Journal of Biopharmaceutical Statistics

ISSN: 1054-3406 (Print) 1520-5711 (Online) Journal homepage: https://www.tandfonline.com/loi/lbps20

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To cite this article: Francisco J. Diaz , Myladis R. Cogollo , Edoardo Spina , Vincenza Santoro , Diego M. Rendon & Jose de Leon (2012) Drug Dosage Individualization Based on a Random-Effects Linear Model, Journal of Biopharmaceutical Statistics, 22:3, 463-484, DOI: 10.1080/10543406.2010.547264

To link to this article: https://doi.org/10.1080/10543406.2010.547264

Published online: 14 Mar 2012.

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Journal of Biopharmaceutical Statistics, 22: 463–484, 2012
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ISSN: 1054-3406 print/1520-5711 online
DOI: 10.1080/10543406.2010.547264

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DRUG DOSAGE INDIVIDUALIZATION BASED ON A RANDOM-EFFECTS LINEAR MODEL

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This article investigates drug dosage individualization when the patient population can be described with a random-effects linear model of a continuous pharmacokinetic or pharmacodynamic response. Specifically, we show through both decision-theoretic arguments and simulations that a published clinical algorithm may produce better individualized dosages than some traditional methods of therapeutic drug monitoring. Since empirical evidence suggests that the linear model may adequately describe drugs and patient populations, and linear models are easier to handle than the nonlinear models traditionally used in population pharmacokinetics, our results highlight the potential applicability of linear mixed models to dosage computations and personalized medicine.

Key Words: Bayesian feedback; Bayes' theorem; Clozapine; Decision theory; Drug dosage individualization; Personalized medicine; Population pharmacokinetics; Random-effects linear models; Therapeutic drug monitoring; Therapeutic window.

1. INTRODUCTION

In the pharmacological treatment of some chronic illnesses, the clinician must search for an appropriate drug dosage D that, after being administered during a prespecified time period to a particular patient, will maximize the probability that a continuous pharmacokinetic or pharmacodynamic response Y_D takes a value between two prespecified values l_1 and l_2. Examples of these treatments are those based on drugs having a narrow therapeutic range, which is the range of plasma (or blood) drug concentrations that yield the desired pharmacological effect without toxicity; in this case, a pharmacokinetic response of interest (Y_D) is

Received August 7, 2010; Accepted December 8, 2010
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usually the steady-state trough plasma drug concentration in the patient, which is measured during routine therapeutic drug monitoring (TDM) (Shirrell et al., 1999). For instance, when administering the antipsychotic drug clozapine to a patient with schizophrenia, the clinician must make efforts to avoid plasma clozapine concentrations in the patient reaching very low or high values, since low concentrations will not reduce psychotic symptoms and high concentrations will increase the risk of severe sedation, seizures, and other undesirable effects (Sabaawi et al., 2006). In this example, D is clozapine dosage and Y_D is plasma clozapine concentration.

Another (classic) example in which the plasma (or blood) concentration of the treatment drug is a response of interest may be found during the treatment for heroin addiction based on methadone. An effective methadone-maintenance treatment requires that the minimum methadone concentration in the patient's blood be kept above the threshold of heroin-withdrawal symptoms, and that the maximum concentration be kept below the threshold of the appearance of narcotic effects (Dole, 1980). Although low methadone concentrations do not overcome heroin-withdrawal symptoms and also increase the risk of relapsing into heroin use, high concentrations will sedate the patient, preventing him/her from enjoying a normal and fruitful life. In this example, D is methadone dosage and Y_D is blood methadone concentration.

There are pharmacological treatments in which the clinician wants to control a continuous response other than plasma concentration of the treatment drug. An example is the use of the anti-coagulant drug warfarin to prevent blood clotting in patients with risk of thrombotic episodes. To monitor the treatment and adjust warfarin dosage, regular blood tests must be performed to measure the clotting tendency of the patient's blood; this measure is usually given as an international normalized ratio, INR (Cuadrado and Khamashta, 2000). The objective of dosage adjustment is to find an optimum dosage that produces an anticoagulation intensity between minimum and maximum prespecified values. Lower dosages than this minimum may not be effective (putting the patient at risk of a new thrombotic episode), and higher dosages than the maximum may produce serious hemorrhages. Here, D is warfarin dosage and Y_D is the INR, which is a pharmacodynamic response of interest.

In the preceding examples and similar ones, the clinician usually assumes that the patient's continuous response (drug plasma or blood concentration in the first two examples and INR in the third example) will become stable after administering a constant drug dosage for a known, fixed period of time. Further, the clinician must take steps to find a dosage that, after being administered for that period of time, maximizes the probability that the patient's response reaches a value that is not too low or too high, and therefore maximizes the chance of relieving the illness symptoms and minimizes the risk of experiencing undesirable or toxic effects. Finding this dosage is usually difficult, since there is usually wide variability across individual patients in response to the same pharmacological treatment. This response variability may be due to personal (e.g., age or gender), genetic, or environmental (e.g., drug–drug interactions) influences on pharmacokinetic and/or pharmacodynamic parameters, or even to patient compliance (Nies, 2001). Efforts have been made to develop drug-dosage individualization procedures based on statistical models that take into account this variability (for a review, see Diaz et al.,

2007). Among these procedures, those based on mixed-effects models seem to be very promising.

The application of mixed-effects models to the individualization of drug dosages was pioneered by Sheiner and his collaborators (see Sheiner and Beal, 1982; Vozeh et al., 1981). Underlying this application is the basic idea that a random coefficient in a mixed-effects model can be viewed as a parameter that is a characteristic constant for a particular patient in the population of patients, but that varies across patients (see Sheiner and Beal, 1980; Whiting et al., 1986). According to this idea, the variability of a random coefficient reflects a real variation in the biological and environmental variables that shape each person in the population as an individual; variability is not a mere mathematical artifact for dealing with a population's heterogeneity. Thus, a mixed-effects model includes parameters with constant values representing the whole population (fixed effects) and parameters with varying values whose particular values represent particular patients (random effects). Usually these parameters measure or reflect patients' pharmacokinetic or pharmacodynamic characteristics. For a history of both the theory and applications of mixed-effects models in pharmacology, see Pillai et al. (2005).

In practice, any drug dosage individualization procedure based on a population mixed-effects model utilizes Bayes' theorem. Before applying a procedure to a particular patient, the fixed effects and variance–covariance matrices of the random effects and errors must be estimated by using one or more samples of patients, or using previous pharmacological knowledge. Then the estimated distribution of the random coefficients is conceived of as a prior distribution for these coefficients, and a few response measurements (e.g., drug plasma concentrations) from the patient are used to compute the conditional distribution of the random coefficients given those measurements. A summary measure of this conditional distribution, such as its mean or mode vector, is considered a predictor of the true values of the patient's coefficients, and therefore is used to compute the patient's individualized dosage. According to this methodology, which is usually called "Bayesian feedback," a prior distribution models real-world random variables (i.e., models the variability of some pharmacokinetic or pharmacodynamic parameters in the patient population). Thus, the prior distribution is not interpreted as a representation of the clinician's system of subjective beliefs about hypothetical, constant population parameters, which would be an orthodox, classic interpretation of the prior distribution underlying Bayes' theorem. Failing to recognize that statistical practice may profit from these two different philosophical conceptions of prior distributions, rather than from the latter one alone, may have contributed to a misunderstanding of the Bayesian feedback methodology in the statistical community, which struggled for decades to understand the philosophical implications of Bayes' theorem.

Diaz et al. (2007) considered the individualization of a drug dosage when the natural log of steady-state drug plasma concentration-to-dosage ratio can be described using a random intercept linear model. In their model, it is assumed that no covariate has a random effect. Specifically, the studied model was

$$\log\left(\frac{Y_D}{D}\right) = \alpha + \boldsymbol{\beta}^T \boldsymbol{X} + \epsilon \tag{1}$$

where Y_D is a trough steady-state drug plasma concentration, D is the steady-state dosage, $\boldsymbol{X}$ is a vector with r covariates, $\boldsymbol{\beta}$ is a vector with regression coefficients that are population constants, and α is a characteristic constant of each patient. At the population level, it is assumed that α is an $N(\mu_\alpha, \sigma_\alpha^2)$ random variable and that ϵ is an intra-individual $N(0, \sigma_\epsilon^2)$ random error. Moreover, it is assumed that α is independent of ϵ. Diaz et al. (2007) suggested interpreting the quantity $\gamma = (\alpha - \mu_\alpha)/\sigma_\alpha$ as a standardized, covariate-adjusted index of metabolic activity, and suggested a procedure for empirically validating this index. (The more rapidly a patient's body eliminates the drug, the lower is his/her value of γ.) This interpretation is a direct consequence of the idea that random coefficients may be viewed as constants for a particular patient. In an independent study, Hu and Zhou (2008) suggested a more precise interpretation of α (and therefore of γ) and a rationale for using model (1) in dosage computations (see also Hu et al., 2009). Assuming linear pharmacokinetics, if CL/F is the patient's apparent clearance, the quantity $e^{\alpha+\boldsymbol{\beta}^T\boldsymbol{X}}$ is a multiple of $(CL/F)^{-1}$. Thus, e^{α} may be viewed as the portion of CL/F that is not explained by the covariates in $\boldsymbol{X}$. Therefore, γ is a covariate-adjusted proxy for apparent clearance, and model (1) quantifies the effects of covariates on apparent clearance (Hu and Zhou, 2008), which is the most important pharmacokinetic quantity to consider when designing a dosage regimen for long-term drug administration.

