A Review of "Once-Weekly Semaglutide in Adults with Overweight or Obesity" by Wilding et al. (2021)

Reviewer 2

January 14, 2026

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> I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.
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> Plato, *The Apology of Socrates*, 21d

> To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Wilding, J.P.H., Batterham, R.L., Calanna, S., Davies, M., Van Gaal, L.F., Lingvay, I., McGowan, B.M., Rosenstock, J., Tran, M.T.D., Wadden, T.A., Wharton, S., Yokote, K., Zeuthen, N., and Kushner, R.F. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. *New England Journal of Medicine*. Vol. 384, No. 11, pp. 989–1002.

URL: https://www.nejm.org/doi/full/10.1056/NEJMoa2032183

Abstract Summary: This double-blind trial assessed the efficacy and safety of once-weekly subcutaneous semaglutide (2.4 mg) plus lifestyle intervention versus placebo in 1961 adults with overweight or obesity without diabetes, finding a mean body weight reduction of 14.9% in the semaglutide group compared to 2.4% in the placebo group.

Key Methodology: Randomized, double-blind, placebo-controlled phase 3 trial (STEP 1 Study) over 68 weeks, comparing semaglutide (2.4 mg) to placebo, both adjunct to lifestyle intervention, using ANCOVA and logistic regression for analysis.

Research Question: Can adults with obesity achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention?

Summary

Is It Credible?

The verdict on this article is one of high confidence in its primary conclusions, tempered only by a series of clerical inconsistencies that suggest a hurried article preparation rather than fundamental scientific flaws. Wilding et al. present a randomized, double-blind, placebo-controlled trial that demonstrates a profound effect of once-weekly semaglutide on body weight. The central claim—that the drug produces clinically relevant weight loss substantially superior to placebo—is supported by an effect size so large that it is immune to the minor statistical and presentational issues identified. The methodology is standard for a large-scale Phase 3 industry-sponsored trial, and while the heavy involvement of the sponsor requires the reader to be vigilant, the data appear robust. The article succeeds in establishing semaglutide 2.4 mg as a distinct escalation in pharmacological efficacy for obesity, bridging the gap between previous medications and bariatric surgery.

The evidence for efficacy is overwhelming. A treatment difference of 12.4 percentage points between the semaglutide and placebo groups is a signal that rises clearly above the noise of any methodological limitations. While there are valid technical discussions to be had regarding the statistical handling of missing data—specifically the reliance on the "Missing At Random" assumption for secondary estimands—the primary analysis utilizes a more robust multiple imputation approach that preserves the intention-to-treat principle. The fact that over half of the participants in the treatment group lost more than 15 percent of their body weight provides a categorical confirmation of the mean results. Even the observation that approximately 10 percent of completers were on sub-maximal doses does not detract from the findings; rather, it suggests that the efficacy profile is resilient even when tolerability issues force dose reductions.

However, the article contains a surprising number of clerical errors and inconsistencies between tables and footnotes, particularly regarding safety data. For instance, there is a direct contradiction between the body of Table 3 and its footnotes regarding the number of deaths in the placebo group, and a similar confusion regarding the precise number of discontinua-

tions due to adverse events. Furthermore, the labeling of observed data percentages as the "treatment policy estimand" in Table 2 is technically inaccurate and potentially confusing. While these errors are likely the result of editorial oversight rather than an attempt to mislead, they represent a lack of precision that is disappointing in a study of this magnitude. They force the reader to cross-reference supplements and footnotes to ascertain exact safety counts, which introduces unnecessary friction into the assessment of the article.

Ultimately, the reality revealed by this article is a significant advancement in the management of obesity. The study convincingly demonstrates that targeting the GLP-1 pathway with high-dose semaglutide can replicate weight loss outcomes previously thought attainable only through surgical intervention. The limitations regarding the homogeneity of the study population (predominantly White and female) and the lack of data from the washout period prevent a definitive conclusion regarding the universality of the effect or the sustainability of weight loss off-treatment. Nevertheless, the article contributes a pivotal piece of evidence to the field, establishing a new benchmark for efficacy in antiobesity pharmacotherapy. The flaws are presentational; the finding is real.

The Bottom Line

Wilding et al. provide compelling, high-quality evidence that once-weekly semaglutide 2.4 mg results in substantial weight loss for adults with obesity, with an effect size that far exceeds that of placebo and previous generation drugs. While the study is robust, the reporting contains occasional inconsistencies, including several clerical contradictions regarding safety counts and imprecise labeling of statistical estimates. These errors reflect deficiencies in the article preparation but do not undermine the validity of the primary conclusion: this intervention represents a step-change in the medical treatment of obesity.

Specific Issues

Sponsor involvement and conflict of interest: The trial was designed, monitored, and analyzed by the sponsor, Novo Nordisk, and several authors are employees or shareholders. While this is standard practice for Phase 3 registration trials, the extensive role of the sponsor in data collation and analysis necessitates a higher degree of scrutiny regarding discretionary analytical choices. The article fully discloses these conflicts, but the inherent potential for bias in industry-led research remains a structural limitation of the evidence base (pp. 990, 1000).

Clerical contradictions in safety reporting: There are multiple numerical inconsistencies between the tables and the article or footnotes. Most notably, Table 3 lists "1" fatal event in the placebo group, yet the accompanying footnote describes three separate deaths (glioblastoma, aspiration pneumonia, and severe sepsis) in that same group (p. 998). Similarly, Table 3 reports 92 discontinuations due to adverse events in the semaglutide group, while the participant flow diagram (Figure S2) lists 91 (p. 998; Appendix, p. 28). These discrepancies, while likely clerical, obscure the precise safety data.

