PERSPECTIVE

Incorporating Placebo Response in Quantitative Systems Pharmacology Models

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Although quantitative systems pharmacology (QSP) models have focused on the descriptions of biological responses to drugs, less attention has been devoted to the placebo effect. Unlike responses driven purely by the drug mechanism of action, placebo responses can be difficult to describe and can have underpinnings in both psychology and neurobiology, making them challenging to incorporate in mechanistic QSP models. In this article, we discuss the pros and cons of various approaches for incorporating placebo responses in QSP models.

BACKGROUND

QSP has been broadly defined as a multidisciplinary mechanistic modeling approach focused on understanding, in a predictive manner, how drugs modulate cellular networks in space and time to impact human pathophysiology.[1] A recently conducted industry survey revealed that there is a wide range of models that can be considered QSP.[2] Although these models are based on biological, chemical, and physiological mechanisms, they often have empirical components. A key feature of these models is to make comparisons between therapies, particularly those with different mechanisms of action (MOA). To properly compare simulated results across therapies, it is often necessary to account for the placebo response.

Placebo response is the improvement in the symptoms of a patient when given a pharmacologically inert substance that looks identical to the drug treatment, often administered in the control arm of a clinical trial. Patient responses from the active arms therefore have contributions from the MOA of the drug as well as the placebo response, which is driven by both psychological and physiological factors.[3] By definition, a mechanistic QSP model is designed to represent the underlying biology of the system of interest and how drugs affect that system. Therefore, a QSP model can only properly represent the responses driven by the MOA of a drug. However, because placebo responses are an unavoidable component of the overall response, there is an important need to discuss the different methods of treating placebo responses within a mechanistic model. This is of particular relevance if the placebo response varies significantly from trial to trial. Consider that it can be unclear how to set calibration targets for simulation in a QSP model for two drugs both with reported treatment effects of 65%, where one has a placebo effect of 35% but the other 20%.

EMPIRICAL MODEL FOR PLACEBO

A common method for dealing with placebo response is to construct a mathematical model that mimics the observed time course of response in patients receiving placebo. These models can take many forms, such as linear, exponential, or polynomial equations. The variability in placebo response between patients is often included as an empirical distribution using a mixed-effects approach. This variability is typically coded as an additive term in the placebo model so that individual patients can have either positive or negative responses. It is generally assumed that this placebo response relationship will be observed in both patients receiving placebo and patients receiving a pharmacological intervention. Therefore, the pharmacological effect of the drug is added to the placebo response in those patients receiving the drug.[4] In practical terms, both placebo and treatment arms are explicitly incorporated within the overall simulated response (**Figure 1**).

The empirical approach has the advantage of simplicity, as these equations are generally easy to implement in any modeling software. However, because of the empirical nature of these models, they are not well suited for extrapolating beyond the range of observed data. In addition, if placebo responses vary across studies, a separate model may be needed for each study. Note that the change in placebo response over time could include aspects of natural disease progression. Although in certain cases natural disease progression is an important part of the overall response, the assumption with this approach is that the placebo response inherently includes some disease progression. Further consideration in the form of separately accounting for disease progression could be warranted for longer term studies, particularly if there is a need to extrapolate beyond available data.

PLACEBO AS REFERENCE

Another approach is to use the placebo data as a reference. There are a couple of different ways this could be carried out. For example, one could subtract the placebo response from the treatment response and use the response above placebo as the observed data for model calibration and qualification (**Figure 1**).[5] Alternatively, one could normalize the treatment response by the placebo response and use the fold change relative to placebo as the observed data

