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ORIGINAL PAPER

Should patients skip late doses of medication? A pharmacokinetic perspective

Elias D. Clark[1] · Sean D. Lawley[1]

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Abstract

Missed doses, late doses, and other dosing irregularities are major barriers to effective pharmacotherapy, especially for the treatment of chronic conditions. What should a patient do if they did not take their last dose at the prescribed time? Should they take it late or skip it? In this paper, we investigate the pharmacokinetic effects of taking a late dose. We consider a single compartment model with linear absorption and elimination for a patient instructed to take doses at regular time intervals. We suppose that the patient forgets to take a dose and then realizes some time later and must decide what remedial steps to take. Using mathematical analysis, we derive several metrics which quantify the effects of taking the dose late. The metrics involve the difference between the drug concentration time courses for the case that the dose is taken late and the case that the dose is taken on time. In particular, the metrics are the integral of the absolute difference over all time, the maximum of the difference, and the maximum of the integral of the difference over any single dosing interval. We apply these general mathematical formulas to levothyroxine, atorvastatin, and immediate release and extended release formulations of lamotrigine. We further show how population variability can be immediately incorporated into these results. Finally, we use this analysis to propose general principles and strategies for dealing with dosing irregularities.

Keywords Nonadherence · Late dose · Missed dose · Mathematical model

Introduction

Managing acute and chronic diseases often requires patients to take medication at a specified sequence of dosing times. Deviations from prescribed dosing regimens constitute major obstacles to treatment efficacy [1]. Such deviations include not taking some doses (i.e. missed doses) and taking doses at times later than the prescribing dosing times (i.e. late doses). Such medication nonadherence is especially problematic in long-term pharmacotherapy for chronic conditions, which typically involves at least one medication dosed one or more times per day [2, 3]. It has been estimated that up to 42% of patients suffering from chronic disease do not take medication as prescribed [4], and the most commonly cited cause of nonadherence is patient forgetfulness [5, 6].

What should a patient do if they realize that they forgot to take their last scheduled dose of medication? Should they take it as soon as possible? Should they skip it? How does this depend on how "late" the dose is? These are some of the most common questions asked by patients, but they generally do not receive adequate instructions regarding late or missed doses [7, 8]. Indeed, a recent analysis of just over 1500 prescription only medicines found that less than half came with any such instructions [9]. Further, definitions of a "late dose" versus a "missed dose," as well as the appropriate remedial steps a patient should take after such a dosing lapse, vary significantly among both patients and clinicians [10].

Answering these questions and developing appropriate remedial strategies is made difficult by the many competing factors in the problem, such as the drug absorption rate, the drug half-life, the therapeutic range of the drug, how late the dose is, and when the next dose is scheduled to be taken. Furthermore, investigating these questions in clinical trials is problematic since trials which force irregular dosing may be unethical [11–13].

✉ Sean D. Lawley
lawley@math.utah.edu

[1] Department of Mathematics, University of Utah, Salt Lake City, UT 84112, USA

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The purpose of this paper is to compare the pharmacokinetic effects of taking late doses versus skipping doses. We employ the standard pharmacokinetic single compartment model with linear absorption at rate k_a and linear elimination at rate k_e [14, 15]. We suppose that the patient is instructed to take doses at regular time intervals of length τ. We further suppose that at some point the patient is faced with the decision of either (i) taking a late dose that is delayed by a given time d or (ii) skipping this dose entirely. This scenario is motivated by a patient who forgets to take a dose and then realizes that they forgot after time d has elapsed. At this point, of course the patient cannot change their prior behavior, and thus they choose option (i) or (ii) (or perhaps taking the dose at even later time, which is included in our analysis).

We use mathematical analysis to study the effects of options (i) and (ii). We derive a formula which measures how taking a late dose causes the drug concentration in the body to deviate from the case that the patient took this dose on time. Comparing this deviation to the deviation caused by skipping the dose then offers insights into the effects of options (i) and (ii). In addition, since taking a late dose may cause the drug concentration to rise above the therapeutic range, we derive formulas which give the maximum drug concentration and maximum drug exposure caused by taking a late dose.