Diaz et al. (2007) proposed a clinical algorithm for drug-dosage individualization based on model (1). The algorithm was deduced from decision-theoretic concepts and consists of a series of steps that the clinician should follow in order to find an appropriate dosage for a particular patient, assuming that model (1) adequately represents the patient population. Before applying the algorithm to a particular patient, the population parameters $\boldsymbol{\beta}$, μ_α, σ_α^2, and σ_ϵ^2 have to be estimated using a sample of patients. A simulation study using a clozapine model built with a U.S. patient sample suggested that the algorithm will perform reasonably well, even including the possibility that parameter estimates are not very close to the true parameter values, and even if clozapine dosages are rounded to the closest multiple of the smallest dosage available from clozapine manufacturers, 25 mg/day (Diaz et al., 2007).

A difficult problem when individualizing a drug dosage using a population mixed-effects model is to decide how many drug plasma concentrations to obtain from the patient, such that an optimum dosage for the patient is computed. Solutions to this problem usually are ad hoc or lack clear justifications. However, Diaz et al. (2007) provided a theoretical framework that enables a solution to this problem for model (1). They introduced the concept of ω-optimum dosage for a patient with metabolic index γ, which, for ω close to 1, is essentially a dosage D that nearly maximizes the conditional probability $P\ (l_1 < Y_D < l_2 \,|\, \gamma)$, where (l_1, l_2) is the range of desired plasma concentrations. Thus, the optimum number of plasma concentrations that must be obtained from the patient is the one that allows computing an ω-optimum dosage for a prespecified, high proportion of patients in the population.

When discussing the Diaz et al. article (2007), it is important to differentiate between model (1) and their proposed algorithm for drug dosage individualization. Although the former is a description of the patient population, the latter is a series of steps for finding an optimum dosage for a particular patient. The algorithm's

applicability relies on the assumption that model (1) correctly describes the population. Diaz et al. (2007) found that model (1) was useful in studying the relationship between plasma concentrations of the antipsychotic clozapine and the covariates gender and smoking, controlling for clozapine dosage. In addition, Diaz et al. (2008) and Botts et al. (2008) suggest that a slightly more general version of model (1) may be useful for investigating drug–drug interactions. In particular, the model allowed the findings that smoking modifies the size of the effect of the anticonvulsant valproic acid on plasma clozapine concentrations (Diaz et al., 2008), and that it also modifies the size of the effect of the anticonvulsant lamotrigine on the plasma concentrations of the antipsychotic olanzapine (Botts et al., 2008). Hu and Zhou (2008) described an even more general version of model (1) that included transformed covariates and both peak and trough steady-state plasma concentrations. They proposed using their linear model to investigate the sensitivity of results from population pharmacokinetics analyses, and studied three drugs (two biologicals and one small molecule) using large, multinational patient samples. However, although the objectives of Hu and Zhou's study did not include searching for empirical evidence in favor of the linear model, they found a remarkable agreement between the conclusions obtained by using this model and those obtained by using traditional, pharmacokinetic nonlinear models. In particular, the average covariate-based dosing adjustment factors provided by linear and nonlinear models were essentially the same regardless of the investigated drug or covariate. The four studies just described (Botts et al., 2008; Diaz et al., 2007, 2008; Hu and Zhou, 2008), which used a total of six different samples of patients representing people from several countries and five different drugs, reported evidence of relatively good fits of the random-intercept linear models to the data, although some caution was advised when there was a possibility of comedication-time interactions (Botts et al., 2008; Hu and Zhou, 2008).

Although there is empirical evidence supporting model (1) and some of its generalizations, at least for some drugs, the Diaz et al. algorithm has been tested only through simulations (Diaz et al., 2007). However, the simulation results, the already-mentioned theoretical developments and evidence in favor of model (1) or similar models, and other authors' successful application of Bayesian feedback suggest that the algorithm is a potential tool for clinical practice and TDM that deserves a closer investigation. In particular, collaborative effort is necessary for precisely estimating population parameters using large samples of patients from particular populations and for particular drugs, and it is essential to compare the performance of the algorithm with that of currently accepted methods that are regularly used in TDM.

Model (1) does not include covariates with random effects, that is, covariates whose corresponding regression coefficients vary across patients. In model (1), the heterogeneity of the individuals is determined only by differences in the intercepts (the α's). This is a limitation, because the model does not allow for the possibility of covariates whose effects on Y_D vary among patients who have the same values on the other covariates and are under the same dosage. In fact, additional analyses of the clozapine data in Diaz et al. (2008), which are described later in section 4, indicated that the goodness of the fit of the random-intercept linear model described in these authors' article may be improved by incorporating random effects for some covariates, including smoking. In particular, this suggests that smoking has

an effect size on plasma clozapine concentrations that varies from patient to patient and, perhaps more importantly, that the extent to which smoking modifies the effect of valproic acid on plasma clozapine concentrations may vary from patient to patient. We do not know whether this differential smoking effect is due to differences in smoking behavior, to differences in personal, genetic, or environmental characteristics of the patients, or to all of these factors (although this difference may not be due to the number of cigarettes smoked daily; Diaz et al., 2008). However, the possible existence of covariates with random effects affecting a continuous pharmacokinetic response has motivated us to investigate whether the drug-dosage individualization algorithm in Diaz et al. (2007) is applicable to the situation where the patient belongs to a population that can be described by a linear model incorporating covariates with random effects.

This article investigates the clinical algorithm proposed by Diaz et al. (2007), and the use of linear mixed models in drug dosage individualization. Specifically, this article has three objectives: (1) to describe how the Diaz et al. algorithm can be applied to situations where some clinical and demographic covariates have random effects on a continuous pharmacokinetic or pharmacodynamic response Y_D, and to situations that include the linear models fitted in Hu and Zhou (2008), Diaz et al. (2008), and Botts et al. (2008) (in these three studies, the D in model (1) was replaced by D^d, where d was a parameter that was estimated); (2) to report decision-theoretic arguments that show that the preceding algorithm may produce better dosages than another method that has traditionally been used in TDM; and (3) to compare the algorithm with this other method using simulated populations of patients taking clozapine. With this article, we also want to highlight the potentially wide applicability of linear mixed models to drug dosage computations and personalized medicine.

Although at present most of the applications of mixed-effects models to drug-dosage individualization have been restricted to plasma drug concentrations as the response variable, other types of response are possible. Thus, in this article, we are concerned with continuous pharmacokinetic or pharmacodynamic responses that can be assumed to become stable after an administration of a constant drug dosage for a known fixed period of time. Hereafter, in model (1) and all models investigated in this article, Y_D represents the value of a (positive) continuous pharmacokinetic or pharmacodynamic response measured after administering a constant drug dosage D during such time period. Of course, this time period depends on the particular drug and response. For instance, when the response is plasma (or blood) drug concentration, this time period usually corresponds to at least 5 drug half-lives, and the drug concentrations measured after that period are usually termed "steady-state" (Winter, 2004). However, a continuous response may not necessarily be a drug plasma concentration, but may be an index of efficacy or toxicity of the drug, a measure of clinical benefit or harm, a clinical endpoint, or even a continuous surrogate marker (Molenberghs et al., 2008). The basic goal of a drug-dosage individualization process is to determine an optimum dosage D for a particular patient, which allows him/her to reach a response Y_D that lies within a range of desired responses (l_1, l_2). (The interval (l_1, l_2) is called the target response range.)

