 kJ; $P < .0001$). Fasting overall appetite suppression scores were improved with semaglutide vs placebo, while nausea ratings were similar. Semaglutide was associated with less hunger and food cravings, better control of eating and a lower preference for high-fat foods. Resting metabolic rate, adjusted for lean body mass, did not differ between treatments. Semaglutide led to a reduction from baseline in mean body weight of 5.0 kg, predominantly from body fat mass.

Conclusion

After 12 weeks of treatment, *ad libitum* energy intake was substantially lower with semaglutide vs placebo with a corresponding loss of body weight observed with semaglutide. In addition to reduced energy intake, likely mechanisms for

semaglutide-induced weight loss included less appetite and food cravings, better control of eating and lower relative preference for fatty, energy-dense foods.

Article 5

Citation:

Melanie Davies, Louise Færch, Ole K Jeppesen, Arash Pakseresht, Sue D Pedersen, Leigh Perreault, Julio Rosenstock, Iichiro Shimomura, Adie Viljoen, Thomas A Wadden, Ildiko Lingvay,
Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial, The Lancet, Volume 397, Issue 10278, 2021, Pages 971-984, ISSN 0140-6736,

https://doi.org/10.1016/S0140-6736(21)00213-0.

Article type:

Randomized control trial

Abstract:

Background This trial assessed the efficacy and safety of the GLP-1 analogue once a week subcutaneous semaglutide 2·4 mg versus semaglutide 1·0 mg (the dose approved for diabetes treatment) and placebo for weight management in adults with overweight or obesity, and type 2 diabetes.

Methods This double-blind, double-dummy, phase 3, superiority study enrolled adults with a body-mass index of at least 27 kg/m² and glycated haemoglobin 7–10% (53–86 mmol/mol) who had been diagnosed with type 2 diabetes at least 180 days before screening. Patients were recruited from 149 outpatient clinics in 12 countries across Europe, North America, South America, the Middle East, South Africa, and Asia. Patients were randomly allocated (1:1:1) via an interactive web-response system and stratified by background glucose-lowering medication and glycated haemoglobin, to subcutaneous injection of semaglutide 2·4 mg, or semaglutide 1·0 mg, or visually matching placebo, once a week for 68 weeks, plus a lifestyle intervention. Patients, investigators, and those assessing outcomes were masked to group assignment. Coprimary endpoints were percentage change in bodyweight and achievement of weight reduction of at least 5% at 68 weeks for semaglutide 2·4 mg versus placebo, assessed by intention to treat. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT03552757 and is closed to new participants.

Findings From June 4 to Nov 14, 2018, 1595 patients were screened, of whom 1210 were randomly assigned to semaglutide 2·4 mg (n=404), semaglutide 1·0 mg (n=403), or placebo (n=403) and included in the intention-to-treat analysis. Estimated change in mean bodyweight from baseline to week 68 was –9·6% (SE 0·4) with semaglutide 2·4 mg vs –3·4% (0·4) with placebo. Estimated treatment difference for semaglutide 2·4 mg versus placebo was −6·2 percentage points (95% CI −7·3 to −5·2; p<0·0001). At week 68, more patients on semaglutide 2·4 mg than on placebo achieved weight reductions of at least 5% (267 [68·8%] of 388 vs 107 [28·5%] of 376; odds ratio 4·88, 95% CI 3·58 to 6·64; p<0·0001). Adverse events were more frequent with semaglutide 2·4 mg (in 353 [87·6%] of 403 patients) and 1·0 mg (329 [81·8%] of 402) than with placebo (309 [76·9%] of 402). Gastrointestinal adverse events, which were mostly mild to moderate, were reported in 256 (63·5%) of 403 patients with semaglutide 2·4 mg, 231 (57·5%) of 402 with semaglutide 1·0 mg, and 138 (34·3%) of 402 with placebo.
Interpretation In adults with overweight or obesity, and type 2 diabetes, semaglutide 2·4 mg once a week achieved a superior and clinically meaningful decrease in bodyweight compared with placebo.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S,	Randomized Control Trial	- In this double-blind trial, 1961 adults with a body-mass index of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly	- The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. - Assessed effects regardless of treatment discontinuation or rescue interventions.	- Mean change in bodyweight from baseline to week 68 was -14.9% in semaglutide group compared with the -2.4% - More participants in the semaglutide group were able to achieve a weight loss greater than 5%, 10%, and 15% compared to placebo group at week 68. - Greater improvement in cardiometabolic risk factors and a	-

