Weight Loss and Nausea from Subcutaneous and Oral Semaglutide Accurately Simulated with a QSP Model

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OBJECTIVE

The recent availability of effective GLP-1R agonist (GLP-1RA) based treatments of obesity has provided great benefit to patients. Understanding the balance between body weight (BW) loss and nausea is paramount in predicting the effectiveness of GLP-1RA based medications, as is potential impact of delivery method. Quantitative systems pharmacology (QSP) modeling can aid in predicting both efficacy and adverse events of compounds, in particular assessing sources of similarities and differences between treatment protocols.

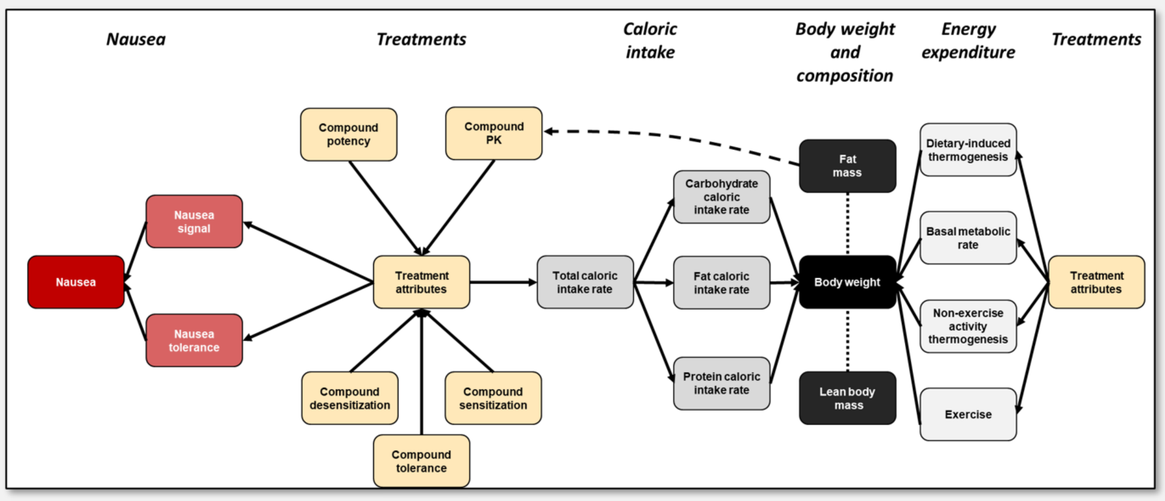
METHODS

OBESITYsym, a QSP model, was developed to enable simultaneous prediction of BW and nausea due to pharmacologic treatments. This mechanistic mathematical model includes components of energy balance: caloric intake, energy expenditure, body composition, adaptation, as described by Hall 2010 (1). It also includes a novel submodel of nausea sensitivity and tolerance, a pharmacology submodel linking compound exposure, energy balance, and nausea with PK models and compound potency. Calibration and validation are described in Siler 2024 (2), including development for the subcutaneous (sc) semaglutide (sema) response. An oral sema representation was built through incorporation of a literature oral PK model (3) and PD based on the calibrated sc response. Simulated dosing included uptitration in accordance with protocols.