In section 2, we describe how the Diaz et al. algorithm can be used in situations where some covariates have random effects and/or the log of dosage has a fixed regression coefficient. In section 3, the algorithm is compared with a popular

TDM method through theoretical arguments. In section 4, a model of plasma clozapine concentrations that has covariates with random effects is described, and some computations that are necessary for performing the Diaz et al. algorithm are illustrated. In section 5, simulations are used to compare the algorithm with the TDM method, assuming accurate parameter estimates. The effects of estimation errors on the algorithm's performance are investigated through simulations in section 6. Section 7 discusses empirical evidence supporting the investigated linear model, and describes additional advantages of using linear over nonlinear models in drug dosage computations. Conclusions are in section 8.

2. APPLICABILITY OF THE DIAZ ET AL. ALGORITHM IN A MORE GENERAL SETTING

This study considers the model

$$\log(Y_D) = \psi + \boldsymbol{\eta}^T \boldsymbol{Z} + \boldsymbol{\beta}^T \boldsymbol{X} + d\log(D) + \epsilon \tag{2}$$

where ϵ is defined as in model (1), $\boldsymbol{Z}$ and $\boldsymbol{X}$ are vectors with k and r (possibly transformed) clinical or demographic covariates, respectively, $\boldsymbol{\beta}$ is a vector of regression coefficients that are population constants, and d is a population constant. Here, ψ and $\boldsymbol{\eta}$ are characteristic constants of a particular patient; they vary from patient to patient. At the population level, it is assumed that ψ is an $N(\mu_\psi, \sigma_\psi^2)$ random variable, that $\boldsymbol{\eta}$ is a k-dimensional $N_k(\boldsymbol{\mu}_\eta, \boldsymbol{V}_\eta)$ random vector, that $(\psi, \boldsymbol{\eta})$ has a joint normal distribution, and that $(\psi, \boldsymbol{\eta})$ and ϵ are independent from each other. Note that although $\boldsymbol{X}$ includes only covariates with fixed effects (the elements of $\boldsymbol{\beta}$), $\boldsymbol{Z}$ includes covariates that have fixed effects (the elements of $\boldsymbol{\mu}_\eta$) and random effects (the elements of $\boldsymbol{\eta} - \boldsymbol{\mu}_\eta$). Therefore, in order for $\boldsymbol{\beta}$ and $\boldsymbol{\mu}_\eta$ to be identifiable, we assume that none of the covariates in $\boldsymbol{X}$ are in $\boldsymbol{Z}$, and vice versa. In the traditional terminology of mixed linear models, the vectors $(\mu_\psi, \boldsymbol{\mu}_\eta^T, \boldsymbol{\beta}^T, d)^T$ and $(\psi - \mu_\psi, (\boldsymbol{\eta} - \boldsymbol{\mu}_\eta)^T)^T$ are called fixed and random effects, respectively (Verbeke and Molenberghs, 2000), with the understanding that μ_ψ and $\psi - \mu_\psi$ do not measure the "effects" of any real-world covariate because ψ represents only an intercept. If Y_D is drug plasma concentration and linear pharmacokinetics is assumed, d may be fixed at 1 (Hu and Zhou, 2008; Hu et al., 2009). Alternatively, the maximum likelihood estimator of d may be used to test the null hypothesis of linear pharmacokinetics, $d = 1$; and d should be estimated if there is evidence of nonlinear pharmacokinetics. When $d = 1$ and $\boldsymbol{\eta} \equiv 0$, model (2) is essentially model (1); in this sense, model (2) is a generalization of model (1).

For a fixed value of $\boldsymbol{Z}$, if we denote $\alpha = \psi + \boldsymbol{\eta}^T \boldsymbol{Z}$ then model (2) can be rewritten as

$$\log\left(\frac{Y_D}{D^d}\right) = \alpha + \boldsymbol{\beta}^T \boldsymbol{X} + \epsilon \tag{3}$$

with $\alpha \sim N(\mu_\alpha(\boldsymbol{Z}), \sigma_\alpha^2(\boldsymbol{Z}))$, where $\mu_\alpha(\boldsymbol{Z}) = \mu_\psi + \boldsymbol{\mu}_\eta^T \boldsymbol{Z}$ and $\sigma_\alpha^2(\boldsymbol{Z}) = \mathrm{Var}(\psi + \boldsymbol{\eta}^T \boldsymbol{Z})$. Thus, for fixed $\boldsymbol{Z}$, model (3) is analogous to model (1), although in model (3) the parameters of α depend on $\boldsymbol{Z}$ and the dosage D has been "transformed" to D^d. Now assume that model (2) describes adequately a population of patients,

and that a clinician wants to find an appropriate, individualized dosage D for a patient who belongs to this population and has a constant but unknown α. The analogy just described and the fact that $\boldsymbol{Z}$ is known and fixed throughout the entire individualization process suggest that the Diaz et al. algorithm can be implemented in the following way in the context of model (2). Here, it is assumed that the values of $\mu_\alpha(\boldsymbol{Z})$, $\sigma_\alpha^2(\boldsymbol{Z})$, $\boldsymbol{\beta}$, σ_ϵ^2, and d are known (or have been estimated with acceptable precision before applying the algorithm), which implies that the distribution $N(\mu_\alpha(\boldsymbol{Z}), \sigma_\alpha^2(\boldsymbol{Z}))$ is our prior distribution of α. When model (2) holds, the steps of the algorithm are as follows:

Step 1: By using $\hat{\alpha}_1' = \mu_\alpha(\boldsymbol{Z})$ and $C_0^* = \sqrt{l_1 l_2}$, compute the initial dosage

$$D_1 = \left(C_0^* e^{-\hat{\alpha}_1' - \boldsymbol{\beta}^T \boldsymbol{X}}\right)^{1/d} \tag{4}$$

Next, administer D_1 to the patient during an appropriate time period so that the response becomes stable, and then measure the stabilized response Y_{D_1}.

Step i, $i \geq 2$: By using the dosage-response pairs (D_j, Y_{D_j}), $j = 1, 2, \ldots, i-1$, which were obtained in the $i-1$ previous steps, compute the ith dosage

$$D_i = \left(C_0^* e^{-\hat{\alpha}_i' - \boldsymbol{\beta}^T \boldsymbol{X}}\right)^{1/d} \tag{5}$$

where $\hat{\alpha}_i'$ is a predictor of α given by

$$\hat{\alpha}_i' = (1 - \lambda_i \sqrt{\rho^{-1} - 1}) \left(\frac{1}{i-1} \sum_{j=1}^{i-1} \log\left(\frac{Y_{D_j}}{D_j^d}\right) - \boldsymbol{\beta}^T \boldsymbol{X} \right) + \lambda_i \sqrt{\rho^{-1} - 1}\, \mu_\alpha(\boldsymbol{Z}) \tag{6}$$

with

$$\rho = \rho(\boldsymbol{Z}) = \sigma_\alpha^2(\boldsymbol{Z}) / \{\sigma_\alpha^2(\boldsymbol{Z}) + \sigma_\epsilon^2\} \tag{7}$$

and λ_i, $i \geq 1$, defined by Eq. (12) in Diaz et al. (2007). (We stress that, in the context of model (2), ρ depends on $\boldsymbol{Z}$.) Administer the new dosage D_i to the patient until the response stabilizes, and then measure the produced, stabilized response Y_{D_i}. Since we are assuming that model (2) holds, we have that $Y_{D_i} = D_i^d e^{\alpha + \boldsymbol{\beta}^T \boldsymbol{X} + \epsilon_i}$, $i \geq 1$, where $\alpha = \psi + \boldsymbol{\eta}^T \boldsymbol{Z}$ is a constant number for the patient and the ϵ_i's are $N(0, \sigma_\epsilon^2)$. The ϵ_i's are assumed to be mutually independent.

For $i \geq 2$, $\hat{\alpha}_i'$ is the mean of the conditional distribution of α given $\log(Y_{D_j}/D_j^d) - \boldsymbol{\beta}^T \boldsymbol{X}$, $j = 1, \ldots, i-1$. By using Eq. (3) and a decision-theoretic argument analogous to the proof of Theorem 3.1 in Diaz et al. (2007), it can be shown that when model (2) holds, the Diaz et al. algorithm is optimal in the sense that at the ith algorithm step, $\hat{\alpha}_i'$ and C_0^* are the predictor $\hat{\alpha}_i$ of α and the target median patient's response C_0, respectively, that minimize the Bayes risk function

$$R(\hat{\alpha}_i, C_0) = 1 - P(l_1 < Y_{D_i} < l_2), \quad (\hat{\alpha}_i, C_0) \in \mathscr{G}_i \times (0, \infty) \tag{8}$$

where $\mathcal{G}_i$ is the set of all predictors $\hat{\alpha}_i$ of α that are normally distributed, satisfy $E[\hat{\alpha}_i] = \mu_\alpha(\boldsymbol{Z})$, and are independent of ϵ_i, and it is assumed that the interval $(0, \infty)$ includes any possible response. (Keep in mind that the value of $\boldsymbol{Z}$ is fixed during the whole dosage individualization process, since the algorithm is applied to a particular patient.) Thus, essentially, the Diaz et al. algorithm aims at finding a good predictor of α in the sense that this predictor maximizes the clinician's degree of confidence that the response Y_D will fall within the target range (l_1, l_2).

