Structural Models Describing Placebo Treatment Effects in Schizophrenia and Other Neuropsychiatric Disorders

Venkatesh Pilla Reddy, 1 Magdalena Kozielska, 1
Martin Johnson, 1 An Vermeulen, 2 Rik de Greef, 3
Jing Liu, 4 Geny M.M. Groothuis, 1 Meindert Danhof 5 and
Johannes H. Proost. 1

Clinical Pharmacokinetics 2011; 50 (7): 429-450

1Division of Pharmacokinetics, Toxicology and Targeting, University of Groningen, Groningen, the Netherlands,
2Advanced PKPD Modelling and Simulation, Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium,
3Clinical PKPD, Merck Research Labs, Merck Sharp & Dohme, Oss, the Netherlands,
4Clinical Pharmacology, Pfizer Global Research and Development, Groton, CT, USA,
5Division of Pharmacology, Leiden/Amsterdam Center for Drug Research, Leiden, the Netherlands
ABSTRACT

Large variation in placebo response within and among clinical trials can substantially affect conclusions about the efficacy of new medications in psychiatry. Developing a robust placebo model to describe the placebo response is important to facilitate quantification of drug effects, and eventually to guide the design of clinical trials for psychiatric treatment via a model-based simulation approach. In addition, high dropout rates are very common in the placebo arm of psychiatric clinical trials. While developing models to evaluate the effect of placebo response, the data from patients who drop out of the trial should be considered for accurate interpretation of the results.

The objective of this paper is to review the various empirical and semi-mechanistic models that have been used to quantify the placebo response in schizophrenia trials. Pros and cons of each placebo model are discussed. Additionally, placebo models used in other neuropsychiatric disorders like depression, Alzheimer’s disease and Parkinson’s disease are also reviewed with the objective of finding those placebo models that could be useful for clinical studies of both acute and chronic schizophrenic disease conditions. Better understanding of the patterns of dropout and the factors leading to dropouts are crucial in identifying the true placebo response. We therefore also review dropout models that are used in the development of models for treatment effects and in the optimization of clinical trials by simulation approaches.

The use of an appropriate modelling strategy that is capable of identifying the potential sources of variable placebo responses and dropout rates is recommended for improving the sensitivity in discriminating between the effects of active treatment and placebo.
INTRODUCTION

Modelling in Schizophrenia and Other Neuropsychiatric Disorders

A modelling and simulation-based approach is increasingly applied to enhance the efficiency of clinical trials in multifaceted pathological conditions like schizophrenia, depression, Alzheimer’s disease and Parkinson’s disease. These disorders have in common that they lack objective measures (laboratory tests or biomarkers) to evaluate the outcome of treatment effects.1 As a result, the evaluations of the severity of illness and the treatment effects are based on the rating scales as assessed by a physician or by a trained rater. Rating scales in psychiatric research have been designed primarily to measure psychopathological symptoms. A rating scale usually consists of several questionnaires (items), where each item is scored based on the severity of the symptom. For example, the Positive and Negative Syndrome Scale (PANSS), developed by Kay et al.,2 is one of the symptom rating scales used to rate the symptom severity in schizophrenia. It consists of 30 items, where each item is scored from 1 through 7 (1 indicating the absence of the symptom and 7 indicating extremely suffering from the symptom). These 30 items are grouped into 3 subscales; positive (7 items), negative (7 items) and general psychopathology (16 items). These rating scales are typically associated with significant placebo responses.3

Schizophrenia is often described in terms of positive symptoms (e.g. delusions, hallucinations), negative symptoms (e.g. lack of motivation, social withdrawal) and cognitive symptoms. The clinical response in schizophrenia is usually measured by the Brief Psychiatric Rating Scale (BPRS)4 and the PANSS.5 The BPRS has a limited scope because it focuses mainly on positive and general psychopathology. The PANSS is an advancement on the BPRS as it also addresses the negative symptoms. Recently, Leucht et al.6 recommended the Clinical Global Impression (CGI)7 rating scale (score range: 1–7) because of lower cost and time saving. A summary of commonly used rating scales for schizophrenia, depression, Alzheimer’s disease and Parkinson’s disease is listed in table I.

In pharmacokinetic-pharmacodynamic modelling and simulation, the outcomes on the basis of rating scales are typically treated as categorical variables. Logistic regression techniques are generally used to model categorical or ordinal variables associated with a treatment and their relationship with drug exposure. When the number of categories in a rating scale is sufficiently large, they can be considered as continuous variables. Longitudinal time-course data on the scores on these rating scales after placebo or drug treatment generally show a nonlinear trend, with an initial drop from baseline followed by maximal improvement in disease condition and, in some cases, worsening of the disease towards the baseline as shown in figure 1a. Figure 1b illustrates the most commonly observed patterns of the time course of the rating scores. These nonlinear trends (e.g. arising from disease progression and from physiological, pharmacokinetic and feedback processes) cause conventional statistics to underperform in the analysis of the...
outcomes of clinical trials, or cause a difficulty in identifying the difference between drug and placebo responses.\textsuperscript{[13]} Recently it has been shown that obstacles in conventional statistical analysis to detect drug-placebo differences can be overcome using pharmacokinetic-pharmacodynamic modelling and simulation-based approaches.\textsuperscript{[14]}

### Table 1. Summary of rating scales commonly used to assess the treatment effects in brain disorders.

<table>
<thead>
<tr>
<th>Brain disorder</th>
<th>Rating scale (typical values)</th>
<th>Individual items (n)</th>
<th>Range</th>
<th>Healthy</th>
<th>Mild disease</th>
<th>Severe disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>PANSS</td>
<td>30</td>
<td>30–210</td>
<td>30</td>
<td>58</td>
<td>116</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>BPRS</td>
<td>18</td>
<td>18–126</td>
<td>18</td>
<td>31</td>
<td>53</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>CGI</td>
<td>7</td>
<td>1–7</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Depression</td>
<td>HAMD-17</td>
<td>17</td>
<td>0–54</td>
<td>0</td>
<td>11</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>MADRS</td>
<td>10</td>
<td>0–60</td>
<td>0</td>
<td>13</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>ADASC</td>
<td>11</td>
<td>0–70</td>
<td>11\textsuperscript{a}</td>
<td>18\textsuperscript{a}</td>
<td>55\textsuperscript{a}</td>
<td>10</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>UPDRS</td>
<td>44</td>
<td>0–176</td>
<td>0</td>
<td>60</td>
<td>140</td>
<td>11</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Derived from the MMSE score, where ADASC = 70 – 2.33 × MMSE.\textsuperscript{[12]}  
\textbf{ADASC} = Alzheimer’s Disease Assessment Scale-Cognitive; \textbf{BPRS} = Brief Psychiatric Rating Scale; \textbf{CGI} = Clinical Global Impression; \textbf{HAMD-17} = 17-item Hamilton Depression Rating Scale; \textbf{MADRS} = Montgomery-Åsberg Depression Rating Scale; \textbf{MMSE} = Mini-Mental State Examination; \textbf{PANSS} = Positive and Negative Syndrome Scale; \textbf{UPDRS} = Unified Parkinson’s Disease Rating Scale.

\textbf{Fig. 1.} (a) Sample plot showing the time course of Positive and Negative Syndrome Scale (PANSS) scores following placebo administration. (b) Various typical trends of longitudinal time-course data following placebo treatment.
Pharmacokinetic-Pharmacodynamic Modelling and Simulation

Pharmacokinetic-pharmacodynamic modelling and simulation-based approaches are increasingly applied in the area of drug development.[15-18] Pharmacokinetic-pharmacodynamic modelling provides a link between the dose and concentration of the drug (pharmacokinetics) to its effects in the body (pharmacodynamics). Normally, population pharmacokinetic-pharmacodynamic modelling utilizes a nonlinear mixed-effects approach (e.g. in the widely used software program NONMEM), where both fixed effects (e.g. the clearance and volume of distribution for pharmacokinetics, or the maximum effect \( E_{\max} \) and the drug concentration producing 50% of the \( E_{\max} \) \( EC_{50} \) for pharmacodynamics) and random effects (interindividual variability [IIV] and residual unexplained variability [RUV]) are included in the model. A typical pharmacokinetic-pharmacodynamic model consists of three submodels: a structural, a stochastic and a covariate model. The structural submodel describes the overall trend in the data (e.g. a one-compartment pharmacokinetic model or an \( E_{\max} \) pharmacodynamic model), using fixed-effect parameters. The stochastic submodel accounts for IIV, interoccasion variability (IOV), variability among trials and the RUV. Finally, the covariate submodel is used to describe a relationship between the structural model parameters and the covariates (e.g. patient characteristics or trial design details). The variation in treatment response among the individuals is explained in part by parameter-covariate relationships. In addition, covariate models help to design the optimal (individualized) dosage regimen.[19]

Simulation is a process that helps in evaluating the robustness of a model and can also be used for predicting the future outcome of a trial with different trial designs, using parameters from the final modelling of observed data from a previously executed trial. An important feature is that pharmacokinetic-pharmacodynamic models are constantly updated, evaluated and subsequently validated at various stages of drug development to be able to include new information. These updated models and simulations support an efficient decision-making process by facilitating the selection of the right compound, dose, dosage regimen and other relevant factors needed to obtain regulatory authority approval. Figure 2 depicts the process of typical modelling and simulation processes.