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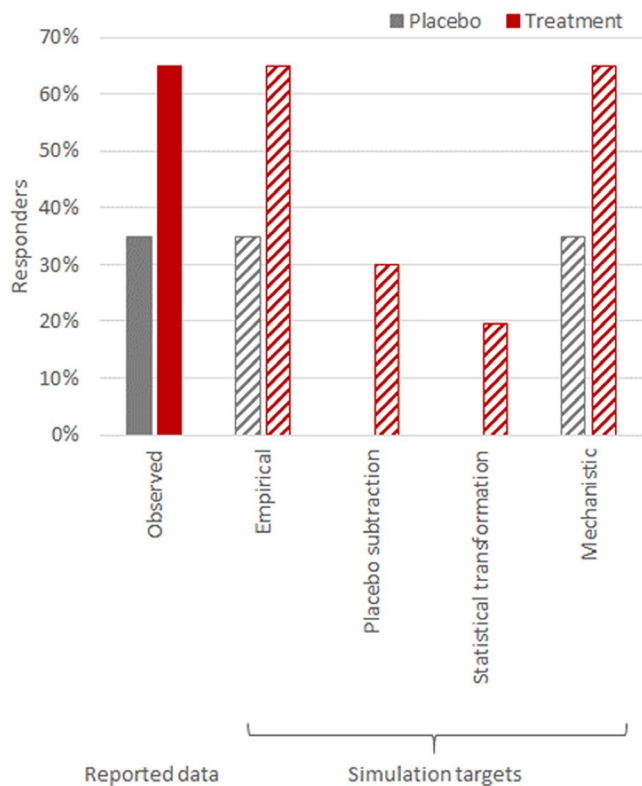
Figure 1 Comparison of calibration/qualification targets (hatched) for quantitative systems pharmacology model relative to observed data (solid) with different methods to account for placebo. Given the observed data, simulation targets can vary depending on the method to account for placebo: empirical, placebo subtraction, statistical transformation, or mechanistic. In the case of simulated targets, the placebo sizes are shown for the methods that explicitly incorporate placebo response within the overall simulated response.

(see **Figure S1**). In either case, placebo is not a part of the overall model-fitted response.

This approach to placebo assumes that the pharmacodynamic response in the model is driven purely by the mechanism of action of the drug. For the purposes of applying a QSP model within a preclinical or clinical team setting, this approach is easy to explain and avoids potential discussions about mathematical transforms or assumptions accounting for the placebo response. Implicit is the assumption that the response above placebo should be treated equally even among trials with significantly varying placebo response sizes. This is of particular concern when comparing against drugs that had similar reported treatment effects but significantly different placebo responses. This concern is amplified with the normalization approach. As absolute placebo responses get smaller, fold differences become magnified. This can introduce bias where the treatment effect is driven not by the drug itself but by a low placebo rate and hence overestimate the impact of the therapy in the QSP model.

Taken together, modeling the response above placebo is feasible if the intent of the model is to compare responses between the drug candidate and standards of care in a specified set of trials, with low variability in placebo responses among trials. However, in cases in which there are large differences in the placebo responses among the trials that are used to calibrate and qualify the model, it is reasonable to argue that the size of the response above placebo should be adjusted based on the size of the placebo response.

STATISTICAL TRANSFORMATION ACCOUNTING FOR PLACEBO

Because placebo response clearly exists, one could adopt the philosophy of studying placebo as one of the treatments. Although difficult to model mechanistically, placebo response has been well studied statistically in some disease states, and certain design factors of clinical trials have been clearly shown to impact the magnitude of placebo response observed in these trials.[6,7] It is therefore natural to apply statistical modeling to placebo response, which in turn should improve the prediction accuracy of responses to active treatments. An advantage is that in a given disease state we generally have more data on placebo response than new treatments, as more or less the same "placebo" was used in historical trials.

Although different statistical approaches exist, here we present a specific method based on the notion of "potential outcomes" from the statistical literature on causal inference.[8] Separately, we can obtain a measure of the placebo response rate (p) from the studies of interest or literature and simulate the biological response assuming a placebo response of zero (b). Under the reasonable assumption that the placebo response is statistically independent of the biological response to the treatment, the probability that a patient would be a responder is one minus the probability that the patient is neither a placebo responder nor a biological responder further subtracted by the probability the patient is only a placebo responder. Mathematically, this can be represented as $1 - (1 - p) \times (1 - b) - p$, simplified to $b - p \times b$. This response is smaller than the biological response rate b; in other words, the placebo response reduces "signal detection" as it is widely known and logically inferred. As a numerical example, if we take a new treatment with a total response rate of 65%, assuming a typical placebo response rate of 35%, the biological population response rate would be $0.3 - 0.35 \times 0.3 = 0.195$ or 19.5% (**Figure 1**), which is quite a bit lower than the placebo subtracted rate of 30% (**Figure 1**), indicating the importance of properly accounting for the placebo response. Subsequently, suppose we calibrate the model to a variety of targets using transformed biological response rates and obtain a response rate of 25% for a novel target. Assuming the same typical placebo response rate of 35%, we can then transform the simulated rate back ($0.25/(1 - 0.35) + 0.35 = 0.735$ or 73.5%) to facilitate comparison with the clinical data. Note that because this approach assumes having placebo and biological response rates, the statistical transformation in its current form is only applicable to outcomes that are rates, for example, response or remission rates.