Yokote K, Zeuthen N, Kushner RF (2021)		assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention.		greater increase in participant-reported physical functioning in the semaglutide group compared to placebo group - More participants in the semaglutide group discontinued treatment due to GI events	
Friedrichsen, M, Breitschaft, A, Tadayon, S, Wizert, A, Skovgaard, D. (2021).	Randomized Control Trial	- A double-blind, parallel-group trial was conducted in 72 adults with obesity, randomized to once-weekly subcutaneous semaglutide (dose-escalated to 2.4 mg) or placebo for 20 weeks	- Gastric emptying was assessed using paracetamol absorption following standardized breakfast. - Subjects reported appetite ratings and Control of Eating Questionnaire (CoEQ) responses were assessed - Energy intake was measured during *ad libitum* lunch.	- Semaglutide reduced hunger and prospective food consumption, and increased fullness and satiety when compared with placebo - The CoEQ indicated better control of eating and fewer/weaker food cravings with semaglutide versus placebo - Bodyweight was reduced by 9.9% with semaglutide and 0.4% with placebo - *Ad libitum* energy intake was 35% lower with semaglutide versus placebo	- Small sample size of 72 adults - CoEQ questionnaire is very subjective from person to person

Patrick M O'Neil, Andreas L Birkenfeld, Barbara McGowan, Ofri Mosenzon, Sue D Pedersen, Sean Wharton, Charlotte Giwercman Carson, Cecilie Heerdegen Jepsen, Maria Kabisch, John P H Wilding (2018)	Randomized Control Trial	- A randomised, double-blind, placebo and active controlled, multicentre, dose-ranging, phase 2 trial. - The study was done in eight countries involving 71 clinical sites. - Eligible participants were adults (≥18 years) without diabetes and with a body-mass index (BMI) of 30 kg/m2 or more. We randomly assigned participants (6:1) to each active treatment group (ie, semaglutide [0・05 mg, 0・1 mg, 0・2 mg, 0・3 mg, or 0・4 mg; initiated at 0・05 mg per day	- The primary endpoint was percentage weight loss at week 52.	- All active treatment groups showed significantly greater estimated reductions in bodyweight than placebo at week 52, and these reductions remained significant after adjustment for multiple testing in the semaglutide groups escalated to final dose on a 4-weekly schedule - For the semaglutide groups escalated every 4 weeks, doses of more than 0·1 mg of semaglutide showed significantly greater weight loss at week 52 than 3·0 mg of liraglutide - Estimated (logistic regression, J2R-MI) weight loss and observed weight loss of at least 5%, 10%, 15%, or 20% of baseline were also dose-dependent for semaglutide - Consistent dose-related improvements in glucose metabolic and most anthropometric outcomes except for waist-to-hip ratio were seen for	- Many of the researchers have received grants and personal fees from Novo Nordisk, the creator of *Wegovy* (semaglutide 2.4mg) injection

		and incrementally escalated every 4 weeks] or liraglutide [3・0 mg; initiated at 0 ・6 mg per day and escalated by 0 ・6 mg per week]) or matching placebo group (equal injection volume and escalation schedule to active treatment group) - Between Oct 1, 2015, and Feb 11, 2016, 957 individuals were randomly assigned (102–103 participants per active treatment group and 136 in the pooled placebo group		semaglutide versus placebo. Systolic and diastolic blood pressures decreased with all active treatments with significant reductions in systolic pressure for liraglutide and all semaglutide doses greater than 0·05 mg compared with placebo. Compared with placebo, there were numeric improvements on semaglutide in other cardiac-associated outcomes (lipids and high-sensitivity C-reactive protein) that reached significance in some groups, without a clear association with dose.	
John Blundell, Graham Finlayson, Mads Buhl	Randomized Control Trial	- Randomised, double-blind, placebo-controlled, two-period crossover	- *Ad libitum* energy intake, ratings of appetite, thirst, nausea and well-being, control of eating, food	- *Ad libitum* energy intake at lunch was approximately 35% lower with semaglutide versus placebo	- Small sample size