Pharmacokinetic-pharmacodynamic models can be divided into two groups: empirical (i.e. 'top-down') models; and mechanistic models based on the concepts of system biology. Empirical models describe the time course of clinical endpoints (e.g. the rating scale and biomarkers) based on fitting a mathematical function to the observed data, often without considering the underlying mechanisms of action. They are simple and descriptive but may have less predictive power than mechanism-based models.[20] Mechanism-based models describe the time course of clinical effects based on parameters assessed in vitro and physiological values. They make a clear distinction between drug-specific parameters and system-specific parameters. Drug-specific parameters describe the interaction between
the drug and the biological system in terms of target binding and target activation. System-specific parameters describe the inherent properties of the biological system (e.g. receptor density, homeostatic feedback and disease progression). An important factor is that system-related factors can be altered due to disease-related factors. This may affect the clinical outcome.[21] Figure 3 illustrates the various factors that could affect the outcome of a pharmacological effect.

**Placebo Response in Neuropsychiatric Disorders**

The term ‘placebo’ is derived from Latin: ‘I shall please’. A placebo is a substance or procedure that is considered pharmacologically inactive for the condition being treated. The use of a placebo treatment in clinical research allows better conclusions relating to efficacy, adverse outcomes and scientific validity of alternative trial designs of new drugs. In addition, it helps to detect the treatment effect and discriminate it from nonspecific effects that may arise from trial design, patient expectancies, demographic differences and medical intervention factors. The current clinical approach of evidence-based drug discovery relies on proving the superiority of a drug treatment compared with a placebo treatment,

![Diagram](image-url)

**Fig. 2.** Schematic representation of the process of pharmacokinetic-pharmacodynamic modelling and simulation.

**Fig. 3.** Factors affecting the drug-response relationships.
implying a central role of placebo treatment in the drug development process. An improvement of the clinical condition of patients in response to the administration of the placebo constitutes a benefit to the patients, but it also obscures quantification of drug effects. Placebo response could be due to psychological effects owing to medical intervention or to non-psychological factors (e.g. trial design and demographic differences). Over the last three decades, understanding of underlying mechanisms of placebo response has improved as an increasing number of researchers have become involved in identifying the possible causes of placebo response.\textsuperscript{[22]}

Approximately 50\% of recent central nervous system (CNS) clinical trials failed to show statistical superiority of the drug over placebo, due to the variable placebo response (20–70\%).\textsuperscript{[23,24]} The trend of placebo responses in antipsychotic trials over the last two decades is shown in figure 4. In addition to placebo response, high dropout rates (40–70\%)\textsuperscript{[3]} from a trial tend to blunt the differences in placebo-drug effect. Table II summarizes the important contributors for variable placebo response and dropout rates in schizophrenia. The impact of these contributors on the outcome of the trial results and possible remedies to overcome these issues have been discussed in detail by many authors.\textsuperscript{[1,24,32,39-41]}

For better quantification of drug effect a robust placebo model is needed. It should account for dropouts and provide an insight into the parameters that contribute to differences in treatment response among patients or studies. A good model combining both placebo and drug effects could eventually guide the design

\textbf{Fig. 4.} Trend of the placebo response: data from short-term trials conducted between 1991 and 2006. The mean reduction in the total Positive and Negative Syndrome Scale (PANSS) score from baseline for patients receiving placebo has increased. (Reproduced from Kemp et al.,\textsuperscript{[3]} by permission of Oxford University Press.)
Table II. Summary of potential contributors for the reduced differences in placebo-drug effect in schizophrenia

<table>
<thead>
<tr>
<th>Contributors</th>
<th>Clinical relevance</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>The dopaminergic system and pharmacokinetics of antipsychotics change with age</td>
<td>25-27</td>
</tr>
<tr>
<td>Sex</td>
<td>Men experience earlier onset of schizophrenia compared to women, with a more debilitating course and more suffering from negative symptoms. Women tend to be treated with lower doses of antipsychotics, as they suffer from antipsychotic drug-induced hyperprolactinemia. These differences could be attributed to hormonal reasons – more specifically, the protective effect of estrogen</td>
<td>27-30</td>
</tr>
<tr>
<td>Race</td>
<td>Ethnic or racial differences in response to placebo or antipsychotic medications are reported due to the difference in genetics, kinetic variations, dietary factors and environmental factors</td>
<td>30,31</td>
</tr>
<tr>
<td>Disease duration and disease condition</td>
<td>Many differences are evident between recent-onset (acute) and chronic schizophrenia regarding morphological changes in the brain, consecutive cognitive impairment, level of compliance or sensitivity to side effects, and these may result in different outcomes in clinical trials for the respective patient subgroup. A higher treatment effect in acute patients compared to chronic patients was reported</td>
<td>32</td>
</tr>
<tr>
<td>BASL</td>
<td>Higher BASLs are associated with higher dropout rates</td>
<td>33</td>
</tr>
<tr>
<td><strong>Methodological issues (trial design, site characteristics and clinical treatment settings)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trial phase</td>
<td>Trial designs are usually different for phase II and phase III clinical trials. There are more stringent criteria for phase II trials compared to phase III trials</td>
<td></td>
</tr>
<tr>
<td>Route of administration and dosage regimen</td>
<td>Poor compliance with oral antipsychotic medications was reported for patients with schizophrenia and can correlate with treatment response and dropouts</td>
<td>34</td>
</tr>
<tr>
<td>Study duration</td>
<td>Negative symptoms tend to respond slowly to treatment and need longer time before they improve. A longer duration of treatment is also helpful for maintenance of the antipsychotic effect. A pronounced placebo response in short-term trials was reported, which might reflect the immediate stabilizing effects of hospitalization. Trials of long duration have shown weakening of the placebo response as a function of time</td>
<td>35,36</td>
</tr>
<tr>
<td>Washout period</td>
<td>The duration of the washout period is crucial, since relatively short washout periods can result in the existence of carryover effects from previous treatments. Longer washout periods can result in worsening of symptoms</td>
<td>1</td>
</tr>
</tbody>
</table>

continued next page
of a clinical trial via a simulation-based approach. Advanced pharmacokinetic-pharmacodynamic modelling and simulation are relatively less explored tools in detecting the true drug effect. A pertinent advantage of a pharmacokinetic-pharmacodynamic modelling approach over traditional statistical approaches is that components of disease progression and potential factors for high placebo response, such as trial design and patient characteristics, are easily implementable.

### Dropouts in Neuropsychiatric Disorders

Dropouts from longitudinal studies are very common in clinical trials of brain diseases. For instance, a dropout rate of 40–70%\[^{[33,42]}\] has been observed in placebo treatment groups of antipsychotic trials (figure 5). Ignoring these missing response values due to dropouts may lead to biased results and affects model building and evaluation. The common reasons for patients to withdraw from the longitudinal clinical trials are: (i) recovery from disease; (ii) lack of efficacy; (iii) adverse events; (iv) unpleasant study design; (v) co-morbidity; and (vi) external factors unrelated to the trial.\[^{[43]}\] Withdrawal due to external factors unrelated to the trial is usually regarded as a completely random dropout (CRD).

---

**Table II.** Summary of potential contributors for the reduced differences in placebo-drug effect in schizophrenia

<table>
<thead>
<tr>
<th>Contributors</th>
<th>Clinical relevance</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of clinical score measurement</td>
<td>Significant effects of visit frequency on adherence to antipsychotic therapy were noted. Frequent visits may be assumed to have a positive impact on the psychological feeling of the patient, which could eventually contribute to higher placebo response and lower dropout rates</td>
<td>37</td>
</tr>
<tr>
<td>Study site</td>
<td>Higher placebo response was reported in studies conducted in the US. Possible reasons could be the differences in ethnicity, kinetic variation, dietary factors, genetics and environmental factors</td>
<td>14</td>
</tr>
<tr>
<td>Clinical endpoint assessment tools</td>
<td>Different rating scales (e.g. PANSS, BPRS or CGI) can show different sensitivity for detection of treatment effect</td>
<td>32,38</td>
</tr>
<tr>
<td>Hospitalization (inpatient/outpatient)</td>
<td>Compliance with the treatment regimen in hospitalized patients, and consequently higher placebo response and lower dropout rates may be expected with hospitalized patients, owing to medical attention</td>
<td>14</td>
</tr>
<tr>
<td>Others</td>
<td>Site characteristics (e.g. academic or commercial, experience and training of personnel, recruitment pressures and procedures, 'recycling' of subjects) may contribute to variable placebo response</td>
<td></td>
</tr>
</tbody>
</table>

**BASL** = baseline score; **BPRS** = Brief Psychiatric Rating Scale; **CGI** = Clinical Global Impression; **PANSS** = Positive and Negative Syndrome Scale.
or ‘non-informative dropout’. If a patient drops out from a trial due to one of the other factors (e.g. lack of efficacy as perceived by the patient [reflected in a higher disease severity score]), such a dropout is regarded as an ‘informative dropout.