RESULTS

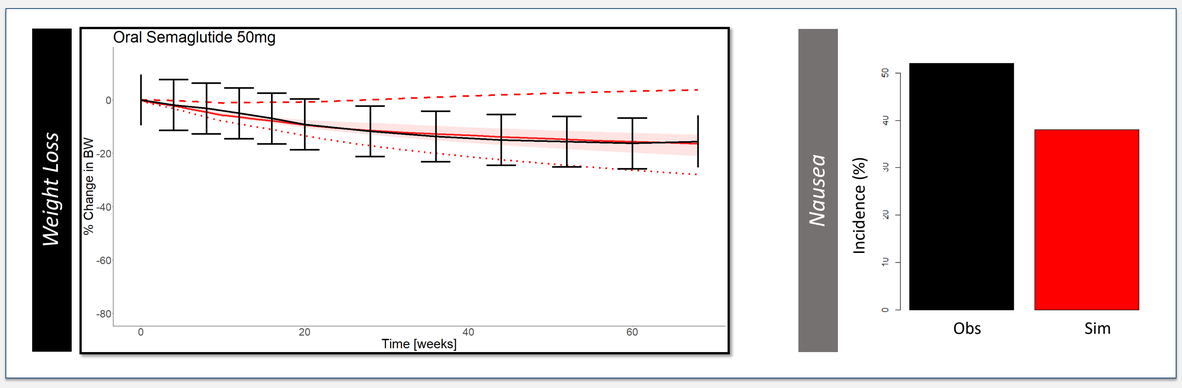
QSP MODEL

Diagrammatic illustration of OBESITYsym. The ability for drugs to affect food intake and/or energy expenditure as well as to influence sensitivity and/or tolerance to nausea is predicted simultaneously.



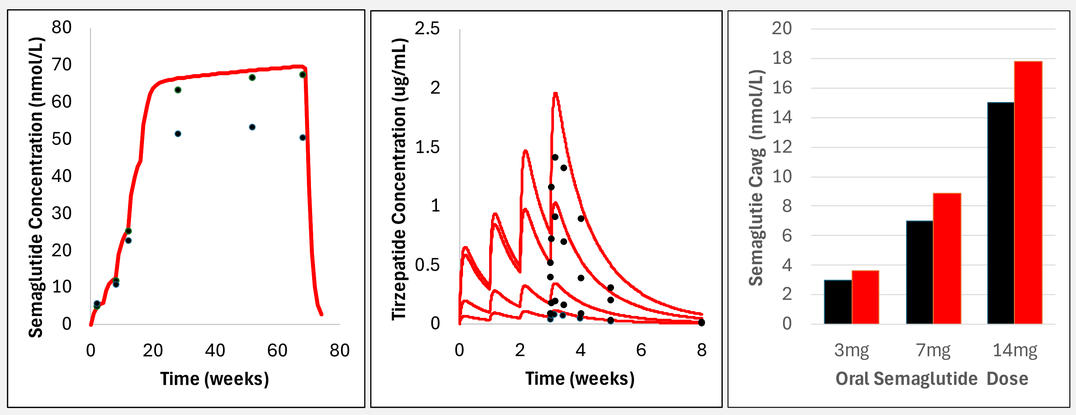
PREDICTION

Simulated weight loss and nausea for oral 50 mg QD (uptitrated) semaglutide. Predicted changes in weight loss (red) align well with reported (9) clinical data (black). Predicted overall nausea incidence was 38% (red bar), aligning well with the reported 52% incidence of individuals (red bar) reporting nausea in (9).