Axelsen, Anne Flint, Catherine Gibbons, Trine Kvist, Julie Hjerpsted (2017)		trial investigated the effects of 12 weeks treatment with once-weekly subcutaneous semaglutide, doseescalated to 1.0 mg, in 30 subjects with obesity - Eligible subjects were ≥18 years of age, with a body mass index (BMI) of 30–45 kg/m2, HbA1c <6.5%, and stable body weight (<3 kg change during the past 3 months prior to screening). Key exclusion criteria: diagnosis of type 1 or 2 diabetes; history of chronic/idiopathic acute pancreatitis; personal/family history of	preference, resting metabolic rate, body weight and body composition were assessed. - The primary endpoint was *ad libitum* energy intake during a lunch meal (5 hours after a standardised breakfast meal), after 12 weeks of treatment. - Secondary endpoints included *ad libitum* energy intake during a subsequent evening meal and from an evening snack box; total day-time *ad libitum* energy intake until midnight; duration of *ad libitum* lunch; ratings of appetite parameters, thirst, nausea, and well-being before and after a standardised breakfast meal; palatability of *ad libitum* meals; energy expenditure (resting metabolic rate [RMR] and respiratory quotient [RQ]);	- Energy intake of food categories in the *ad libitum* evening snack box showed an approximately 35% lower intake from high-fat and non-sweet foods with semaglutide versus placebo - At the standardised breakfast meal, fasting overall appetite suppression score was higher with semaglutide versus placebo, indicating less appetite with semaglutide - Postprandial increases from fasting VAS ratings showed greater increases in satiety with semaglutide versus placebo - The COEQ indicated less hunger, better control of eating and meal portion size, less food cravings, particularly for savoury foods, and lower ratings for the pleasantness of food for semaglutide versus placebo	- 2/3 of population were male - Questionnaire very subjective -

		medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; previous surgical treatment for obesity; smoking or use of any nicotine products; use of any medication that could interfere with the trial results; or anticipated change in lifestyle (e.g. eating, exercise or sleeping pattern) during the trial - 30 subjects, 2/3 were male	control of eating and food cravings over the past week; food preference; body weight; and body composition (fat and fat-free mass). - In addition, the multiple-dose pharmacokinetics (PK) and safety and tolerability of semaglutide were investigated.	- After 12 weeks of treatment with semaglutide, a change from baseline in mean body weight of –5.0 kg was observed, versus +1.0 kg with placebo. A three-fold greater loss of mean fat over lean body mass was observed with semaglutide versus placebo - Semaglutide-induced weight loss was associated with proportionally greater losses of body fat than lean body mass.	
Melanie Davies, Louise Færch, Ole K Jeppesen, Arash Pakseresht, Sue D	Randomized Control Trial	- Double-blind, double-dummy, phase 3, superiority study enrolled adults with a body-mass index of at least	- Co-primary outcomes were percentage change in bodyweight from baseline to week 68 and loss of at least 5% of baseline weight at week 68	- There was high completion of treatment (1058 [87%] of 1210) and the trial (1164 [96%] of 1210 - Patients were more likely to achieve at least a 5% reduction	- Many of the researchers declared fees from makers of semaglutide for consultancy,

Pedersen, Leigh Perreault, Julio Rosenstock, Iichiro Shimomura, Adie Viljoen, Thomas A Wadden, Ildiko Lingvay (2021)		27 kg/m² and glycated haemoglobin 7–10% (53–86 mmol/mol) who had been diagnosed with type 2 diabetes at least 180 days before screening. Patients were recruited from 149 outpatient clinics in 12 countries across Europe, North America, South America, the Middle East, South Africa, and Asia - June 4 to Nov 14, 2018, 1595 patients were screened, of whom 1210 were randomly assigned to semaglutide 2·4 mg (n=404), semaglutide 1·0 mg (n=403), or	(semaglutide 2·4 mg *vs* placebo). - Secondary outcomes were proportions of patients achieving bodyweight reductions of at least 10% or 15% at week 68, change from baseline to week 68 in waist circumference, percentage change in bodyweight (semaglutide 2·4 *vs* 1·0 mg) at week 68, change from baseline to week 68 in HbA1c, systolic blood pressure, SF-36v2 physical functioning score, and IWQOL-Lite-CT physical function score - Safety was assessed in all patients who received at least one dose of study drug.	in baseline bodyweight at week 68 (coprimary endpoint) with semaglutide 2·4 mg than with placebo - Similarly, more patients achieved reductions of at least 10%, 15%, or 20% at week 68 with semaglutide 2·4 mg compared with either semaglutide 1·0 mg or placebo - Benefits significantly favouring semaglutide 2·4 mg versus placebo were seen for changes in waist circumference and systolic blood pressure - Improvements were also noted in lipid profile and inflammatory markers - The proportion of patients reporting adverse events was 353 (87·6%) of 403 with semaglutide 2·4 mg, 329 (81·8%) of 402 with semaglutide 1·0 mg, and 309 (76·9%) of 402 with placebo. Gastrointestinal disorders were the most frequently reported events. The most common gastrointestinal events were	advisory board memberships, and speaking from pharmaceutical companies