In New Drug Applications (NDAs) submitted to the US FDA, the last-observation-carried-forward (LOCF) approach is still a widely used statistical approach to account for dropouts. The use of LOCF may not be ideal, particularly in chronic progressive disorders, as it assumes that there is no change in the score (or other clinical endpoint) after the event of dropout, while in reality the patient might have experienced worsening or improvement of the disease condition. If the dropout mechanism is independent of any observed or non-observed variable (where dropout can be ignored), the use of LOCF may give unbiased results. However, if the dropout mechanism is dependent on any observed or unobserved variables, or in the case of unequal dropout rates between treatment arms, use of LOCF is biased, with the bias being determined by the tendency of the data and the ratio of the dropout rates. In regulatory settings, one of the reasons that LOCF is commonly used is perhaps because it is straightforward and familiar to researchers, clinicians and statisticians. In addition, potential bias arising from LOCF could lead to a more conservative analysis outcome. In the context of drug development, conservative can be thought of as providing protection against falsely concluding that a drug is more effective than the placebo arm.

Mixed modelling of repeated measurements (MMRM), an advanced statistical approach, has been shown to be superior to LOCF for accounting for dropouts.
The MMRM approach is a member of likelihood-based mixed-effects analyses, where this analysis takes account of nonlinear response to a set of parameters of interest and takes account of the correlation between measurements. In addition, IIV and IOV can also be handled appropriately. The MMRM method uses the generalized linear model approach to predict the time course of clinical response and considers all the data collected from patients (those who drop out and those who complete the study). In this approach, the observations from each patient are assumed to originate from a multivariate normal distribution, with different means for each time point and with a correlation between each measurement, which is determined via a correlation matrix. MMRM leads to unbiased estimates irrespective of dropout mechanisms, i.e. independent of or dependent on any observed or unobserved variables. The main objective of confirmatory clinical trials is typically to delineate the differences between drug and placebo treatment and not the effectiveness of treatment. Siddiqui et al. have demonstrated the superiority of the MMRM approach over LOCF in their analysis using 25 NDAs datasets of neurological and psychiatric drug products. Due to the robustness of MMRM against dropout it is recommended in the regulatory setting, as well as in statistical analysis of longitudinal clinical trials. However, MMRM requires explicit modelling choices and implementation expertise, hindering its use in regulatory drug approvals compared to LOCF. In addition, with MMRM it is not easy to incorporate mechanistic components such as the disease system (disease progression) and drug-specific characteristics (adverse events and pharmacokinetic profile).

Integration of pharmacokinetic-pharmacodynamic concepts helps to account for and identify predictors of dropout. In this respect, different dropout models (see section 3) can be incorporated as an integral part of the pharmacokinetic-pharmacodynamic analysis to reduce the bias by accounting for underlying missing data. Recently, Friberg et al., Frame et al. and Gomeni et al. have shown the utility of an advanced pharmacokinetic-pharmacodynamic modelling approach by combining the results of dropout rates and a pharmacokinetic-pharmacodynamic model (derived from rating scales) to describe the association of drug and placebo treatment to dropout events.

**Covariate Modelling**
Identification of covariates that are important contributors of the placebo response and dropout could help to design efficient prospective clinical trials and thereby increase the success rate of clinical trials. Covariates are characteristics describing the patient, the conditions of the drug treatment, the trial design or other factors potentially influencing the clinical outcome. The covariates may be constant within an individual (e.g. sex) or change over time (e.g. age). With regard to covariates, typically a distinction is made between categorical and continuous covariates. Categorical covariates are variables which can be binary (e.g. disease condition: acute/chronic), ordered (e.g. severity of side effects: none, mild,
moderate, and severe) or non-ordered (e.g. race). Continuous covariates have a defined scale and can be quantified (e.g. bodyweight and age).

A covariate model describes the relations between covariates and model parameters. Clinically relevant covariates are usually included in the pharmacokinetic-pharmacodynamic model as factors which influence the values of structural parameters and random effects.\cite{56} In this regard they account for a part of the observed IIV. There are several methods to build covariate models, such as automated stepwise covariate modelling\cite{57} and generalized-additive modelling.\cite{58} Covariate-parameter relationships can be modelled using different functional forms like linear, piece-wise linear, power and exponential functions.

Table II summarizes the important contributors for variable placebo response and dropout rates particularly in relation to schizophrenia, which necessitate the use of a covariate model in conjunction with the placebo and dropout models.

**Item-Response Analysis of Rating Scales**

From a psychiatric drug-development perspective, the question is not only to establish the relationship between the mechanism of action and the clinical response but also to ensure that the clinical scales are sufficiently sensitive to differentiate between the treatment effects. Rating scales may be suitable and reliable but may lack sensitivity in discriminating between the effects of active treatment and placebo.\cite{59} Several authors\cite{38,60,61} have explored the sensitivity of the individual items of the rating scales and the consequences for the assessment of clinical efficacy in diseases such as depression and schizophrenia. For example, in depression trials, the 17-item Hamilton Depression Rating Scale (HAMD-17) total score has been the gold-standard tool for establishing and comparing the efficacy of treatments. However, the HAMD is a multidimensional measure and is a weak index of depressive syndrome severity. This may reduce its ability to detect differences between treatments – in particular, changes in the core symptoms of depression. There have been a number of analyses to improve the rating scales, such as by combining the scores of the individual items that are more sensitive, and these studies often have included an empirical statistical analysis approach (e.g. a linear mixed-effects modelling approach for repeated measures\cite{61} or principal component analysis\cite{38}).

Recently, Santen et al.\cite{60,61} explored the sensitivity of individual items of the HAMD and Montgomery-Åsberg Depression Rating Scale (MADRS), using the difference between responders and non-responders instead of the traditional contrast between active treatment and placebo. The results showed that the HAMD subscales were more sensitive to the treatment effect than the MADRS. Similarly, in schizophrenia, Lader\cite{62} and Santor et al.\cite{38} have suggested that not all of the PANSS items are sensitive to detect the true treatment effects. Such a difference in the sensitivity between scales and the presence of items insensitive to response may explain the high failure rate in detecting statistically significant separation between active- and placebo-treated arms for most psychiatric drugs. It is clear
that new endpoints for clinical trials in psychiatric research should be developed which do not only describe the symptoms but also accurately characterize the disease severity on different levels. The pharmacokinetic-pharmacodynamic modelling approaches are underutilized in this context and we envisage that pharmacokinetic-pharmacodynamic model-based analysis could potentially be used to identify the most sensitive items.

**Placebo-Response Models**

In pharmacokinetic-pharmacodynamic modelling, it is essential to first develop a disease progression and a placebo model, before adding a model for the drug effect. The status of the patient is a reflection of the state of the disease at any given point in time. The disease status changes with time; therefore, modelling of the disease status in the absence of treatment describes the expected changes in the patient’s disease progression. The disease progression model can be extended by including the treatment effects (placebo or drug) that refer to all the underlying pharmacokinetic and pharmacodynamic processes involved in producing a treatment effect on the time course \( (t) \) of disease progression, as shown below (equation 1):\[63\]

\[
\text{Disease status } (t) = \text{disease state } (t_0) + \text{disease progression } (t) + \text{placebo } (t) + \text{drug response } (t)
\] (Eq. 1)

where \( t_0 \) is the time at the start of the trial. The pharmacological effectiveness of the drug is usually estimated on top of the placebo effect. A model for disease progression and placebo response can be developed separately for diseases such as Alzheimer’s and Parkinson’s disease, due to linear disease progression.\[64,65\] However, in other cases, it is difficult to separate disease progression from placebo response due to the episodic nature of the disease (e.g. schizophrenia and depression); in such cases, disease progression and placebo response can be considered as a single entity. Figure 6 illustrates the natural time course of disease severity in schizophrenia during ageing. A complicating factor is that in most brain diseases, characterization of the natural time course of the disease in an untreated condition is not possible due to ethical reasons. In such circumstances, it is not possible to distinguish between placebo response and disease progression. In some cases, clinical measurements obtained during the washout period (i.e. at the beginning of trial initiation or during the screening period) can provide a basis to describe disease progression.

In practice, typically, several placebo models are investigated, and the one that describes the time course of the clinical endpoint best is taken further to integrate with the drug-effect models.\[63\] While developing a drug-effect model, the placebo-response model parameters are initially fixed (sequential analysis), and then different drug-effect models are explored. Subsequently, all the parameters of the final placebo and drug-effect models are simultaneously estimated. By utilizing
the population pharmacokinetic-pharmacodynamic approach with combined placebo and drug-effect models, one can estimate the placebo parameters for the drug treatment group.