Suppose that a population of patients satisfies model (2), and that a particular patient from the population has characteristic constants ψ and $\boldsymbol{\eta}$ and, therefore, a characteristic $\alpha = \psi + \boldsymbol{\eta}^T \boldsymbol{Z}$. Assume that the Diaz et al. algorithm is applied to this patient. An important question is: How many algorithm steps are necessary to obtain an appropriate dosage for the patient? This question is answered by using the concept of ω-optimum dosage (Diaz et al., 2007). Specifically, in the context of model (2), for $0 < \omega < 1$, an ω-optimum dosage for the patient is a dosage D that satisfies

$$P(l_1 < Y_D < l_2 \,|\, \gamma) \geq \omega \left\{ \sup_{i \geq 1} \; P\,(l_1 < Y_{D_i} < l_2 \,|\, \gamma) \right\} \tag{9}$$

where $\gamma = [\alpha - \mu_\alpha(\boldsymbol{Z})]/\sigma_\alpha(\boldsymbol{Z})$. Thus, when model (2) holds, the largest attainable probability that the response of the patient reaches a value within the target range (l_1, l_2) is m, and the minimum number of algorithm steps that are necessary to reach an ω-optimum dosage for the patient is $I(\gamma, \omega)$, where m and $I(\gamma, \omega)$ are defined by Eqs. (14) and (16) in Diaz et al. (2007), respectively. (Observe that, besides depending on γ and ω, $I(\gamma, \omega)$ depends on both m and ρ, where ρ is given by Eq. (7) if model (2) holds.)

In practice, since the patient's γ is unknown, it is necessary to stop the algorithm at the earliest step that yields an ω-optimum dosage for at least a fraction p of patients, $0 < p < 1$. When model (2) holds, the minimum number of algorithm steps that are necessary to obtain an ω-optimum dosage for at least $p \times 100\%$ of the patients in the population is i^*, which is defined by Eq. (18) in Diaz et al. (2007). In practice, the values of ω and p should be fixed close to 1 before starting the algorithm. (These statements can be proven analogously to the proof of Theorem 3.2 in Diaz et al. (2007).) Note that in the context of model (2), i^* depends on the particular value that $\boldsymbol{Z}$ takes on in the patient, although i^* does not depend on $\boldsymbol{X}$. Moreover, although the definition of an ω-optimum dosage given by (9) formally depends on an infinite sequence of future dosages, only a finite number of administered dosages is needed to compute a dosage that has at least a $p \times 100\%$ possibility of being ω-optimum for the patient. This number is $i^* - 1$.

3. A COMPARISON WITH THERAPEUTIC DRUG MONITORING

The Diaz et al. algorithm may be considered an optimal method for dosage adjustment in a TDM setting when the patient belongs to a population that satisfies model (2) and Y_D is drug plasma concentration. To understand why this may be so, let us compare the Diaz et al. algorithm with a popular method for dosage adjustment, which is advocated in a number of pharmacology textbooks.

This method, which assumes linear pharmacokinetics, adjusts the patient's dosage using the formula

$$\text{Adjusted dosage} = \frac{\text{Previous dosage}}{\text{Measured concentration}} C_0 \tag{10}$$

where C_0 is a target drug steady-state trough concentration. Let A and B be two patients from a population that satisfies model (2) with $d = 1$, and who are independently treated with the drug. [The condition $d = 1$ insures linear pharmacokinetics (Hu and Zhou, 2008; Hu et al., 2009).] Assume that the two patients have the same covariate values in $\boldsymbol{X}$ and $\boldsymbol{Z}$, and have the same but unknown value of α, where $\alpha = \psi + \boldsymbol{\eta}^T \boldsymbol{Z}$, so that the patients are closely comparable. Suppose that we want to obtain steady-state trough plasma concentrations that fall within a target range (l_1, l_2), and that patients A and B are initially administered dosages D_1 and $D_{b,1}$, respectively, where $D_1 = D_{b,1}$ and D_1 is given by Eq. (4). Suppose that the dosage for patient A is adjusted n times using the Diaz et al. algorithm as described in section 2 (using C_0^* as target concentration and $\hat{\alpha}_i'$ as a predictor of α), and that the dosage for patient B is adjusted n times using (10), where C_0 may not be equal to C_0^*. The following argument shows that, after any dosage adjustment, patient A will have a higher chance of reaching the target concentration range than patient B.

Let (D_i, Y_{D_i}), $i = 1, \ldots, n+1$, be the dosage–concentration pairs obtained from patient A. Thus, $Y_{D_i} = D_i e^{\alpha + \boldsymbol{\beta}^T \boldsymbol{X} + \epsilon_i}$, $i = 1, \ldots, n+1$, where the ϵ_i's are mutually independent random errors with a $N(0, \sigma_\epsilon^2)$ distribution. From patient B, we obtain dosage–concentration pairs $(D_{b,i}, Y_{D_{b,i}})$, $i = 1, \ldots, n+1$, which satisfy $D_{b,i} = (D_{b,i-1}/Y_{D_{b,i-1}})C_0$ and $Y_{D_{b,i}} = D_{b,i} e^{\alpha + \boldsymbol{\beta}^T \boldsymbol{X} + \epsilon_{b,i}}$, where the $\epsilon_{b,i}$'s are $N(0, \sigma_\epsilon^2)$ random errors that may be reasonably assumed to be mutually independent and independent of the ϵ_i's. But for $i \geq 2$,

$$Y_{D_{b,i}} = \left(C_0 e^{-\hat{\alpha}_i - \boldsymbol{\beta}^T \boldsymbol{X}} \right) \left(e^{\alpha + \boldsymbol{\beta}^T \boldsymbol{X} + \epsilon_{b,i}} \right), \tag{11}$$

where $\hat{\alpha}_i = \log(Y_{D_{b,i-1}}/D_{b,i-1}) - \boldsymbol{\beta}^T \boldsymbol{X}$. Thus, applying formula (10) is equivalent to applying the Diaz et al. algorithm, except that C_0 and $\hat{\alpha}_i$ are used in place of C_0^* and $\hat{\alpha}_i'$ [cf. Eq. (5) with $d = 1$]. Now observe that $\hat{\alpha}_i \in \mathcal{G}_i$, where $\mathcal{G}_i$ is defined after Eq. (8). Thus, if $C_0 \neq C_0^*$, then

$$P(l_1 < Y_{D_{b,i}} < l_2) < P(l_1 < Y_{D_i} < l_2) \tag{12}$$

for all $i = 1, \ldots, n+1$ (see proof of Theorem 3.1 in Diaz et al., 2007). To see why inequality (12) is also valid when $C_0 = C_0^*$, denote $\hat{\alpha}_i'' = \frac{1}{i-1} \sum_{j=1}^{i-1} \left(\log\left(\frac{Y_{D_j}}{D_j}\right) - \boldsymbol{\beta}^T \boldsymbol{X} \right)$. Note that $E[\hat{\alpha}_i \mid \alpha] = \alpha = E[\hat{\alpha}_i'' \mid \alpha]$. For $i \geq 2$, $E[(\hat{\alpha}_i - \alpha)^2 \mid \alpha] = \sigma_\epsilon^2 \geq \sigma_\epsilon^2/(i-1) = E[(\hat{\alpha}_i'' - \alpha)^2 \mid \alpha]$. Thus, if $C_0 = C_0^*$ and $i \geq 2$, $E[(\hat{\alpha}_i - \alpha)^2] \geq E[(\hat{\alpha}_i'' - \alpha)^2] > E[(\hat{\alpha}_i' - \alpha)^2]$ because $\hat{\alpha}_i'$ is a Bayes estimator of α under the squared error loss but $\hat{\alpha}_i''$ is not; since $\hat{\alpha}_i \in \mathcal{G}_i$, inequality (12) holds. Thus, there is a higher probability of reaching the target concentration range when the Diaz et al. algorithm is used instead of formula (10).

Even more, a slight modification of the proof of Theorem 3.1 in Diaz et al. (2007) allows proving that inequality (12) is also valid for $i \geq 2$ when the initial

dosage D_1 is other than that given by Eq. (4), provided that dosage adjustments for patient A are performed using Eqs. (5) and (6) with $i = 2, \ldots, n+1$. This should not be a surprise, because, in general, the distribution of Y_{D_j}/D_j does not depend on the method used to compute D_j, although, of course, the distribution of Y_{D_j} does.