		placebo (n=403) and included in the intention-to-treat analysis**.** - Patients were randomly allocated (1:1:1) via an interactive web-response system and stratified by background glucose-lowering medication and glycated haemoglobin, to subcutaneous injection of semaglutide 2·4 mg, or semaglutide 1·0 mg, or visually matching placebo, once a week for 68 weeks, plus a lifestyle intervention.		nausea, vomiting, diarrhea, and constipation, which were mostly transient and mild to moderate in severity and the majority of patients continued the trial product and recovered.	

Conclusions:

1. Wilding et al., concluded that participants with overweight or obesity, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight.
2. Friedrichsen et al., concluded that subjects with obesity, once-weekly subcutaneous semaglutide 2.4 mg suppressed appetite,
   improved control of eating, and reduced food cravings, a*d libitum* energy intake and bodyweight versus placebo.
3. O'Neal et al., concluded that combination of dietary and physical activity counselling, with semaglutide, was well tolerated over 52 weeks and showed clinically relevant weight loss compared with placebo at all doses.
4. Blundell et al., 12 weeks' treatment, *ad libitum* energy intake was substantially lower with semaglutide versus placebo with a corresponding loss of body weight observed with semaglutide.
5. Davies et al., adults with overweight or obesity, and type 2 diabetes, semaglutide 2·4 mg once a week achieved a superior and clinically meaningful decrease in bodyweight compared with placebo.

Overarching conclusion:

The use of semaglutide, once weekly injections, along with lifestyle intervention, can produce clinically significant body weight reductions over an extended period of time.

Clinical Bottom Line:

The GLP-1 agonist, semaglutide, is a known diabetes type II injectable medication. Over the past decade, research has been conducted to determine if this drug can induce clinically significant body weigh reductions. Many of the articles specified that participants who received the semaglutide injections weekly also participated in lifestyle alterations that could decrease body weight. As of June 4th, 2021, based on many high clinical trials, the U.S. Food and Drug Administration approved Wegovy (semaglutide) injection (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight with at least one weight-related condition (such as high blood pressure, type 2 diabetes, or high cholesterol), for use in addition to a reduced calorie diet and increased physical activity. I believe this can be first step in the right direction for the U.S. to promote and assist its citizens in achieving a healthy weight and lifestyle. As a future clinician, I will do my best to promote a healthy diet and active lifestyle, but if my future patients need that extra push, semaglutide 2.4 mg once weekly injections will most certainly make an impact on their lives in achieving their body weight reduction goals.

Weight of Evidence:

1. This article was a randomized control trial, which included 1,961 adults, followed over a 68-week period, to study the percentage change in body weight reduction of at least 5%.
2. This article was a randomized control trial, which included 72 adults, followed over a 20-week period to study gastric emptying, appetite, and energy intake in subjects with obesity.
3. This article was a randomized control trial, which included 957 individuals, who were followed over a 52-week period to study the percentage weight loss.
4. This article was a randomized control trial, which included 30 subjects, 2/3 of which were male, who were followed over a 12-week period to assess *ad libitum* energy intake during a lunch meal among many other secondary endpoints.
5. This article was a randomized control trial, which included 1,210 patients, who were followed over a 68-week period to determine the percent change in body weight of at least 5%.

Magnitude of Effects:

1. The mean change in body weight from baseline to week 68 was -14.9% in the semaglutide group as compared with -2.4% with placebo, for an estimated treatment difference of -12.4 percentage points (95% confidence interval [CI], -13.4 to -11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was -15.3 kg in the semaglutide group as compared with -2.6 kg in the placebo group (estimated treatment difference, -12.7 kg; 95% CI, -13.7 to -11.7). Those who initiate CU by age 15 and age 18 demonstrate more symptoms of Schizophrenia by age 26 as compared with neverusers.19 A noteworthy study has shown that as the duration of CU increases from first use (6 years), the odds of development of a nonaffective psychosis increase (adjusted OR [aOR] D 2.2), as well as number/severity of delusions (aOR D 4.3) and hallucinations (aOR D 2.8).38 These associations held true for sibling pairs, decreasing the likelihood that unmeasured confounding factors affected outcomes.
2. *Ad libitum* energy intake was 35% lower with semaglutide versus placebo (1736 versus 2676 kJ; estimated treatment difference: –940 kJ; *P* <0.0001). Semaglutide reduced hunger and prospective food consumption, and

increased fullness and satiety when compared with placebo (all P <0.02). The CoEQ indicated better control of eating and fewer/weaker food cravings with semaglutide versus placebo (P <0.05). Bodyweight was reduced by 9.9% with semaglutide and 0.4% with placebo. Safety was consistent with the known profile of semaglutide.