In this review paper, we mainly focus on the placebo-response models, which also account for dropouts and predictors of placebo response in psychiatric research. A thorough search for placebo models was conducted in MEDLINE, including published clinical trial results and exposure-response analyses from 1980 to 2010. We also looked at the Drugs@FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) for summary basis of approvals (SBAs/NDAs) and the Population Approach Group in Europe website (http://www.page-meeting.org/), the American Conference on Pharmacometrics website (http://www.go-acop.org/) and the American Society for Clinical Pharmacology and Therapeutics website (http://www.ascpt.org/) for abstracts or posters. We searched for placebo- or drug-effect modelling results in neuropsychiatric disorders irrespective of the rating scale used. In the area of antipsychotic pharmacokinetic-pharmacodynamic placebo-effect modelling, various empirical models such as the linear model, the power model, the Weibull model, the bi-linear model and the exponential model have been used to describe the time course of the PANSS score following a placebo treatment. A schematic representation of various empirical model plots is shown in figure 7. More recently, semi-mechanistic models like the indirect-response model (IRM) have also been proposed to describe the time course of the natural disease progression (table III). Alternative

---

**Fig. 6. Natural history of schizophrenia.** The disease progresses from a state of no symptoms (presymptomatic) to the prodromal stage with cognitive and negative symptoms (but not positive symptoms) and ultimately to first-episode psychotic symptoms (progressive stage). The solid line indicates deterioration of normal functional abilities of a schizophrenic patient over time. The dashed line shows the incidence of psychotic symptoms over time. Drug treatment is more effective during the prodromal stage than in the later stages.
placebo-response models (which have been explored in other brain disorders such as depression, Alzheimer’s disease and Parkinson’s disease) such as polynomial functions,\textsuperscript{[13]} transit models\textsuperscript{[72]} and inverse Bateman functions (IBFs)\textsuperscript{[72-74]} are presented in table IV. Sections 2.1 and 2.2 describe these models in detail. Table V shows typical parameter values for each of the placebo models.

**Empirical Models**

**Linear Model**
The mathematical function describing linear model for placebo response is represented in equation 2:
The linear placebo model, using the BPRS score, was utilized to anticipate phase III trial outcomes based on the phase II trial results in a placebo-controlled clinical trial for quetiapine.\(^{[66]}\) A slope parameter (SLOP) and baseline score (BASL) as the intercept at time (t) zero describe the time course of the BPRS in the placebo group treated for 6 weeks. The parameter values of this model were estimated by mixed-effects linear regression analysis.

In this analysis the IIV in the BASL and SLOP parameters was evaluated according to log-normal distribution and normal distribution, respectively. The normal distribution of the IIV for the SLOP parameter allows the placebo effect to be negative or positive. This is important as some patients show improvement and others show deterioration in rating scores. Kimko et al.\(^{[66]}\) reported that their phase II modelling and phase III simulation results showed a significant favourable placebo response, but the actual phase III trial placebo group results showed a worsening of the disease condition (3% increase in BPRS score). Furthermore, the linear model failed to describe their phase III placebo data by simulation. There are at least three possible explanations for the poor performance of this model. Firstly, the linear model may not have captured a nonlinear trend in the BPRS score. The use of a different placebo model (a nonlinear model) to describe

\[
\text{SCORE} = \text{BASL} + \text{SLOP} \times t
\]  
(Eq. 2)

Table III. Summary of placebo models tested in the area of schizophrenia.

<table>
<thead>
<tr>
<th>Placebo model</th>
<th>Active treatment</th>
<th>Route</th>
<th>Placebo model parameters (n)</th>
<th>Estimation method</th>
<th>Dropout model</th>
<th>Model evaluation criteria</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>Quetiapine</td>
<td>Oral</td>
<td>2</td>
<td>FOCE/ODE</td>
<td>Exponential-TTE</td>
<td>OFV, GOFP</td>
<td>66</td>
</tr>
<tr>
<td>Power</td>
<td>Aripiprazole</td>
<td>Oral</td>
<td>3</td>
<td>FOCE/ODE</td>
<td>NT</td>
<td>OFV, GOFP</td>
<td>67</td>
</tr>
<tr>
<td>Bi-linear</td>
<td>Paliperidone</td>
<td>Oral</td>
<td>5</td>
<td>FOCE/ODE</td>
<td>LRM</td>
<td>VPC, bootstrap</td>
<td>68</td>
</tr>
<tr>
<td>Exponential</td>
<td>Olanzapine</td>
<td>Oral</td>
<td>2</td>
<td>FOCE/Laplace</td>
<td>Exponential-TTE</td>
<td>VPC, PPC</td>
<td>69</td>
</tr>
<tr>
<td>Weibull</td>
<td>Asenapine</td>
<td>SL</td>
<td>4</td>
<td>FOCE/PRED</td>
<td>LRM</td>
<td>VPC, bootstrap</td>
<td>14</td>
</tr>
<tr>
<td>IRM</td>
<td>Paliperidone</td>
<td>Oral</td>
<td>3</td>
<td>FOCE/ODE</td>
<td>Linear</td>
<td>VPC, PPC</td>
<td>70</td>
</tr>
<tr>
<td>IRM</td>
<td>Risperidone</td>
<td>Oral/IM</td>
<td>3</td>
<td>FO/ODE</td>
<td>Linear</td>
<td>GOFP</td>
<td>71</td>
</tr>
</tbody>
</table>

\(\text{FO}\) = first-order approximation; \(\text{FOCE}\) = first-order conditional estimation; \(\text{GOFP}\) = goodness-of-fit plots; \(\text{IM}\) = intramuscular; \(\text{IRM}\) = indirect-response model; \(\text{LRM}\) = logistic regression model; \(\text{NT}\) = not tested; \(\text{ODE}\) = ordinary differential equations; \(\text{OFV}\) = objective function value; \(\text{PPC}\) = posterior predictive checks; \(\text{PRED}\) = prediction subroutine in NONMEM; \(\text{SL}\) = sublingual; \(\text{TTE}\) = time-to-event dropout model; \(\text{VPC}\) = visual predictive checks.
the placebo response might have been more appropriate, but the authors justified the use of a linear model based on its performance in the phase II BPRS data. Secondly, the inclusion of a CRD model may not have been adequate, as this model ignores the disease progression information. Use of informative dropout models instead of a CRD model would have been more appropriate for the simulations. Thirdly, no covariate analysis on the BASL structural parameter was tested that might have explained part of the variability in placebo response.

In Parkinson’s disease the linear model has been used successfully to describe both the trajectory of disease progression and the change in the disease status pertaining to the placebo response. In contrast, in Alzheimer’s disease the linear model was employed to model disease progression while the IBF (for details see section 2.1.7) was used to describe the placebo effect.

The linear model is a simplistic model with two parameters and can be a reasonable model for describing the time course of symptom scores when measured for a short period of time (4–6 weeks). It has been suggested that placebo response is usually more pronounced at the beginning of the placebo treatment but decreases with time. For this reason the linear model may be less useful for trials of longer duration. In addition, the linear model is incapable of determining a maximum placebo effect as it never reaches a steady state or plateau, whereas such a steady state or plateau is often observed in clinical studies.

**Power Model**

The mathematical model describing a curvilinear change in disease severity is shown in equation 3:

\[ \text{SCORE} = \text{BASL} + \text{SLOP} \times t^{\text{POW}} \]  

(Eq. 3)

Compared to the linear model, the power model utilizes an additional exponent shape parameter (POW) to describe the time course of the disease score. This model was used to describe the time course of PANSS in the placebo group of a clinical trial of the antipsychotic drug aripiprazole. In this analysis the covariates influencing the placebo response were included in the model on the SLOP parameter. The BASL of the patient was an important covariate for the placebo response. Inclusion of POW helps to describe the shape of the PANSS time-course curve. The estimated value of the shape parameter is influenced by study duration or the PANSS measurement frequency. Like the linear model, the power model is also incapable of determining a maximum placebo effect.

**Bi-Linear Model**

The mathematical function describing a bi-linear trajectory of change in disease status is presented in equation 4:

\[ \text{SCORE} = (1 - \text{SHIFT}) \times (\text{BASL}_1 + \text{SLOP}_1 \times t) + \text{SHIFT} \times (\text{BASL}_2 + \text{SLOP}_2 \times t) \]  

(Eq. 4)
The bi-linear model describes the time course of a score as a combination of two linear functions. The SHIFT describes the transition between the two slopes (SLOP$_1$ and SLOP$_2$ in equation 4). The SHIFT is not discrete but is estimated by a hyperbolic function (equation 5):

$$\text{SHIFT} = \frac{t^\gamma}{t^\gamma + \text{BREAK}^\gamma}$$  \hspace{1cm} (Eq. 5)

where BREAK is the transition time and the exponent $\gamma$ is the shape parameter. SHIFT is required to obtain a smooth transition between the two slopes. This model was successfully used to describe prolactin elevation as a predictor of the clinical effect (PANSS) following the treatment with placebo or paliperidone in schizophrenia trials.$^{[69]}$ In this analysis a normal distribution of the IIV was included for the SLOP and BASL parameters. The bi-linear model is an interesting model, as it can describe different time-course patterns – for example, patients with only improvement or worsening in score, or patients with improvement and then worsening or vice-versa.

**Exponential Model**

The mathematical model describing an exponential change in disease severity with time is shown in equation 6:

$$\text{SCORE} = \text{BASL} - \text{PE} \times [1 - \exp(-k \times t)]$$  \hspace{1cm} (Eq. 6)

The basic exponential model (equation 6) was used to characterize the placebo effect over time in schizophrenia, using the PANSS score of 51 subjects.$^{[69]}$ In this model, $k$ is a rate constant that characterizes the rate of change in disease severity (placebo response) and PE is a parameter describing the magnitude of the placebo effect, which is additive to BASL. The authors reported that this model adequately described the time course of the PANSS score.