A further modification of the proof also allows proving that if (D_i, Y_{D_i}), $i = 1, \ldots, n$ are n steady-state dosage–concentration pairs provided by patient A in other circumstances, for instance, during a TDM that did not necessarily implement the Diaz et al. algorithm, and if Y_{D_i}/D_i, $i = 1, \ldots, n$, are mutually and conditionally independent given γ, then inequality (12) is also valid for $i = n+1$, provided that D_{n+1} is computed using Eqs. (5) and (6) with $i = n+1$. Interestingly, under these more general conditions, if i^* is given by Eq. (18) in Diaz et al. (2007) and $n+1 \geq i^*$, then the probability that D_{n+1} is ω-optimum is at least p, that is, D_{n+1} still enjoys an optimality property; however, due to inequality (12), $D_{b,n+1}$ may not have this property. Finally, if $n+1 < i^*$, then the clinician may use D_{n+1} as an initial dosage for patient A and perform at least $i^* - n - 1$ algorithm steps in order to obtain a dosage that is ω-optimum for patient A with a probability of at least p.

In summary, our computations show that formula (5) may produce better results than formula (10), even if the dosages and concentrations inputted to formula (6) are not obtained through a complete or strict application of the Diaz et al. algorithm. Moreover, if the number of dosage–concentration pairs is sufficient ($\geq i^*$), only one application of formula (5) may be enough to obtain a desired dosage optimality, regardless of how the pairs were obtained. The objective of a complete application of the algorithm, however, is to ensure that the probability of the drug concentration falling within the target range is maximized each time a dosage is computed.

4. APPLICATION TO CLOZAPINE INDIVIDUALIZATION

Clozapine is an antipsychotic drug used to treat patients with severe schizophrenia. Diaz et al. (2008) fit a linear model with only a random intercept and fixed-effect covariates to 415 steady-state (trough) plasma clozapine concentrations provided by 255 schizophrenia patients. Some schizophrenia patients need to be treated not only for their psychotic symptoms but also for depression with antidepressants or seizures with anticonvulsants. Thus, the objective of the study just described was to measure the size of co-medication effects on plasma clozapine concentrations, using a measure of average effect size that is also described in Botts et al. (2008) and de Leon et al. (2007a,b) and is based on relative percentiles (Diaz et al., 2007; Muñoz and Xu, 1996). The fitted model was similar to model (2), except that $\boldsymbol{\eta} - \boldsymbol{\mu}_\eta$ was assumed to be 0; that is, no random effects for the investigated covariates were included. In the Diaz et al. study (2008), Y_D was the steady-state plasma clozapine concentration produced by the clozapine dosage D, and the covariates included in the final model were: taking fluoxetine, taking fluvoxamine, taking paroxetine, taking phenobarbital, taking valproic acid, smoking, and the natural log of clozapine dosage ($\log(D)$). All covariates except the last were dichotomous. Also, an interaction between taking valproic acid and smoking was included in the model.

To examine whether some of these covariates have random effects, we reanalyzed the Diaz et al. (2008) data (Table 1). SAS PROC MIXED was used for computations (Littell et al., 2006). As a result, we found that the model in

Table 1 Fixed effects and effect sizes (E) for variables significantly associated with the natural log of plasma clozapine concentration, according to a linear mixed-effects model that includes random effects for smoking and taking fluoxetine ($n = 255$)

Variable	Fixed effects[a]	95% CI[b,c]	p-value[d]	E[e]	95% CI[f]
Taking fluoxetine[g]	0.33	(0.15, 0.51)	0.0013	+39%	(16, 67)
Taking fluvoxamine[g]	1.25	(1.04, 1.47)	<0.001	+249%	(183, 335)
Taking paroxetine[g]	0.26	(0.12, 0.39)	<0.001	+30%	(13, 48)
Taking phenobarbital[g]	−0.34	(−0.53, −0.14)	<0.001	−29%	(−41, −13)
Taking valproic acid[g]	0.14	(0.014, 0.27)	0.03		
Nonsmokers				+15%	(1, 31)
Smokers				−22%	(−44, 8)
Smoking[h]	−0.24	(−0.42, −0.055)	0.011		
Not taking valproic acid				−21%	(−34, −5)
Taking valproic acid				−47%	(−62, −25)
Valproic acid–smoking interaction	−0.39	(−0.74, −0.038)	0.03		
Log (dose)	1.23	(1.09, 1.38)	<0.001		

Note. 95% CI = 95% confidence interval. This table looks similar to Table 2 in Diaz et al. (2008) but describes a different model. Following the notation in section 2, the model for plasma clozapine concentrations was $\log(C) = \alpha - 0.24Z_1 + 0.33Z_2 + 1.25X_1 + 0.26X_2 - 0.34X_3 + 0.14X_4 - 0.39X_5 + 1.23\log(D) + \epsilon$, where Z_1 = smoking, Z_2 = taking fluoxetine, X_1 = taking fluvoxamine, X_2 = taking paroxetine, X_3 = taking phenobarbital, X_4 = taking valproic acid, $X_5 = Z_1X_4$, C = plasma clozapine concentration, and D = clozapine dosage. The intra-individual variation, σ_ϵ^2 was 0.027 [95% CI, (0.022, 0.035)]. The mean of ψ was −1.05 (−1.89, −0.21). If $\boldsymbol{\eta}$ is the vector of random regression coefficients corresponding to $\boldsymbol{Z} = (Z_1, Z_2)^T$, then the variance–covariance matrix of the random effects, $\mathrm{Var}[(\psi - \mu_\psi, (\boldsymbol{\eta} - \boldsymbol{\mu}_\eta)^T)^T]$ was a diagonal matrix whose components were as follows: variance of ψ, 0.20 (0.16, 0.26); variance of the coefficient of smoking, 0.19 (0.10, 0.51); and variance of the coefficient of taking fluoxetine, 0.083 (0.037, 0.34).

[a]The numbers in this column are the components of $\boldsymbol{\mu}_\eta$, $\boldsymbol{\beta}$, or d.

[b]95% CI for the fixed effect.

[c]The standard errors of the fixed-effects estimators were 0.43 (intercept), 0.084 (taking fluoxetine), 0.11 (fluvoxamine), 0.068 (paroxetine), 0.099 (phenobarbital), 0.065 (valproic acid), 0.092 (smoking), 0.1770 (valproic acid–smoking interaction), and 0.075 (log of dose). The standard errors of the variance estimators were 0.024 for the variance of ψ, 0.044 for the variance of the coefficient of taking fluoxetine, 0.076 for the variance of the coefficient of smoking, and 0.0034 for the intra-individual variation.

[d]Tests the null hypothesis that the fixed effect is equal to 0 vs. the hypothesis that it is different from 0.

[e]The effect size E measures the (adjusted) percentage change in the mean or median (or any other percentile) of plasma clozapine concentrations due to co-administration of the corresponding drug.

[f]95% CI for E.

[g]The dichotomous variable was defined as 1 if the patient was taking the co-medication and 0 otherwise.

[h]The dichotomous variable was defined as 1 if the patient was a smoker and 0 otherwise.

Diaz et al. (2008) could be improved by including random effects for the covariates smoking and taking fluoxetine. These random effects were statistically significant at the 0.05 level of significance. Also, Akaike information criteria were 405.3 and 385.6 for the model in Diaz et al. (2008) and the model with covariate random effects, respectively, suggesting that the latter fit better. Table 1 describes the new model. Residual analyses suggested that the model fit well. When the fifth column in Table 1 is compared with the corresponding column in Table 2 of Diaz et al. (2008),

Table 2 Initial clozapine dosages (in mg/day) used in simulations. These dosages are optimal for an "average patient" from a population that satisfies the model in Table 1 and a target steady-state, plasma clozapine concentration range of 350–600 ng/ml

				Phenobarbital (no); valproic acid:		Phenobarbital (yes); valproic acid:	
Smokers	Fluvoxamine	Fluoxetine	Paroxetine	No	Yes	No	Yes
No	No	No	No	350	300	450	400
			Yes	275	225	350	300
		Yes	No	250	225	350	300
			Yes	200	200	275	250
	Yes	No	No	125	100	175	150
			Yes	100	100	125	125
		Yes	No	100	75	125	100
			Yes	75	75	100	100
Yes	No	No	No	425	500	550	675
			Yes	325	425	450	550
		Yes	No	325	400	425	525
			Yes	250	325	350	425
	Yes	No	No	150	175	200	250
			Yes	125	150	150	200
		Yes	No	125	150	150	175
			Yes	100	125	125	150

we observe that excluding the random effects of smoking and taking fluoxetine from the model did not substantially affect the estimates for the average effect sizes of all covariates included in the model. At the 0.05 level of significance, the statistical significance of these estimates and of fixed-effect estimates was not affected either.