MECHANISTIC REPRESENTATION

Given that QSP models are mechanistic by definition, it can be nonintuitive to understand how placebo responses can be implemented and whether they are even necessary. For very objective end points such as blood glucose levels in diabetes or lipoprotein concentrations in cardiovascular disease, placebo responses are likely limited and could

be related to circadian rhythms or other normal variations. QSP models that focus on these types of end points typically do not consider placebo responses to be significant and hence reasonably ignore them.[9]

Placebo responses could be mechanistically tied to an input with known variation such as the circadian rhythm[4] or the time and nature of food intake in diabetes studies. However, placebo responses are rooted in both psychology and neurobiology. A mechanistic representation of placebo in models that address these therapeutic areas is particularly warranted provided there are appropriate hypotheses with supporting mechanistic data.[10] With either mechanistic approach, both placebo and treatment effects are simulated and the QSP model calibrated/qualified against the raw reported data (**Figure 1**). In contrast, if these mechanisms do not overlap with the scope of biology in the QSP model, there may be little incentive to incorporate them as the increased model complexity would likely not lead to improved utility of the model.

CONCLUSIONS

Response to placebo is a key component of clinical trials and critical for the interpretation of response in the treatment arms. Similarly, how placebo is treated when using QSP models can influence the interpretation of simulation results. The choice of the most appropriate approach to placebo depends on several factors, including the application of the QSP model, nature of the placebo data, and whether the placebo responses can be directly tied to an understood and mathematically representable MOA. The disease area focus of the QSP model can influence these factors based on the nature of the clinical outputs (e.g., objective vs. subjective, continuous vs. binary) and biological mechanisms represented. **Table 1** illustrates the appropriate placebo models to use in various circumstances, including those in which ignoring the placebo response may be reasonable. In addition, a table summarizing the pros and cons of each approach is included in the supplemental information (**Table S1**) as well as an illustration showing the impact of the different placebo

approaches using clinical trial data for rheumatoid arthritis (**Figure S1**). Through careful consideration of the placebo response, the implications of simulation results using QSP models can be more fully understood and the risk of erroneous conclusions or decisions reduced.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

Figure S1. Observed placebo and drug clinical trial data for the percentage of patients achieving the American College of Rheumatology 20% improvement criteria (ACR20) response in selected rheumatoid arthritis are shown on the left. Simulation/calibration targets for each drug are shown on the right using each method for incorporating the placebo response: (**a**) empirical, (**b**) placebo as reference by subtraction, (**c**) placebo as reference by normalization, (**d**) statistical transformation, and (**e**) mechanistic.
Table S1. Pros and cons of placebo approaches in QSP models.

Conflict of Interest. The authors declared no competing interests for this work.

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Table 1 Appropriate placebo models to use in various modeling situations

Modeling aims	Appropriate placebo models
Compare data from trials where the sizes of placebo responses are very similar	Empirical model, placebo as reference
Compare data from trials in which the sizes of placebo responses are not very similar	Statistical transformation
Compare data from trials in which the placebo response is high relative to treatment responses	Statistical transformation
Compare data from trials in which the placebo response is low relative to treatment responses	Empirical model, placebo as reference
Disease area where the placebo response can be directly tied to an understood mechanism of action or known variations in input parameters	Mechanistic representation
Prioritization of candidates or investigation of mechanisms of action for candidate compounds	Not applicable