Holford$^{[75]}$ used a slight modification of this model for depression trials (equation 7) to account for the delay in the placebo response ($t_{\text{lag}}$):

$$\text{SCORE} = \text{BASL} - \text{PE} \left[ 1 - \exp \left( - \frac{\ln 2}{\text{TREM}} \times (t - t_{\text{lag}}) \right) \right]$$  \hspace{1cm} (Eq. 7)

$$k = \frac{\ln 2}{\text{TREM}}$$

where TREM is the time to reach 50% of remission.

Both exponential models (equations 6 and 7) assume that placebo response reaches a plateau at infinite time ($\infty$). Compared to the linear and power models, the exponential model can approximate nonlinear response curves better.
Table IV. Summary of placebo models tested in the area of depression, Alzheimer’s and Parkinson’s diseases.

<table>
<thead>
<tr>
<th>Placebo model</th>
<th>Active treatment</th>
<th>Route</th>
<th>Placebo model parameters (n)</th>
<th>Estimation method</th>
<th>Dropout model</th>
<th>Model evaluation criteria</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exponential model with t_plm</td>
<td>4 antidepressant drugs</td>
<td>NM</td>
<td>4</td>
<td>NM</td>
<td>NM</td>
<td>OFV, GOFP and VPC</td>
<td>75</td>
</tr>
<tr>
<td>Mixed Weibull and linear function</td>
<td>Paroxetine</td>
<td>Oral</td>
<td>4</td>
<td>FOCE/Laplace</td>
<td>Exponential-TTE</td>
<td>OFV, GOFP (NONMEM)</td>
<td>13</td>
</tr>
<tr>
<td>Polynomial</td>
<td>Paroxetine</td>
<td>Oral</td>
<td>3</td>
<td>NA</td>
<td>NT</td>
<td>DIC, GOFP (Winbugs)</td>
<td>13</td>
</tr>
<tr>
<td>IBF</td>
<td>2 antidepressant drugs</td>
<td>NM</td>
<td>4</td>
<td>FOCE</td>
<td>Exponential-TTE</td>
<td>OFV, GOFP and VPC</td>
<td>73</td>
</tr>
<tr>
<td>IBF</td>
<td>Tacrine</td>
<td>NM</td>
<td>4</td>
<td>FO</td>
<td>NT</td>
<td>OFV</td>
<td>73</td>
</tr>
<tr>
<td>IBF</td>
<td>Levodopa</td>
<td>Oral</td>
<td>4</td>
<td>FOCE</td>
<td>Exponential-TTE</td>
<td>OFV, GOFP and VPC</td>
<td>65</td>
</tr>
<tr>
<td>IBF</td>
<td>Paroxetine</td>
<td>Oral/IV</td>
<td>4</td>
<td>FOCE/PRED</td>
<td>NT</td>
<td>VPC, NPC, shrinkage and bootstrap</td>
<td>72</td>
</tr>
<tr>
<td>IBF</td>
<td>Paroxetine</td>
<td>Oral</td>
<td>4</td>
<td>NA</td>
<td>NT</td>
<td>DIC, GOFP (Winbugs)</td>
<td>13</td>
</tr>
<tr>
<td>IRM</td>
<td>Paroxetine</td>
<td>Oral/IV</td>
<td>3</td>
<td>FOCE/ODE</td>
<td>NT</td>
<td>VPC, NPC, shrinkage and bootstrap</td>
<td>72</td>
</tr>
<tr>
<td>Transit model</td>
<td>Paroxetine</td>
<td>Oral/IV</td>
<td>3</td>
<td>FOCE/ODE</td>
<td>NT</td>
<td>VPC, NPC, shrinkage and bootstrap</td>
<td>72</td>
</tr>
</tbody>
</table>

DIC = deviance information criterion; FO = first-order approximation; FOCE = first-order conditional estimation; GOFP = goodness-of-fit plots; IBF = inverse Bateman function; IRM = indirect-response model; IV = intravenous; LRM = logistic regression model; NA = not applicable; NM = not mentioned; NPC = numerical predictive checks; NT = not tested; ODE = ordinary differential equations; OFV = objective function value; PRED = prediction subroutine in NONMEM; t_plm = delay in the placebo response; TTE = time-to-event dropout model; VPC = visual predictive checks.
Weibull Model
The mathematical model describing complex nonlinear patterns of placebo-
response progression (the Weibull function) is shown in equation 8:

\[ \text{SCORE} = \text{BASL} \times \left[ 1 - \text{PE}_{\text{max}} \times \left( 1 - \exp\left( -\left(\frac{t}{\text{TD}}\right)^{\text{POW}}\right) \right) \right] \]  
(Eq. 8)

The Weibull model describes the decrease of the score from baseline which
eventually reaches a plateau. \( \text{PE}_{\text{max}} \) is the maximum placebo effect, \( \text{TD} \) is the time
when 63.2% of maximum change from baseline is reached. The Weibull model is
an extension of the basic exponential model including \( \text{POW} \), and it reduces to the
exponential model when \( \text{POW} = 1 \). Friberg et al.\[14\] successfully used the Weibull
model to describe the placebo response in a clinical trial of the antipsychotic drug
asenapine. In this analysis the placebo effect was included as being proportional to
the PANSS BASL, as illustrated in equation 8. This model also enabled demonstration
of the importance of covariates for the outcome of the modelling. Both disease
duration and clinical trial phase were important contributory factors to the placebo
response. A limitation of the Weibull model is that it lacks the flexibility to describe
the worsening of the disease condition after initial improvement or vice versa. To
overcome this deficit, Gomeni et al.\[55\] proposed a mixed Weibull model with an
additional linear function (with a slope parameter called \( \text{DRIFT} \)) to describe the
placebo response in a major depressive disorder trial of paroxetine (equation 9):

\[ \text{SCORE} = \text{BASL} \times \exp\left( -\left(\frac{t}{\text{TD}}\right)^{\text{POW}} \right) + \text{DRIFT} \times t \]  
(Eq. 9)

This model is generic and therefore appropriate for modelling other diseases like
depression and Alzheimer’s disease. The Weibull model may be one of the best
choices to model data that show initial improvement followed by a plateau (as is
often seen in placebo groups in antipsychotic drug trials). In addition, the Weibull
model also takes into account the individuals with a flat placebo response.
Furthermore, a linear or other suitable function has to be added to the basic
Weibull function in order to describe the data that has a parabolic shape.

Polynomial Function
The mathematical expression of a polynomial function is shown in equation 10:

\[ \text{SCORE} = \text{BASL} + \text{SLOP} \times t + \text{QUAD} \times t^2 \]  
(Eq. 10)

where \( \text{SLOP} \) and \( \text{QUAD} \) are the linear and the quadratic coefficients, respectively.
A polynomial function was used to describe the time course of the MADRS
score following venlafaxine treatment in depression. The model predicted the time course of the MADRS score reasonably well after including plasma drug concentration as a covariate. Gomeni and Merlo-Pich attempted various longitudinal placebo models to describe the HAMD-17 scores in depression, one of them being the polynomial function. It is not clear from this paper whether the polynomial function described the HAMD-17 scores adequately. The presence of the QUAD parameter in equation 10 helps to account for the curvature in the response and allows worsening of the disease after initial improvement, or vice versa.

**Inverse Bateman Function**

The mathematical model of the IBF is shown in equation 11:

\[
\text{SCORE} = \text{BASL} - \text{DREC} \left( \frac{k_{\text{rec}}}{k_{\text{rec}} - k_{\text{on}}} \right) \times \left( \exp(-k_{\text{on}} \times t) - \exp(-k_{\text{rec}} \times t) \right)
\]  

(Eq. 11)

The IBF contains two exponential expressions. The first exponential expression describes the improvement with a placebo treatment, while the second exponential expression is used to account for worsening of disease. In this function, \(k_{\text{rec}}\) is the rate constant of improvement after placebo dosing, \(k_{\text{on}}\) is the rate constant of score worsening, and the DREC parameter reflects the amplitude of score improvement during recovery. The placebo response is assumed to be due to the time course of a hypothetical placebo concentration (CEON) after a placebo dose at time zero (the start of the trial). A basic pharmacokinetic first-order absorption and elimination model is then used to describe the placebo effect. Differences in the rate of response appearance and loss of response are determined by the absorption and elimination half-lives. Originally, Holford and Peace proposed IBF to predict the hypothetical CEON. The predicted CEON was then used to model the time course of the Alzheimer’s Disease Assessment Scale-Cognitive (ADASC) score in Alzheimer’s disease.

Recently, many authors have used the IBF to predict the time course of the disease score without the need to predict the CEON. Holford et al. used the IBF to account for the placebo response in depression, mainly due to the cyclical nature of the disease, and an expectation of improvement and worsening of the score over time. Since the IBF is empirical in nature, there are no requirements for model parameter estimates to be positive and to constrain the initial estimates that allow description of the patients worsening at an early stage and then improving at a later stage.

In placebo-controlled studies, placebo response is usually dominant at the beginning of the treatment but decreases as the time progresses. \(k_{\text{on}}\) and its derived parameter, \(t_{\text{on}}\) (the half-life of worsening), which is calculated by equation 12 may not be identifiable with shorter-duration trials, which lack information on relapse.
Table V. Parameter values for various placebo models used to assess the placebo effects in neuropsychiatric diseases.