By using Eq. (14) in Diaz et al. (2007), $l_1 = 350$ ng/ml, $l_2 = 600$ ng/ml, and the error variance σ_ϵ^2 of the model in Table 1, which includes random effects for smoking (Z_1) and taking fluoxetine (Z_2), we obtain $m = 0.90$. Moreover, by using Eq. (7) with $\boldsymbol{Z} = (Z_1, Z_2)^T$, the values of $\rho(\boldsymbol{Z})$ are calculated as $\rho(1, 1) = 0.95$, $\rho(1, 0) = 0.93$, $\rho(0, 1) = 0.91$, and $\rho(0, 0) = 0.88$. Thus, if we use formulas (16) and (18) in Diaz et al. (2007) as explained in section 2, and assume that the model in Table 1 is used to implement an individualization algorithm in particular patients, we can compute that 3 algorithm steps are sufficient to reach a 0.9-optimum dosage for at least 95% of the patients, regardless of the value of $\boldsymbol{Z}$. In other words, to calculate such a dosage for a particular patient, only two blood samples would be required from the patient. (Note that i^* does not depend on $\boldsymbol{Z}$ in this particular example; however, in general, i^* does not always take on the same value for all values of $\boldsymbol{Z}$.)

5. COMPUTER SIMULATIONS ASSUMING ACCURATE PARAMETER ESTIMATES

We conducted a simulation study that compared the performance of the Diaz et al. algorithm with that of an iterative application of formula (10), assuming that the model described in Table 1 is a reasonable representation of the patient population, and using $l_1 = 350$ ng/ml and $l_2 = 600$ ng/ml. The main purpose of

these simulations was to explore differences between the two approaches, using realistic values for model (2) parameters. The issue of whether and how parameter estimates can be improved is out of the scope of this article and is the topic of a great deal of research (see, e.g., Verbeke and Molenberghs, 2000).

The simulation program was written with SAS/IML (SAS Institute, Inc., 2008). For each combination of values of the covariates included in the model, a population of 10,000 patients that satisfied the model was simulated. Specifically, a simulated realization of the random vector $(\psi, \boldsymbol{\eta})$ represented "a patient." In the two approaches, initial dosages were computed with formula (4) (Table 2). For each hypothetical patient, the clozapine dosage was adjusted three times using the Diaz et al. algorithm; that is, four steps of the algorithm were implemented. After each algorithm step i, the proportion p_i of patients whose steady-state plasma clozapine concentration reached the target concentration range, 350–600 ng/ml, was calculated, $i = 1, \ldots, 4$. (That is, $p_i = P(350 < Y_{D_i} < 600) \times 100$.) The "patients" were also used to simulate a traditional TDM in which clozapine dosages were iteratively adjusted three times using formula (10) with $C_0 = C_0^*$. For this simulated TDM, the proportion of patients whose clozapine concentration reached the target range after the $(i-1)$th dosage adjustment was computed and denoted by q_i, $i = 2, 3, 4$, and the proportion of patients who reached the target range after receiving the initial dosage was denoted by q_1. Since the initial dosages were the same in both simulated clinical procedures, $p_1 = q_1$. Since oral clozapine dosages are available as multiples of 25 mg, dosages computed with formulas (4) and (5), or with formula (10), were rounded to their closest multiple of 25 before "administering" them to the patients (i.e., before using the model to compute the resultant plasma clozapine concentrations). All dosages were of at least 25 mg/day.

Table 3 shows the simulation results for nonsmokers. Specifically, the table shows the obtained values of p_i and q_i, $i = 1, \ldots, 4$, for each possible combination of covariate values. As seen in Table 3, for any combination of covariate values, $p_i > q_i$, $i = 2, \ldots, 4$. For instance, after performing the third dosage adjustment with the Diaz et al. algorithm in nonsmokers who were taking only valproic acid as a co-medication, the proportion of patients who reached the target concentration range was $p_4 = 84.4\%$. In contrast, after the third dosage adjustment with formula (10) in comparable patients, the proportion was lower, $q_4 = 68.6\%$ (Table 3). In general, when compared with the dosage adjustments performed with formula (10), the dosage adjustments performed with the Diaz et al. algorithm always yielded dosages that had a substantially higher likelihood of producing clozapine concentrations within the target range.

Interestingly, $p_1 < p_2 < p_3 < p_4$, regardless of the patient subpopulation (Table 3). In contrast, in most subpopulations, $q_3 \approx q_4$. Thus, after two dosage adjustments, the traditional TDM did not produce any additional improvement in the dosages. The Diaz et al. algorithm, however, was able to further improve the dosages in the third dosage adjustment. Conclusions from the simulation results for smokers were essentially the same as those from nonsmokers.

In summary, even after accounting for the fact that oral clozapine dosages are available only in discrete amounts that are multiples of 25 mg, the Diaz et al. clinical algorithm produced better dosages than a TDM based on formula (10), in that the algorithm may produce substantially higher proportions of patients reaching the target clozapine concentration range.

Table 3 Proportions of nonsmokers who reached a target clozapine concentration range of 350–600 ng/ml under the Diaz et al. algorithm (p_i), and under a TDM method based on formula (10) (q_i)

				Phenob (no)				Phenob (yes)			
				Valpro (no)		Valpro (yes)		Valpro (no)		Valpro (yes)	
Fluvox	Fluox	Parox	Step i	p_i	q_i	p_i	q_i	p_i	q_i	p_i	q_i
No	No	No	1	42.1	42.1	43.5	43.5	43.7	43.7	42.6	42.6
			2	76.7	66.4	75.8	65.9	75.6	66.6	76.1	65.6
			3	82.2	68.1	81.6	67.7	81.7	68.3	81.9	68.8
			4	84.2	68.9	84.4	68.6	84.8	68.4	84.3	69.2
		Yes	1	43.1	43.1	42.9	42.9	42.7	42.7	42.20	42.2
			2	76.8	65.8	76.2	65.8	77.1	66.8	76.4	66.3
			3	82.2	68.2	81.2	69.1	82.3	68.4	81.5	68.9
			4	83.8	69.3	84.1	69.0	84.7	68.6	84.1	69.4
	Yes	No	1	36.8	36.8	37.5	37.5	37.5	37.5	37.5	37.5
			2	75.6	64.7	75.8	64.1	76.5	63.8	76.3	65.1
			3	81.7	68.5	80.8	68.0	82.2	68.5	81.6	68.0
			4	84.0	68.5	84.2	68.5	85.0	68.9	84.5	68.5
		Yes	1	36.3	36.3	36.3	36.3	37.2	37.2	37.1	37.1
			2	74.7	64.4	74.8	63.9	76.2	65.3	75.3	64.0
			3	81.0	68.1	80.9	68.1	81.3	68.5	81.2	67.3
			4	83.6	68.3	82.8	68.2	84.3	68.4	83.5	67.9
Yes	No	No	1	43.2	43.2	40.8	40.8	41.1	41.1	42.2	42.2
			2	74.1	64.3	72.5	63.5	76.1	64.8	74.4	64.8
			3	78.7	65.8	78.0	67.0	80.3	67.9	79.4	66.6
			4	80.7	66.0	80.9	67.0	83.2	68.4	82.0	68.2
		Yes	1	43.2	43.2	40.8	40.8	42.6	42.6	42.4	42.4
			2	72.0	63.9	71.8	62.5	74.0	65.2	73.7	64.8
			3	77.4	65.3	75.6	64.1	80.2	66.9	78.9	66.8
			4	78.5	66.2	77.3	64.4	81.3	66.3	80.9	66.9
	Yes	No	1	36.8	36.8	35.2	35.2	37.3	37.3	36.4	36.4
			2	71.0	61.4	70.0	60.2	73.5	63.0	73.0	62.7
			3	75.6	64.4	73.9	63.7	78.9	67.0	77.0	65.7
			4	77.8	64.5	75.7	63.8	80.5	67.8	79.4	65.4
		Yes	1	37.5	37.5	36.2	36.2	37.2	37.2	36.3	36.3
			2	69.0	59.1	68.1	59.0	72.1	61.9	70.7	61.1
			3	73.4	62.5	71.4	61.5	76.7	64.3	75.4	64.3
			4	75.3	62.5	73.7	61.5	78.5	64.8	77.1	64.5

Note. These simulations assume that the patients satisfy the model in Table 1. Fluvox, fluvoxamine; Fluox, fluoxetine; Parox, paroxetine; Phenob, phenobarbital; Valpro, valproic acid.