Inaccurate labeling of statistical estimands: Table 2 is titled "End Points for the Treatment Policy Estimand," implying the results are derived from the multiple imputation model used for the primary analysis. However, a footnote clarifies that the percentages reported (e.g., the proportion achieving ≥ 5 percent weight loss) are actually based on the observed data from participants available at week 68. This conflation of modeled estimates and raw observed rates is technically inaccurate and potentially confusing regarding the handling of missing data (pp. 996, 997).

Omission of washout period data: The trial design included a 7-week washout period following the 68-week treatment phase to assess off-drug effects. However, the article does not report any data regarding weight regain during this period. This omission limits the ability to assess the "sustained" nature of the weight loss once the pharmacological intervention ceases, a critical question for long-term weight management (p. 990).

Demographic limitations: The study population was predominantly female (74.1 percent) and White (75.1 percent). While the authors acknowledge this limitation, it restricts the gen-

eralizability of the findings to men and other racial or ethnic groups who may have different risk profiles or responses to GLP-1 receptor agonists (pp. 992, 1000).

Reporting of safety signals in the supplement: Significant safety signals are relegated to the Supplementary Appendix. Specifically, semaglutide was associated with an increase in resting pulse rate (estimated treatment difference of 4.26 bpm) and an increase in serum lipase levels (ratio to baseline 1.41) (Appendix, p. 26). While the article mentions the lack of clinical pancreatitis cases, the biomarker data suggesting pancreatic stress and cardiovascular autonomic effects are relegated to the Supplementary Appendix and not presented in the main text.

Limitations of indirect comparisons: The authors compare their results to the SCALE trial of liraglutide, claiming superior efficacy. While they acknowledge that this is an indirect comparison between studies with different populations and designs, such cross-trial comparisons are methodologically weak and should be interpreted with caution (p. 999).

Statistical assumptions regarding missing data: For the "trial product estimand," the analysis utilizes a Mixed Model for Repeated Measurements (MMRM), which assumes data are "Missing At Random" (MAR) (Appendix, p. 14). Given that adverse events drove a higher rate of discontinuation in the treatment group, the MAR assumption may not fully hold, potentially biasing the secondary estimand. However, the primary "treatment policy estimand" used a more robust multiple imputation method.

Dosing variability among completers: The supplement notes that approximately 10 percent of participants who completed the trial on semaglutide were not on the target 2.4 mg dose due to tolerability issues (Appendix, p. 28). While this reflects real-world usage, it introduces heterogeneity into the exposure-response relationship, although the intention-to-treat analysis correctly accounts for this.

Methodological variability in body composition analysis: In the DXA substudy, the measurement of visceral fat was inconsistent, utilizing different anatomical regions (L4, android, or gynoid) depending on the scanner available at the specific site (Appendix, p. 24). This lack of standardization introduces noise into the body composition data.

Demographic differences in the substudy: The subpopulation selected for the DXA analysis

was older and had a higher proportion of White participants than the main study population (Appendix, p. 17). This selection bias, while disclosed in the supplement, limits the applicability of the body composition findings to the full study cohort.

Baseline imbalance in prediabetes: There was a baseline imbalance in the prevalence of prediabetes (45.4 percent in the semaglutide group vs. 40.2 percent in the placebo group) (p. 992). While randomization does not guarantee perfect balance, this discrepancy could theoretically influence the magnitude of metabolic improvements observed.

Lack of detail on rescue medications: The article notes that a small number of participants received "other antiobesity medication" as a rescue intervention but fails to specify which medications were used (p. 991). While the number of participants is negligible (n=5 in the treatment group), this represents a gap in the reporting of concomitant interventions.

Mathematical consistency of BMI change: A discrepancy was noted between the percentage change in weight and the percentage change in BMI derived from the tables (p. 992, p. 996; Appendix, p. 19). This is mathematically expected, as the mean of percentage changes is not equivalent to the percentage change of the means, but it can appear as an inconsistency to a lay reader.

Increased incidence of hepatobiliary disorders: The article reports a higher incidence of hepatobiliary disorders (2.5 percent vs. 0.8 percent) in the treatment group (p. 998). While this is a known risk of rapid weight loss, it represents a specific safety burden that accompanies the efficacy benefits.

Future Research

Evaluation of post-treatment weight trajectory: Future research must prioritize the collection and publication of data following the cessation of therapy. The current article leaves the "washout" period opaque. A study designed specifically to track weight regain kinetics after withdrawal of the 2.4 mg dose is required to determine if the treatment modifies the underlying disease process or functions solely as a maintenance therapy.

Diverse population efficacy and safety: To address the demographic limitations of the current article, a trial specifically powered to evaluate efficacy and safety in men and non-White populations is necessary. This research should investigate whether the magnitude of weight loss and the profile of adverse events (particularly gastrointestinal) remain consistent across different biological sexes and ethnic backgrounds.

Long-term cardiovascular outcomes: While the article demonstrates improvements in surrogate markers (blood pressure, HbA1c), future research must move beyond surrogates to hard clinical endpoints. A long-term cardiovascular outcomes trial is needed to confirm that the weight loss and metabolic improvements induced by semaglutide 2.4 mg translate into a reduction in myocardial infarction, stroke, and cardiovascular death.

Mechanistic analysis of pulse rate elevation: Given the signal of increased resting heart rate found in the supplementary appendix, mechanistic studies are required to elucidate the cause of this chronotropic effect. Research should determine whether this increase is a compensatory hemodynamic response to weight loss and vasodilation or a direct effect on the sinoatrial node, and whether it carries long-term arrhythmogenic risk.

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