<table>
<thead>
<tr>
<th>Model</th>
<th>Disease</th>
<th>Rating scale</th>
<th>Structural parameters</th>
<th>Parameter values</th>
<th>Interindividual variability (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>Schizophrenia</td>
<td>BPRS</td>
<td>BASL</td>
<td>38.6</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLOP (h⁻¹)</td>
<td>−0.0077</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (% CV)</td>
<td>31</td>
<td>−</td>
</tr>
<tr>
<td>Bi-linear</td>
<td>Schizophrenia</td>
<td>PANSS</td>
<td>BASL</td>
<td>90.2</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLOP (units/day)</td>
<td>−0.73</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLOP₂ (units/day)</td>
<td>0.17</td>
<td>365</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRÉAK (days)</td>
<td>10</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (% CV)</td>
<td>NA</td>
<td>−</td>
</tr>
<tr>
<td>Power</td>
<td>Schizophrenia</td>
<td>PANSS</td>
<td>BASL</td>
<td>85.6</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLOP</td>
<td>−1.04</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POW</td>
<td>0.371</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (% CV)</td>
<td>9</td>
<td>−</td>
</tr>
<tr>
<td>Exponential</td>
<td>Schizophrenia</td>
<td>PANSS</td>
<td>BASL</td>
<td>92.1</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PE (units)</td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>k (week⁻¹)</td>
<td>0.3</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (% CV)</td>
<td>29</td>
<td>−</td>
</tr>
<tr>
<td>Weibull</td>
<td>Schizophrenia</td>
<td>PANSS</td>
<td>BASL</td>
<td>90.5</td>
<td>13 (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PEₘ₃</td>
<td>0.085</td>
<td>0.16 (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TD (days)</td>
<td>13.2</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POW</td>
<td>1.24</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (SD)</td>
<td>3.5</td>
<td>44</td>
</tr>
<tr>
<td>Weibull + linear</td>
<td>Depression</td>
<td>HAMD-17</td>
<td>BASL</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TD</td>
<td>7.2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DRIFT</td>
<td>0.91</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POW</td>
<td>0.51</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (% CV)</td>
<td>NA</td>
<td>−</td>
</tr>
</tbody>
</table>

continued on next page

\[ t_{on} = \frac{\ln 2}{k_{on}} \]  

(Eq. 12)

IBF could be a useful model for longer-duration trials that might have enough information on the relapse of disease conditions. However, correlations among the rate constant parameters are common and should be considered during optimization of a clinical trial using a simulation approach. IBF parameter estimates are usually dependent on study duration. Like the Weibull model, this model has been extensively used in various disease conditions like depression, Alzheimer's disease and Parkinson's disease. The use of the IBF for the modelling of placebo response in schizophrenia has not been reported.
Table V. Parameter values for various placebo models used to assess the placebo effects in neuropsychiatric diseases.

<table>
<thead>
<tr>
<th>Model</th>
<th>Disease</th>
<th>Rating scale</th>
<th>Parameter (units)</th>
<th>Parameter value</th>
<th>Interindividua variability (%CV)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polynomial</td>
<td>Depression</td>
<td>MADRS</td>
<td>BASL</td>
<td>34.1</td>
<td>4.9 (SD)</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLOP</td>
<td>-2.22</td>
<td>1 (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QUAD</td>
<td>0.046</td>
<td>0.04 (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (SD)</td>
<td>4.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>IBF</td>
<td>Depression</td>
<td>HAMD-17</td>
<td>BASL</td>
<td>21.6</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DREC</td>
<td>7.65</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>k_{rec}</td>
<td>0.72</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>k_{on}</td>
<td>0.037</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (SD)</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>IRM</td>
<td>Depression</td>
<td>HAMD-17</td>
<td>k_{in} (day^{-1})</td>
<td>0.11</td>
<td>8</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>k_{out} (day^{-1})</td>
<td>0.005</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLOP</td>
<td>0.94</td>
<td>223</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (SD)</td>
<td>3.4</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Transit</td>
<td>Depression</td>
<td>HAMD-17</td>
<td>BASL</td>
<td>21.8</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>model</td>
<td></td>
<td></td>
<td>MTT (days)</td>
<td>10</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLOP</td>
<td>0.06</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RUV (SD)</td>
<td>4</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

BASL = baseline score; BPRS = Brief Psychiatric Rating Scale; BREAK = transition between two slopes; CV = coefficient of variation; DREC = amplitude of score improvement during recovery; DRIFT = slope parameter; HAMD-17 = 17-item Hamilton Depression Rating Scale; IBF = inverse Bateman function; IRM = indirect-response model; k = rate of change in disease severity; k_{in} = zero-order rate constant; k_{on} = rate constant of score worsening; k_{out} = first-order rate constant; k_{rec} = rate constant of improvement after placebo dosing; MADRS = Montgomery-Åsberg Depression Rating Scale; MTT = mean transit time; PANSS = Positive and Negative Syndrome Scale; PE = magnitude of the placebo effect; PE_{max} = maximum placebo effect; POW = shape parameter; QUAD = quadratic coefficient; RUV = residual unexplained variability; SD = standard deviation; SLOP = slope; TD = time when 63.2% of maximum change from baseline is reached.

**Semi-Mechanistic Models**

The IRM and transit models are semi-mechanistic in a pharmacological sense for a drug treatment but are not necessarily semi-mechanistic for a placebo effect. These models for the placebo treatment are still rather empirical in nature with a hypothetical CEON but may be considered as semi-mechanistic models when the mechanism of placebo effect is known. Benedetti\textsuperscript{[22]} reviewed possible mechanisms of placebo treatment in many CNS diseases. Increased understanding of placebo-response mechanisms in recent years creates a challenging opportunity for pharmacometricans to gather such data, account for the mechanism(s) of the placebo effect via pharmacokinetic-pharmacodynamic modelling and subsequently link it to the clinical endpoint.
**Indirect-Response Model (IRM)**

The IRM describes the change in disease severity score as the net result of the rate of worsening (as reflected in the zero-order rate constant \( k_{in} \)) and the rate of improvement (as reflected in the first-order rate constant \( k_{out} \)) processes. In this model, a pharmacokinetic driving function is used to reflect the time course of the hypothetical CEON, which is assumed to affect either \( k_{out} \) or \( k_{in} \) (i.e., a stimulatory effect on \( k_{out} \) or an inhibitory effect on \( k_{in} \)). Shang et al.\(^{72}\) have successfully used equation 13 to model the natural course of the HAMD-17 score.

\[
\frac{d\text{SCORE}}{dt} = k_{in} - k_{out} \left(1 + \text{SLOP} \times \text{CEON}\right) \times \text{SCORE} 
\]  
(Eq. 13)

A hypothetical steady-state CEON allowed \( k_{out} \) to be affected linearly with a SLOP parameter or nonlinearly (e.g., with \( E_{max} \) model parameters). The model was found to be over parameterized, hence BASL was not considered as a model parameter and the system was initialized to the BASL. Alternatively, one of the rate constants and the BASL may be estimated as parameters, and the other rate constant can then be derived indirectly from equation 14, assuming steady-state conditions.

\[
\text{BASL} = \frac{k_{in}}{k_{out}} 
\]  
(Eq. 14)

Various approaches to estimate the time course of CEON have been proposed in the literature. The first approach by Shang et al.\(^{72}\) used a one-compartment linear placebo pharmacokinetic model with a multiple bolus dose of placebo (1 unit) and first-order elimination (equation 15). The values of the clearance (\( \text{CL}_{\text{placebo}} \)) and the volume of distribution (\( V_{\text{placebo}} \)) were fixed to certain values in order to derive the elimination rate constant (\( k_e \)).

\[
\frac{d\text{CEON}}{dt} = -k_{e,\text{placebo}} \times \text{CEON} 
\]  
(Eq. 15)

\[
k_{e,\text{placebo}} = \frac{\text{CL}_{\text{placebo}}}{V_{\text{placebo}}} 
\]

The second approach was called the kinetic pharmacodynamic (K-PD) model,\(^{81}\) where \( k_e \) was estimated in order to derive the hypothetical CEON values. The third approach by Post\(^{82}\) used an exponential infusion type of K-PD function to predict CEON following a placebo dose at the beginning of the trial. The CEON was assumed to increase as an infusion input and remain at a steady-state concentration of 1 unit until the end of the study (equation 16):

\[
\text{CEON} = \text{PLAC} \times \left[1 - \exp\left(-k_e \times (t-t_{\text{start}})\right)\right] 
\]  
(Eq. 16)
The pharmacokinetic input for placebo treatment depends on an onset function presented in equation 16, where the switch, PLAC, initializes the placebo treatment effect with PLAC(0 | 1) = 1, if t > t_{start}. The parameter $k_e$ gave the elimination rate constant for the placebo dosing. However, usually the values of the $k_e$ and $k_{out}$ parameters are correlated, which limits the use of this approach. To overcome this parameter-correlation issue, one could fix the value of $k_e$ based on the simulations and estimate only $k_{out}$. Our NONMEM data analysis showed that the exponential infusion type of the K-PD function seems to have fewer numerical difficulties and a shorter run time compared with other approaches.\(^{[83]}\)

In schizophrenia, Ortega et al.\(^{[70]}\) proposed a complex IRM to describe the time course of PANSS following placebo/paliperidone treatment. The change in the clinical score of the patient was described by a balance between the rate of deterioration and the rate of amelioration of the disease. Amelioration was assumed to be proportional to the current value of the score and the proportionality coefficient, $K$. Deterioration was assumed to be proportional to the asymptotic value (at time $\infty$) of the score (RP) with the same $K$ of amelioration (equation 17):

$$\frac{d \text{SCORE}}{dt} = K \times (\text{RP} - \text{SCORE}) \quad \text{(Eq. 17)}$$

At the beginning of a trial, i.e. at time zero, $\text{SCORE} = \text{BASL}$. It was assumed that the treatment reduces RP and thereby the rate of deterioration. If $\text{RP} > \text{BASL}$ the patient's condition deteriorated, and $\text{RP} < \text{BASL}$ indicated improvement in the patient's condition. Hence, $\text{RP}$ was considered a composite parameter incorporating disease progression, PE, drug effect and effect of dropouts. RP was constrained within the PANSS score boundaries (30–210), using logit transformation.