6. A COMPARISON WITH TRADITIONAL TDM UNDER PARAMETER ESTIMATION ERRORS

In section 5, the parameters used to compute dosages with the Diaz et al. algorithm were the same as those used to simulate the subjects' pharmacokinetic responses to dosages from both the algorithm and formula (10). Thus, it was assumed that the available parameter estimates were very precise estimations of the true model parameters. In practice, parameter estimates must be used by the clinician to compute dosages with the Diaz et al. algorithm; however, these

estimates may not be exactly the same as the true parameters that generate the actual pharmacokinetic responses via model (2). Diaz et al. (2007) explored through simulations the effect of parameter estimation errors on algorithm performance by using a model of plasma clozapine concentrations that was built with data from a double-blind clozapine trial. Although they did not compare the performance of their algorithm with that of other approaches, they found that unless model parameters are very far from their estimates, the algorithm still performs well when the estimates are used in dosage computations in place of the true parameters. Specifically, even when the potentially true parameters were all at a distance of 1 standard error from their estimates, there was a high probability that D_{i^*} would be 0.9-optimum (Diaz et al., 2007). Considering that maximum likelihood estimators are consistent and usually utilized in the estimation of linear model parameters, the Diaz et al. simulation results increase our confidence in their algorithm.

In this section, we use simulations to compare the Diaz et al. algorithm with formula (10) under the assumption that the form of the linear model representing the patient population is the same as that described in Table 1, but incorporating the possibility that parameter-estimate values may not be exactly the same as the true parameter values. Observe that the model in Table 1 has 13 real-valued parameters, including variances and all elements of the fixed-effects vector. Following an approach to simulation similar to that in Diaz et al. (2007, p. 2066), let ϑ_i, $i = 1, \ldots, 13$, denote the true parameters. Let $\hat{\vartheta}_i$ be the estimate of ϑ_i and $\text{se}(\hat{\vartheta}_i)$ its corresponding standard error, $i = 1, \ldots, 13$; these are numbers described in Table 1. For a fixed $r > 0$, consider the set S_r of 13-tuples $(\vartheta_1, \ldots, \vartheta_{13})$ for which the ratio $(\hat{\vartheta}_i - \vartheta_i)/\text{se}(\hat{\vartheta}_i)$ is either r or $-r$ for all i. That is, S_r is the set of all possible combinations of potentially true parameter values that are at a distance of r standard errors from their corresponding estimates. Observe that, for fixed r, S_r has $2^{13} = 8192$ elements.

As in section 5, we used a target plasma clozapine concentration range of 350–600 ng/ml, and p_3 and q_3 were defined as the proportion of patients who reached this range after 2 dosage adjustments using the Diaz et al. algorithm and formula (10), respectively. (Recall that i^* was estimated to be 3 in section 4.) For each patient subpopulation determined by the values of $\boldsymbol{X}$ and $\boldsymbol{Z}$, and $r = 0.2, 0.4, \ldots, 1.6, 1.8$, we computed p_3 and q_3 for each element of S_r by assuming that such an element was the true combination of parameter values. Each computation of p_3 and q_3 used 10,000 simulated patients. A particular value of the vector $(\psi, \boldsymbol{\eta})$, which represented a patient, was generated by using the assumed true values of μ_ψ, σ^2_ψ, $\boldsymbol{\mu}_\eta$, and $\boldsymbol{V}_\eta$. Regardless of the drug individualization method, the pharmacokinetic response of the patient to a dosage D was simulated by first generating one value of the random error ϵ, using the assumed true value of σ^2_ϵ; then Y_D was computed with the formula $D^d e^{\alpha + \boldsymbol{\beta}^T \boldsymbol{X} + \epsilon}$, using $\alpha = \psi + \boldsymbol{\eta}^T \boldsymbol{Z}$ and the assumed true values of $\boldsymbol{\beta}$ and d. Independent random errors were used across iterations of the Diaz et al. algorithm or formula (10), and across the two individualization procedures. Dosages were always rounded to the closest, positive multiple of 25 before computing Y_D. To compute dosages with the Diaz et al. algorithm, parameter estimates in Table 1 were entered into formulas (4)–(7). (The parameter estimates were not used to compute dosages with the traditional TDM approach, since formula (10) does not require them.) As in section 5, the initial dosages used in both individualization procedures were those shown in Table 2, and we let $C_0 = C_0^*$ in formula (10).

For fixed r, the number of elements of S_r for which $p_3 > q_3$ was computed, divided by 2^{13}, and multiplied by 100. The resultant percentage, denoted by Ω_r, was interpreted as the proportion of potentially true parameter combinations in S_r under which the Diaz et al. algorithm outperformed formula (10) after 2 dosage adjustments. Table 4 shows Ω_r for all subpopulations and particular values of r. Remarkably, for all patient subpopulations, $\Omega_r > 98\%$ when $r \leq 1.2$. (Regardless of the subpopulation investigated, $\Omega_r = 100\%$ when $r \leq 1$.) Another computation showed that when $r \leq 1$, the average of the differences $p_3 - q_3$, taken over all

Table 4 Proportion Ω_r of combinations of potentially true parameters that are at a distance of r standard errors from their estimates under which the Diaz et al. algorithm outperformed formula (10) after two clozapine dosage adjustments, for particular values of r and subpopulations of patients

				Phenob (no)				Phenob (yes)			
				Valpro (no)		Valpro (yes)		Valpro (no)		Valpro (yes)	
Fluvox	Fluox	Parox	r	NSMO	SMO	NSMO	SMO	NSMO	SMO	NSMO	SMO
No	No	No	≤1.2	100	100	100	100	≥99.9	100	≥99.2	100
			1.4	88.3	100	91.3	97.4	88.6	98.8	87.8	96.5
			1.6	75.0	92.8	77.0	88.3	78.0	88.0	78.1	88.5
			1.8	75.0	80.4	75.0	81.5	75.0	78.5	75.0	81.6
		Yes	≤1.2	100	100	100	100	≥99.5	100	≥98.7	100
			1.4	92.3	99.8	90.2	97.9	88.4	98.8	89.5	96.8
			1.6	78.2	90.3	78.3	90.3	78.3	90.8	79.8	88.6
			1.8	75.0	79.2	75.0	83.5	75.0	81.4	76.1	82.1
	Yes	No	≤1.2	100	100	100	100	100	100	100	100
			1.4	98.1	100	97.4	99.0	96.8	99.7	96.3	98.2
			1.6	83.3	95.5	87.1	91.7	86.9	92.5	84.7	91.2
			1.8	76.0	84.1	77.8	84.3	78.0	82.8	77.6	83.5
		Yes	≤1.2	100	100	100	100	100	100	100	100
			1.4	97.3	100	98.5	98.9	97.0	99.6	96.5	98.5
			1.6	86.8	93.7	90.0	92.6	85.2	94.0	87.1	91.4
			1.8	77.9	83.0	80.0	85.3	78.0	84.5	79.5	84.4
Yes	No	No	≤1.2	100	100	100	100	100	100	≥99.0	100
			1.4	93.6	99.9	91.2	97.8	92.9	99.1	92.0	97.7
			1.6	81.4	94.4	81.4	90.7	83.6	92.2	83.1	91.1
			1.8	75.4	84.9	76.7	84.0	78.1	83.0	77.5	84.4
		Yes	≤1.2	100	100	100	100	≥98.8	100	≥99.2	100
			1.4	93.6	99.8	94.7	98.3	91.7	98.9	93.2	97.9
			1.6	84.1	93.9	85.9	92.0	82.6	91.5	84.5	91.1
			1.8	77.9	84.8	79.7	85.3	76.9	83.2	79.0	84.7
	Yes	No	≤1.2	100	100	100	100	100	100	100	100
			1.4	98.9	100	97.6	99.4	98.1	99.6	96.2	98.3
			1.6	90.1	97.2	88.5	94.2	90.4	95.0	87.5	92.1
			1.8	82.4	89.0	80.8	87.4	82.2	86.6	80.2	85.1
		Yes	≤1.2	100	100	100	100	100	100	100	100
			1.4	98.3	100	99.0	99.3	97.5	99.6	98.1	98.7
			1.6	90.8	96.6	92.2	95.0	88.9	95.2	91.3	93.0
			1.8	82.2	88.6	84.3	88.4	81.6	87.2	84.0	86.6

Note. Fluvox, fluvoxamine; Fluox, fluoxetine; Parox, paroxetine; Phenob, phenobarbital; Valpro, valproic acid; NSMO, nonsmoker; SMO, smoker.

elements of S_r, was $\geq 8.6\%$. This suggests that even if all true parameters are at a distance of 1 standard error from their corresponding estimates in Table 1, a substantially higher percentage of patients may reach the target concentration range if the Diaz et al. algorithm is used in place of the traditional TDM method.