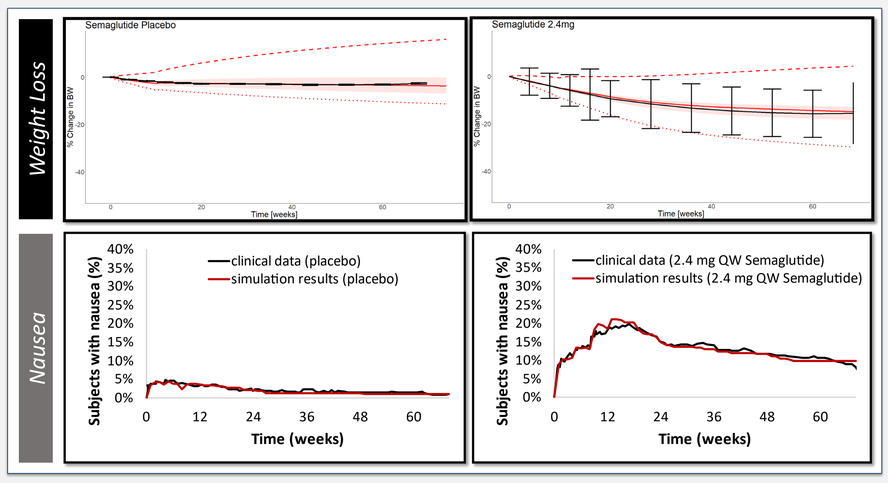


CALIBRATION

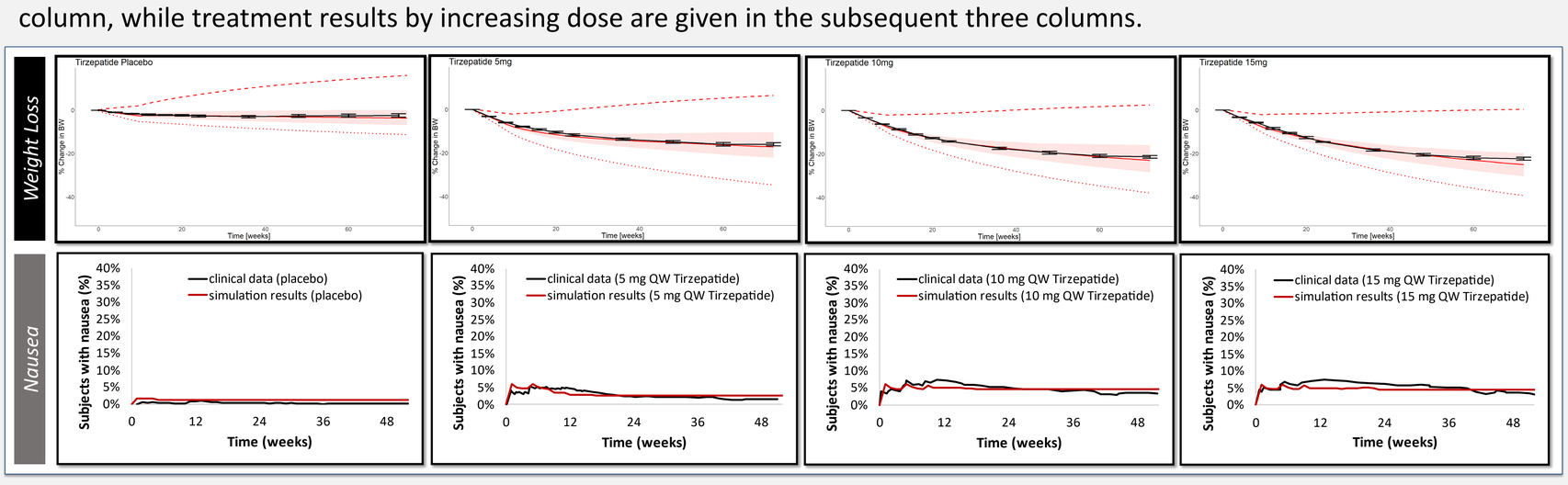
Simulated pharmacokinetic profiles for semaglutide (sc, oral) and tirzepatide (sc). Predicted central compartment mean values (red) align well with reported (3, 4, 5) clinical data (black). Semaglutide sc results are given on the left, tirzepatide sc results in the middle, and semaglutide oral on the right.



Simulated weight loss and nausea for subcutaneous 2.4 mg QW (uptitrated) semaglutide and placebo. Predicted changes in weight loss and nausea (red) align well with reported (6) clinical data (black). Placebo results are given on left, while treatment results are on the right.



Simulated weight loss and nausea for subcutaneous 5, 10, or 15 mg QW tirzepatide and placebo. Predicted changes in weight loss and nausea (red) align well with reported (7, 8) clinical data (black). These simulation results includes the interactions between GLP-1 and GIP receptor agonism to enhance weight loss and minimize nausea. Placebo results are given on leftmost column, while treatment results by increasing dose are given in the subsequent three columns.



CONCLUSION

- OBESITYsym can be used to evaluate the efficacy and nausea potential for novel treatments, including oral GLP-1RA and compounds that utilize additional mechanisms to adjust energy balance
- PD/MoA for sc and oral sema was the same in all simulations, indicating that regardless of delivery route similar results can be achieved if similar levels of compound can be reached in the systemic circulation.

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