Weight Loss and Nausea from Obesity Treatments are Accurately Simulated with OBESITYsym

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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 oral GLP-1RA based medications
- Quantitative systems pharmacology (QSP) modeling can aid in predicting both efficacy and adverse events of compounds, particularly when clinical data are available

METHODS

- OBESITYsym, a QSP model, has been developed to enable simultaneous prediction of BW and nausea due to pharmacologic treatments targeting caloric intake and/or energy expenditure (Figure 1)
- This mechanistic, mathematical model enables prediction of body weight changes, body composition via direct and indirect effects of caloric intake and energy expenditure (1)
- The novel submodel of nausea includes both sensitivity and tolerance, establishing the link between compound exposure, and nausea with PK models and compound potency
  - —*in vitro* measured GLP-1R potency values (EC50) from the literature were employed for each compound.
  - —Compound exposure was predicted utilizing pharmacokinetic models within OBESITYsym
- The model has been **calibrated** with clinical data from compounds **administered both subcutaneously and orally** including **semaglutide** (sema, 2.4 mg QW with uptitration (2)), **liraglutide** (lira, 3 mg QD with uptitration (3)), **tirzepatide** (tirze, 5, 10, and 15 mg QW with uptitration(4,5)), and **orforglipron** (orfo, 12 and 45 mg QD with uptitration (6)) via simulations of phase 2 or 3 clinical trial protocols in a simulated obese population (SimPops)
- Orfo 24 and 36 mg (6) doses (QD for 36 weeks) were used to validate OBESITYsym

FIGURES

Figure 1: 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.

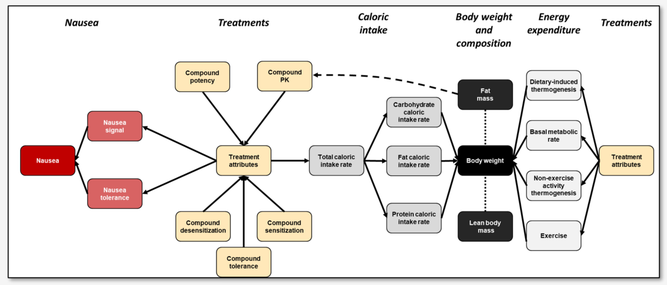


Figure 2: Validation predictions of weight loss and nausea for oral oforglipron. Predicted changes in weight loss over time and nausea (red) align well with reported (6) clinical data (black), providing validation of OBESITYsym. Weight loss results are given on left, while nausea results are on the right.

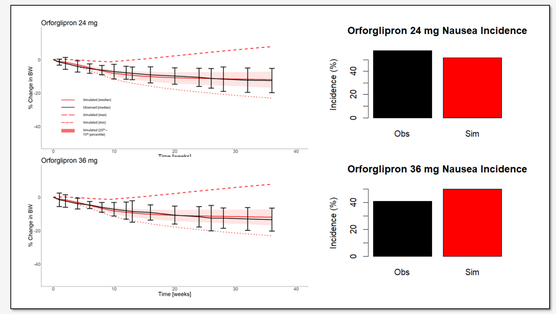


Figure 3: Simulated weight loss and nausea for subcutaneous 2.4 mg QW (uptitrated) semaglutide and placebo. Predicted changes in weight loss and nausea (red) align well with reported (2) clinical data (black). Placebo results are given on left, while treatment results are on the right.

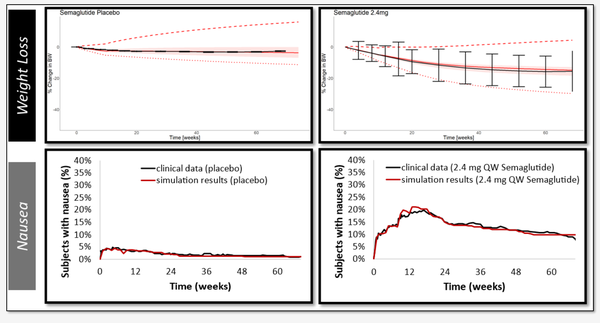


Figure 4: Simulated weight loss and nausea for subcutaneous 3.0 mg QD (uptitrated) liraglutide and placebo. Predicted changes in weight loss and nausea (red) align well with reported (3) clinical data (black). Placebo results are given on left, while treatment results are on the right.