To model the PE and to account for the tolerance in placebo response, Ortega et al.\(^{[70]}\) used an exponential model with a parameter, $t_{lag}$, that described the time after which the placebo effect decreased with a first-order rate constant ($k_t$). As the tolerance was not observed in all patients, they employ a mixture model on the $k_t$ parameter to differentiate the patients who were tolerant or non-tolerant of placebo treatment (equation 18):

$$\text{PE} = \text{PE}_0, \text{if } t < t_{lag}, \text{else}$$

$$\text{PE} = \text{PE}_0 \times \exp^{-k_t \times (t - t_{lag})} \quad \text{(Eq. 18)}$$

Moreover, Ortega et al.\(^{[70]}\) also accounted for time-dependent changes in the dynamics of disease progression of schizophrenia. An asymptotic change in the PANSS score from the baseline of 23 units was reported with a disease progression rate constant of 0.0294/day. This decreased disease severity could be explained by stabilization of the acute schizophrenic episode. They also reported that no clinically relevant covariates could be identified with their final placebo model.
The IRM model is still rather empirical in nature with a hypothetical CEON, but it may be considered as a semi-mechanistic model when the mechanism of placebo effect is known\(^{22}\) or when a drug component is included in the model. For example, in schizophrenia, \(D_2\) receptor binding is believed to influence the clinical outcome. Therefore, linking rate of improvement (or deterioration) to \(D_2\) receptor occupancy rather than to plasma concentration may lead to better results. Alternatively, one could use predicted drug concentration in biophase (e.g., using preclinical data via a translational approach). A generic schematic IRM is shown in figure 8.

**Transit Model**

Shang et al.\(^{72}\) and Mould et al.\(^{74}\) used a transit model to describe the time course of the HAMD-17 score in depression. Two transit compartments were used to describe the change in HAMD-17 scores over time. A pertinent feature of a transit model is that it incorporates a parameter called mean transit time (MTT), which describes the delay in the placebo effect (equation 19):

\[
\text{MTT} = \frac{n}{k_{TC}} \tag{Eq. 19}
\]

where \(n\) = number of transitions and \(k_{TC}\) is the first-order rate constant between transit compartments.

Figure 9 and equation 20 depicts the transit model structure and its differential equations:

**Fig. 8.** Indirect-response model used to describe the change in score over time. \(C_p\) = concentration in plasma; \(k_{in}\) = zero-order rate constant; \(k_{out}\) = first-order rate constant.
where PRE represents the precursor status.

The influence of placebo was handled by creating a pharmacokinetic driving function for the placebo effect as described above for the IRM. When there is one transit compartment, the transit model and IRM are interchangeable. Shang et al.\cite{72} reported that the transit model performed slightly better than the IRM in describing the HAMD-17 score in depression. A transit model may be a better model to describe the delay in treatment response as is usually seen in depression trials, unlike schizophrenia trials.

**Dropout Models**

Dropouts are common events in longitudinal clinical trials. Subjects may drop out of an ongoing clinical trial due to several reasons. Missing data based on the reasons why patients drop out could be of three basic types.\cite{84,85} The first type is ‘missing completely at random’ (MCAR), also commonly known in the pharmacokinetic-pharmacodynamic area as CRD, where the missingness is independent of the observed data and/or covariates. The estimation-based inferences, model evaluation and clinical trial simulation results are usually unaffected if the missing mechanism is MCAR. However, the MCAR mechanism affects the standard errors as the sample size is lower. Consequently, the confidence intervals predicted through simulations would be larger. The second type is ‘missing at random’ (MAR) or ‘random dropout’ (RD), where the missingness is related to the observed data. The third type is ‘not missing at random’ (NMAR) or ‘non-random dropout’ (NRD), where the missingness is related to the observed data but the relationship is not known.

**Fig. 9.** Schematic representation of the transit compartment model used to describe the change in scores over time.\cite{74} $k_{TC}$ = first-order rate constant between transit compartments; PRE = precursor status; $TC_1$ = transit compartment 1; $TC_2$ = transit compartment 2; $TC_n$ = transit compartment $n$. 
response (such as drug concentration or clinical endpoint) and/or covariates. The estimation-based inferences are usually not influenced by the MAR mechanism if appropriate modelling methodology (e.g. likelihood-based methods) is used to estimate the model parameters. However, the results of model evaluation and clinical trial simulations are influenced if the missing mechanism is MAR. The third type is ‘missing not at random’ (MNAR) or informative dropout, where the dropout is related to one or more predicted (unobserved) response variables. The results of estimation-based inferences, model evaluation and clinical trial simulation results are potentially affected if the missing mechanism is MNAR. Often, MAR and MNAR are regarded as informative dropout as the missing data contains information on the disease progression, drug efficacy and safety.

Wu and Carroll[86] jointly modelled disease progression and probability of dropping out, using a statistical generalized linear model approach. Since disease progression, pharmacokinetic and pharmacodynamic observations frequently show nonlinear trends, Hu and Sale[85] extended the joint modelling efforts, using a nonlinear pharmacokinetic-pharmacodynamic modelling approach along with statistical principles to evaluate whether the dropout mechanism is MCAR, MAR or MNAR. Parametric time-to-event (TTE) and logistic regression models are commonly used to investigate the relationship between the clinical response and the dropout event.

**Time-to-Event Dropout Models**

TTE models predict the probability of a patient dropping out by describing the hazard for the event. Hazard is the instantaneous rate of the dropout event: \( H(t) \). The cumulative hazard (CHZ) predicts the risk of a patient dropping out from a study over the time interval, which is obtained by integrating the hazard with respect to time: The probability of survival (not dropping out) can be predicted from the CHZ: \( \exp(-CHZ) \). Hazard over time is usually integrated numerically using software programs (e.g. NONMEM, WINBUGS, R, etc.) with the help of user-defined differential equations. The commonly used TTE models in the area of brain disorders are the exponential dropout model (Parkinson’s disease, schizophrenia, Alzheimer’s disease and depression),[55,65,69,87] the Gompertz dropout model (generalized anxiety disorder)[54] and the Weibull dropout model (depression).[88]

The exponential dropout model assumes the probability of dropout to be constant over time for the entire study duration. In contrast, a time factor is considered in the Gompertz and the Weibull dropout model. Further basic discussions on various models to account for missing data can be found elsewhere.[89-91]

In schizophrenia, Goyal[69] used an exponential dropout model to integrate with clinical efficacy (the MNAR pattern). In depression, Parkinson’s and Alzheimer’s diseases the most commonly used TTE was the exponential dropout model.[55,65,69,87] Recently, the Weibull dropout model has been also evaluated in depression trials. No dropout models have been reported with power[67] and polynomial[13,79] placebo models.
**Longitudinal Logistic Regression Dropout Model**

The longitudinal logistic regression model describes a probability (P) of a patient dropping out, which always lies in the range between zero and one. The general form of the longitudinal logistic regression model is shown in equation 21:

\[
\text{Logit } P(X) = \ln\left[ \frac{P(X)}{1 - P(X)} \right]
\]

where \( P(X) = \frac{1}{1 + \exp\left( -\alpha + \sum \beta X \right)} \)  
(Eq. 21)

The logit transformation transforms the 0 to 1 probability scale to a \(-\infty \) to \(+\infty \) scale, allowing for the development of linear models to describe the relationship between the success probability and various predictors. In equation 21, \( \alpha \) denotes the probability of a patient dropping out at the time of trial initiation, while \( \beta \) determines the change in \( P(X) \) relating to one or more predictor variables \( X \). As in linear regression, a value of zero for \( \beta \) indicates that the score is independent of \( X \). The logistic regression model is shown to be advantageous in adding extensions to the model to test for nonlinear functions, interactions between covariate effects or other more complicated functions within the same general framework.

In schizophrenia, the longitudinal logistic regression model has been used by Friberg et al.\(^{14}\) and Petersson et al.\(^{68}\) Both authors used an empirical description of the PANSS time course and combined it with a logistic regression model of dropout to improve their model fit. The important predictors of dropout were found to be the study site (US or non-US), hospitalization, the change in the PANSS score from baseline, the time since start of study, the score on previous occasion and the difference between the last two scores. The logistic regression dropout model is flexible and allows inclusion of many predictors at a time. No integrated logistic regression dropout model with a drug-effect model has been reported for depression, Alzheimer’s disease or Parkinson’s disease.