Starting from $r = 1.0$, Ω_r gradually decreased as r increased. For instance, among nonsmokers who were taking phenobarbital as their only co-medication, $\Omega_{1.0} = 100\%$, $\Omega_{1.2} = 99.9\%$, $\Omega_{1.4} = 88.6\%$, $\Omega_{1.6} = 78.0\%$, and $\Omega_{1.8} = 75.0\%$ (Table 4). However, even when $r = 1.6$, which is an appreciable distance between an estimate and its corresponding parameter, Ω_r was relatively large in most subpopulations of patients (Table 4). In fact, for 56 out of the 64 subpopulations, $\Omega_{1.6} \geq 80\%$; for all subpopulations, $\Omega_{1.6} \geq 75\%$.

We conclude that if the true values of the parameters of the clozapine model reported in Table 1 are not very far from the reported estimates (i.e., ≤ 1.2 standard errors), the Diaz et al. algorithm will still be superior in performance to the traditional individualization approach based on formula (10). If moderately higher levels of error affected parameter estimation (between 1.2 and 1.6 standard errors), there is still an acceptable likelihood that the former outperforms the latter approach. These simulation results are consistent with those of Diaz et al. (2007), who found that their algorithm is robust to errors in the estimation of model parameters, at least in the context of clozapine individualization.

7. DISCUSSION

This article examines the algorithm proposed by Diaz et al. (2007), which is a rational approach to computing individualized optimum dosages that is based on a precise definition of dosage optimality. Diaz et al. (2007) assumed that the patient belongs to a population that can be described by model (1). This model represents patients' heterogeneity through both covariates and a random intercept. As described in section 2, the algorithm can be applied to a more general situation, described by model (2), which has two additional features: covariates with random effects that add more flexibility to heterogeneity modeling, and a regression coefficient d for the log of dosage that may reflect nonlinear pharmacokinetics when different from 1 (Hu and Zhou, 2008; Hu et al., 2009). This suggests that the Diaz et al. algorithm may have wide applicability.

According to the Diaz et al. algorithm, once the parameters in model (2) are estimated using population data from phases III or IV, parameter estimates are used to compute a recommended initial dosage D_1. Then, after a few dosage adjustments, these parameter estimates are combined with measurements from a particular patient in order to compute a dosage that is optimum for the patient with a high probability. Parameter estimates are also used in these dosage adjustments.

There is empirical evidence that model (2) may be a useful tool for describing the effects of covariates on drug steady-state concentrations (Botts et al., 2008; Diaz et al., 2007, 2008; Hu and Zhou, 2008). Some less general versions of this model have been used to compute average dosage correction factors that allow incorporating covariate information in the design of dosage regimes. Our results show that the model may also be used to incorporate individual information that is not explained by available covariates, which is modeled through random regression coefficients. This approach may benefit some patients whose pharmacokinetic

or pharmacodynamic characteristics are considerably different from those of an average patient with comparable covariate values.

A version of model (2) that is essentially a random intercept linear model was used by Hu and Zhou (2008) in the analyses of Phase III data from three different drugs; their data were obtained from very large patient samples. Similar linear models were used by Diaz et al. (2008) and Botts et al. (2008) in analyses of Phase IV data. Hu and Zhou (2008) used their linear model only as a method for investigating the robustness of results obtained through compartmental pharmacokinetic models. However, they found a close similarity between covariate-based, average dosage adjustment factors computed with compartmental models and those computed with their linear model, which supports the validity of the linear model as a description of their patient samples and investigated drugs. Thus, although Hu and Zhou did not originally intend to gather evidence in favor of model (2), their work nicely provides very strong empirical and theoretical support for this model. Hu and Zhou appear to be aware of this fact, since they explicitly suggest the possibility that this model may be used to perform primary analyses for regulatory submissions, at least in some situations. (These authors, unfortunately, do not explicitly describe these situations.) This suggestion is also made by Hu et al. (2009).

A reasonable explanation for the similarity just described between results from model (2) and those from compartmental models may be that in the case of Y_D being steady-state drug plasma concentration, model (2) is essentially a model of apparent clearance when the drug follows linear pharmacokinetics, that is, when d is 1 or close to 1 (Hu and Zhou, 2008; Hu et al., 2009), and apparent clearance is the main determinant of the association between drug dosage and steady-state plasma concentrations (Winter, 2004). In Hu et al. (2009), an agreement between the pharmacokinetic conclusions from linear and nonlinear modeling was also observed for a drug that did not follow linear pharmacokinetics; in our opinion, this confirms the potentially wide applicability of linear mixed models to drug dosage computations. In general, linear models are easier to build and fit to Phase III or IV data than the nonlinear models that are at the core of traditional pharmacokinetic methods. Thus, model (2) may be a useful tool to compute dosages that are adjusted for covariate values or other individual information. The sparse sampling designs that usually characterize Phase III and IV studies, which impede a clear determination of absorption parameters (Jiao et al., 2009), may also be a reason for preferring model (2) when using data from these studies. Sparse sampling is also a reason for focusing only on steady-state concentrations when using Phase III or IV data (Hu and Zhou, 2008; Jiao et al., 2009). Its use in primary analyses for regulatory submissions is a potential application of model (2), as suggested by Hu and Zhou (2008) and Hu et al. (2009). More research is needed to explore this possibility and to examine whether the inclusion of covariates with random effects may provide more precise dosage computations.

8. CONCLUSION

The main conclusion of this investigation is that if model (2) holds, the Diaz et al. algorithm may produce better personalized dosages than some traditional dosage-adjustment methods used in TDM. This conclusion, along with empirical findings showing that linear mixed models may provide accurate representations of

pharmacokinetic data and the fact that linear models are much easier to handle than the nonlinear models that are traditionally used in population pharmacokinetics, suggests a potential use of linear mixed models in drug dosage computation. Moreover, the results in section 3 show that the algorithm may easily be modified to incorporate steady-state concentrations previously measured through another dosage adjustment procedure, provided that there is no evidence that apparent clearance or covariate values in the patient have substantially changed. (If the values in $\boldsymbol{X}$ have not changed, the stability of apparent clearance may be monitored by examining the stability of the empirical Bayes estimates of α, which coincide with the $\hat{\alpha}_i'$'s when the algorithm is applied [Verbeke and Molenberghs, 2000]). Also, if for some particular reason the clinician decides to change the dosage computed with formula (5) at a particular algorithm step (perhaps because of an observed unwanted reaction from the patient, or just because he/she has to administer a dosage rounded to the closest available dosage), the clinician may still incorporate the obtained concentration into formula (6), treating this concentration as if it were one obtained through an application of the algorithm. Our results show that the dosage computed at the next algorithm step will have the same optimality property as the dosage that would be obtained if the clinician had not changed the dosage. Future clinical studies that compare the Diaz et al. algorithm with dosage-adjustment methods routinely used in TDM are needed in order to quantify the clinical importance of differences between dosages. More research is needed to investigate how to deal with changes in covariate values or apparent clearance during an application of the algorithm, and to explore the implications for the algorithm's performance of not considering, at the population-modeling stage, variables with important effects on Y_D.

ACKNOWLEDGMENTS

The clozapine study described in this article was conducted at the Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, and IRCCS Centro Neurolesi "Bonino-Pulejo," Messina, Italy. In 1997, Dr. de Leon lectured once supported by Novartis. In the year since January 11, 2009 he has taken part in a National Institutes of Health (NIH) grant in collaboration with Genomas. He has never been a consultant for a pharmaceutical or pharmacogenetic company. M. R. Cogollo was partially supported by the grant "Apoyo a Estudiantes Sobresalientes de Posgrado" from the Universidad Nacional, Colombia. Dr. Diaz was partially supported by the "Vicedecanatura de Investigación" of the Faculty of Sciences of the Universidad Nacional, Medellin. Dr. Diaz's involvement in this work lasted $4\frac{1}{2}$ years; the first 3 years were at the Universidad Nacional, Medellin, Colombia, and the remaining $1\frac{1}{2}$ years at the University of Kansas, Kansas City, KS. In the last year, Dr. Spina has lectured supported by Eli Lilly, Janssen, AstraZeneca, and Bristol-Myers Squibb. Lorraine Maw, MA, helped edit the article.

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