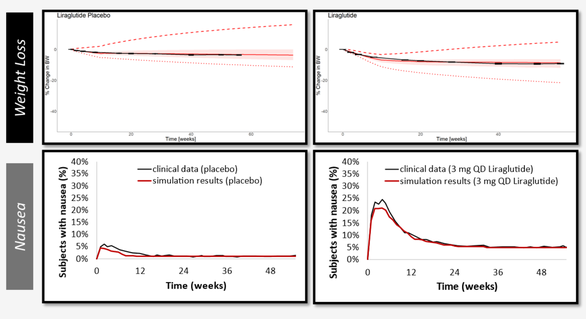
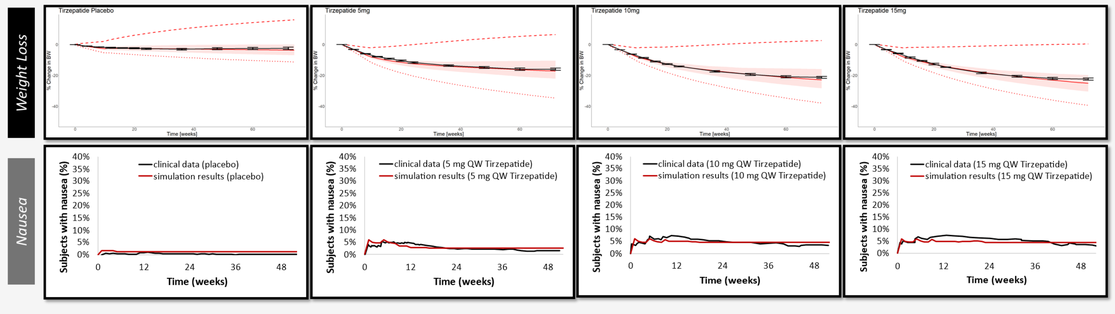


Figure 5: Simulated weight loss and nausea for subcutaneous 5, 10, or 15 mg QW tirzepatide and placebo. Predicted changes in weight loss and nausea (red) align well with reported (4,5) clinical data (black). These simulation results includes the interactions between GLP-1 and GIP receptor agonism to enhance weight loss and minimize nausea. Placebo results are given on left, while treatment results are on the right.



RESULTS

- OBESITYsym is able to simulate the time-dependent weight loss and nausea responses to various obesity treatments, including placebo effects.
- Validation predictions with orfo (Figure 2) align well with clinical data (6), demonstrating the ability for OBESITYsym to predict weight loss and nausea.
- Calibration simulations with semaglutide and liraglutide (Figures 3,4) demonstrate the ability for the model to capture the weight loss effects as well as sensitivity and tolerance to GLP-1RA.
- Calibration simulations with multiple doses of tirzepatide (Figure 5) demonstrate the ability for the model to capture the weight loss effects as well as sensitivity and tolerance to dual GLP-1 + GIP receptor agonists. The model includes mechanistic interactions between these two targets to enhance weight loss and minimize nausea sensitivity.
- The influence of lifestyle modification, as represented by the placebo effects, can be captured with OBESITYsym.

CONCLUSION

OBESITYsym successfully represents the effects of obesity treatments sema, lira, tirze, and orfo on weight loss and nausea; this includes placebo effects. OBESITYsym is inclusive of different drug delivery routes (subcutaneous, oral), and it can support the evaluation of other weight loss treatments to maximize weight loss while minimizing nausea in monotherapy and combination settings.

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