3. Estimated mean weight loss was −2・3% for the placebo group versus −6・0% (0・05 mg), −8・6% (0・1 mg), −11・6% (0・2 mg), −11・2% (0・3 mg), and −13・8% (0・4 mg) for the semaglutide groups. All semaglutide groups versus placebo were significant (unadjusted p≤0・0010), and remained significant after adjustment for multiple testing (p≤0・0055). Mean bodyweight reductions for 0・2 mg or more of semaglutide versus liraglutide were all significant (−13・8% to −11・2% *vs* −7・8%). Estimated weight loss of 10% or more occurred in 10% of participants receiving placebo compared with 37–65% receiving 0・1 mg or more of semaglutide (p<0・0001 *vs* placebo).
4. *Ad libitum* energy intake at lunch was approximately 35% lower with semaglutide versus placebo (primary endpoint; estimated treatment difference (ETD) [95% confidence interval (CI)] –1255 kJ [–1707; –804]; P<0.0001) In addition, *ad libitum* food intake and meal duration were significantly lower with semaglutide versus placebo. Lower *ad libitum* energy and food intake were also observed at subsequent evening meals and the evening snack box. Total energy intake across all *ad libitum* meals was approximately 24% lower with semaglutide versus placebo (ETD [95% CI] –3036 kJ [–4209; –1864]; P<0.0001). Energy intake of food categories in the *ad libitum* evening snack box showed an approximately 35% lower intake from high-fat and non-sweet foods with semaglutide versus placebo (P=0.0184). Macronutrient compositions of foods consumed in the *ad libitum* evening meal and evening snack box were similar between treatments.
5. Estimated change in mean bodyweight from baseline to week 68 was –9·6% (SE 0·4) with semaglutide 2·4 mg *vs* –3·4% (0·4) with placebo. Estimated treatment difference for semaglutide 2·4 mg versus placebo was −6·2 percentage points (95% CI −7·3 to −5·2; p<0·0001). At week 68, more patients on semaglutide 2·4 mg than on placebo achieved weight reductions of at least 5% (267 [68·8%] of 388 *vs* 107 [28·5%] of 376; odds ratio 4·88, 95% CI 3·58 to 6·64; p<0·0001). Adverse events were more frequent with semaglutide 2·4 mg (in 353 [87·6%] of 403 patients) and 1·0 mg (329 [81·8%] of 402) than with placebo (309 [76·9%] of 402). Gastrointestinal adverse events, which were mostly mild to moderate, were reported in 256 (63·5%) of 403 patients with semaglutide 2·4 mg, 231 (57·5%) of 402 with semaglutide 1·0 mg, and 138 (34·3%) of 402 with placebo.

Clinical Significance:

It is estimated that more than 2 in 3 adults are overweight or have obesity. Obesity is directly related to numerous chronic health conditions that can easily be prevented with proper diet and regular activity. It is not easy task, hence why the recent FDA approval of semaglutide, can provide additional benefits to already existing weight management programs. This is the first drug that is approved for chronic weight management since 2014. The FDA will most likely be determined to approve more drugs that can help Americans who have weight issues. Maintaining a healthy weight can prevent many of the chronic medical conditions that the U.S. is heavily known for: diabetes type II, hypertension, hyperlipidemia, metabolic syndrome, and many more. It will be interesting to see the impact *Wegovy* (semaglutide) has on the U.S. within the next 5-10 years.

Any other considerations:

Although semaglutide has produced clinically significant weight loss reduction in its patients, adverse effects are a big component to consider. The main adverse effects of semaglutide are nausea, diarrhea, vomiting, constipation, abdominal pain and many more. Pts may feel reluctant to begin semaglutide or even discontinue its use if they cannot tolerate the adverse effects anymore. Perhaps soon, we may see newer obesity/weight loss medications that are associated with fewer side effects. At the end of the day, patients must always remember that the effects demonstrated within the clinical trials were all associated in combination with lifestyle changes. Semaglutide should not be considered a magical drug to cure obesity but rather an extra push for those who may struggle with more conservative means of losing weight.