Instead of the above-mentioned TTE models and logistic dropout modelling approach, Ortega et al.\(^{70}\) have used a simple linear dropout model to account for dropouts in an antipsychotic drug trial. They used the following model structure (equation 22):

\[
\text{Dropout} = k_{LO} \times (t_{LO} - t_{ES})
\]

where \( t_{LO} \) is the time from the commencement of the study to the last PANSS observation for each patient, \( t_{ES} \) is the scheduled trial duration and \( k_{LO} \) is a parameter that determines the dropout effect. The dropout effect was then
allowed to influence the PANSS score via the RP function as shown in equation 17. For further details see Ortega et al.\cite{70}

**DISCUSSION AND CONCLUSIONS**

Developing a new drug for CNS disorders has always been challenging, and even if the research and development groups have managed to come up with a 'promising' molecule, they have often failed to prove its efficacy in clinical trials. Clinical trials aiming to prove the efficacy of drugs in CNS diseases typically compare the efficacy of the newly developed molecule to placebo treatment in placebo-controlled trials. However, many clinical trials fail to prove the superiority of the molecule – for example, failure rates of up to 50% have been reported in clinical trials conducted for antidepressants which were introduced later on to the market.\cite{68,93}

Important possible reasons for such high failure rates are considerable magnitude and variability in placebo response, high dropout rates and low sensitivity of the subjective rating scales used for assessing the treatment effect. Usually, non-model-based approaches make the general assumption that both the placebo effect and disease progression are constant over time, which is often not factual and could lead to a biased trial outcome. Conversely, using advanced model-based assessment tools with higher sensitivity, such as pharmacokinetic-pharmacodynamic modelling and simulation-based approaches, would increase the power and the chance of discriminating among the disease progression, placebo and drug effects. This would also help in designing highly powered studies with the need for less money and time spent on studies with a large number of subjects. The FDA and the European Medicines Agency have appreciated the potential of pharmacokinetic-pharmacodynamic modelling and its impact on decision-making by publishing the guidance to industry.\cite{94-96} Examples of psychiatric drugs where the pharmacokinetic-pharmacodynamic model-based approaches have been utilized in the NDA to obtain regulatory approvals are aripiprazole\cite{67} and asenapine.\cite{97}

Placebo response is a 'background noise' that impedes the likelihood of detecting the signal of an effective drug. Addressing the placebo-response issue is one of the most important challenges facing the future of psychiatric drug development. Variable placebo response is a big problem with multi-centred clinical trials. Different magnitudes of placebo response in different trial centres may affect the detection of drug effects. The definition of dose/exposure response and the comparison of drug response across studies would require normalization of the quantifiable treatment effect by the level of placebo response. In modelling, one should consider possible differences in the study designs, study centres, patient characteristics and other important factors such as dropouts and disease progression.
The empirical placebo models demonstrated their potential to predict the clinical trial results via a simulation approach, but sometimes parameter estimates are dependent on the study design and study duration. In contrast, the parameter estimates of semi-mechanistic or mechanistic models are often more robust, uncorrelated and independent of the study design and duration. In addition, the parameters will be more clinically meaningful by considering physiological mechanisms. For instance, clinical translation of pharmacological mechanisms of treatment effects to their efficacy and safety can be implemented using mechanism-based models, while it is difficult with empirical models. Post et al.\cite{98} and de Winter et al.\cite{99} have successfully shown the advantages of the mechanistic models over the empirical models with data on antidiabetic drugs. However, mechanism-based models usually, but not always, require the use of differential equations, leading to longer run times (e.g. using NONMEM) and numerical difficulties. Currently, there is a scarcity of (semi)-mechanistic models in neuropsychiatric disorders as they require better understanding of the disease and the mechanism of treatment effects. However, a few semi-mechanism-based models have been published in the area of schizophrenia\cite{100} and depression.\cite{101} Della Pasqua et al.\cite{59} and Gobburu and Lesko\cite{102} emphasized in their reviews that the development of mechanism-based models in neuropsychiatric disorders is essential. Such models can be developed by integrating specific features of a disease (e.g. individual symptoms or items in a clinical rating scale) with information from the disease biomarkers (e.g. hippocampal volume reduction, tryptophan depletion in depressive patients).

Recently, Nucci et al.\cite{103} reviewed various model-based approaches to increase the efficiency of drug development in schizophrenia. They proposed evaluation of the empirical placebo models that performed the best in depression trials, i.e. IBF, a mixed Weibull and linear function, and a mixed exponential and linear function. Based on our modelling experience, the Weibull model and the IRM\cite{14,72,83} were the best models among all the above-reviewed placebo models to describe the time course of the PANSS score.

In addition to the large placebo response, high dropout rates may blunt the placebo-drug differences. Dropout events are often used as an outcome measure in clinical trials of CNS medications and they are usually related to the change in the clinical score from the baseline or between the last two visits. Patients can perceive the treatment effect (whether improvement or deterioration) relative to the disease status at the beginning of the trial, and this might lead to dropout. Ignoring missing data due to dropouts may bias the model-simulated trial outcome (thus biasing the prediction of future trial results). In the pharmacokinetic-pharmacodynamic modelling area, TTE dropout models are preferred over logistic regression models when exposure information is available. In many trials, covariate information is available. During the drug development process, we are typically interested in identifying the covariates that lead to increased probability
of dropout and the effect of these covariates that are known to influence the probability of dropout (i.e. the magnitude of the covariate effect). TTE models pose numerical difficulties as the number of covariates increase in the model. Conversely, logistic regression dropout models have fewer numerical difficulties and can accommodate many covariates.\textsuperscript{104} Integration of the dropout model with the clinical-response model is often helpful in making the right decisions with respect to selection of dose, dosing regimen and dosage adjustment.

To solve the issue of low sensitivity of the subjective rating scales used for assessing the treatment effect, one should look further into the currently used rating scales and explore components separately to try and find out which one is more sensitive than the others. Such an approach has already been used in depression by Santen et al.\textsuperscript{[60,61]} and in schizophrenia by Lader\textsuperscript{[62]} and Santor et al.\textsuperscript{[38]} In depression, Santen et al.\textsuperscript{[60,61]} have shown that the use of change in the HAMD-17 from baseline as the primary endpoint contributes to failures in the assessment of treatment efficacy. They successfully managed to come up with a subscale (HAMD-7) derived from the original HAMD-17 rating scale of depression. This subscale was composed of the most sensitive individual items and it showed higher sensitivity to detect the drug effect than the HAMD-17 rating scale. Similarly, in schizophrenia, Lader\textsuperscript{[62]} and Santor et al.\textsuperscript{[38]} have suggested that not all of the PANSS items are sufficiently sensitive to detect true treatment effects. The positive and negative subscales are more sensitive to change than the PANSS total score and, thus, they may constitute a 'mini PANSS' that may be more reliable for future research. To further examine the findings of Santor et al.\textsuperscript{[38]} we are currently investigating the performance of the different PANSS subscales separately and individual items utilizing pharmacokinetic-pharmacodynamic and simulation tools. Such a study could yield the most sensitive individual items that are capable of better detecting changes due to treatment.

Complete integration of disease-progression models, placebo-response models, drug-response models, covariate models and dropout models enables reliable prediction of the outcome of future trials through model-based simulation with consideration of various predictors of the placebo response and dropout. Model-based simulations help in determining the appropriate clinical trial design by selecting the right population, treatment duration, disease condition, etc., and thereby improve the detection of the signal of the drug effect by maximizing drug- and placebo-effect differences. As there is growing knowledge of the mechanisms of the placebo response in brain diseases, one can adopt several conceptual, statistical and mathematical approaches to confine different aspects of this biological system. Finally, we believe there is a need for a repository of disease progression models, placebo response models and dropout models, using pooled clinical data to identify the potential sources of higher placebo responses and dropout rates in failed clinical trials.
ACKNOWLEDGEMENTS

We would like to thank Ahmed Abbas Suleiman, Gijs Santen, Lena Friberg, Nisha Kuzhuppilly Ramakrishnan and Teun Post for their suggestions. We also thank the referees of an earlier version of this paper for valuable comments and suggestions, which have been incorporated into this version.

This review was performed within the framework of project no. D2-104 of the Dutch Top Institute Pharma (Leiden, the Netherlands; www.tipharma.com). The authors have no conflicts of interest that are directly relevant to the content of this review.

REFERENCES

1. Kane JM, Leucht S. Unanswered questions in schizophrenia clinical trials. Schizophr Bull 2008; 34 (2): 302-9


75. Holford N. The time course of placebo response in clinical trials - do antidepressants really take two weeks to work? [keynote presentation]. AAPS Annual Meeting and Exposition; 2005 Nov 6-10; Nashville (TN)

76. Holford NHG, Peace KE. Results and validation of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. Proc Natl Acad Sci U S A 1992; 89 (23): 11466-70


82. Post TM. Disease system analysis between complexity and over simplification [dissertation]. Leiden: University of Leiden, 2009


87. Holford N. Simultaneous modelling of disease progression and time to event with NONMEM-likelihood ratio test criteria for random and informative dropout models and an evaluation of two methods affecting the quality of parameter estimates [abstract no. 722]. 14th Annual Meeting, Population...


103. Nucci G, Gomeni R, Poggesi I. Model-based approaches to increase efficiency