We emphasize that these formulas are given as explicit functions of the absorption rate k_a, the elimination rate k_e, the dosing interval τ, and the delay d. In particular, these metrics allow us to quickly investigate how the effects of a late dose depend on the various parameters in the problem. Furthermore, in contrast to numerical simulations of specific examples, our metrics can be immediately applied to any drug whose pharmacokinetics can be described by a single compartment linear model, assuming merely that the parameters k_a, k_e, and τ can be estimated (our results are expressed relative to a perfectly adherent patient so that parameters such as dose size, bioavailability, and volume of distribution do not factor in). To illustrate, we apply our metrics to levothyroxine, atorvastatin, immediate release (IR) lamotrigine, and extended release (XR) lamotrigine. We further show how our results immediately extend to a population pharmacokinetic model in which k_a and k_e vary among individual patients in a population according to given probability distributions. We have also created a simple web-based app [16] to allow pharmacometricians to use our metrics to study the consequences of late doses for other drugs and dosing scenarios.

The rest of the paper is organized as follows. We present and analyze the pharmacokinetic model in Methods (Sect. 2), and we present the results of analyzing this model in Results (Sect. 3). In the Discussion (Sect. 4), we discuss our results in the context of IR and XR drugs, delineate other salient pharmacological implications of this study, and offer some intuition behind our results. We also compare and contrast our approach to related work and describe the limitations of our model and analysis. Details of the mathematical analysis are collected in the Appendix.

Methods

Below, we first introduce the standard pharmacokinetic model of oral administration in a single compartment with first order (i.e. linear) absorption and elimination [14, 15] in a way that will facilitate our analysis. We then derive the metrics which we use in Methods to analyze late doses.

Pharmacokinetic model

Let $c(t)$ denote the drug concentration in the body at time $t \in \mathbb{R}$. Assume c satisfies the following ordinary differential equation,

$$\frac{\mathrm{d}c}{\mathrm{d}t} = k_a \frac{g}{V} - k_e c, \tag{1}$$

where k_a is the absorption rate, k_e is the elimination rate, V is the volume of distribution, and g is the amount of the drug at the absorption site. Assume

$$\frac{\mathrm{d}g}{\mathrm{d}t} = -k_a g + I(t), \tag{2}$$

where $I(t)$ is the drug input.

Without loss of generality, suppose the patient takes a dose of size $Df_n \geq 0$ at time $t_n \in \mathbb{R}$ for $n \in \mathbb{Z}$, where $\{f_n\}_{n\in\mathbb{Z}}$ is a nonnegative sequence and $\{t_n\}_{n\in\mathbb{Z}}$ is an increasing sequence of times (it is convenient to allow the index $n \in \mathbb{Z}$ to vary over positive and negative integers). For example, $f_n = 1$ means that the patient takes a dose of size D at time $t_n \in \mathbb{R}$, whereas $f_n = 0$ means that the patient does not take a dose at time $t_n \in \mathbb{R}$. Using this notation, the drug input is

$$I(t) = DF \sum_{n\in\mathbb{Z}} f_n \delta_{\mathrm{dirac}}(t - t_n), \quad t \in \mathbb{R}, \tag{3}$$

where $F \in (0, 1]$ denotes the bioavailability fraction and δ_{dirac} denotes the Dirac delta function. The superposition principle implies that the drug concentration time course $\{c(t)\}_{t\in\mathbb{R}}$ satisfying (1) is then

$$c(t) = \sum_{n\in\mathbb{Z}} f_n c_0(t - t_n), \tag{4}$$

where $c_0(t)$ denotes the concentration after time $t \in \mathbb{R}$ has elapsed since a single dose of size D,

$$c_0(t) := \begin{cases} \frac{DF}{V}\frac{k_a}{k_a - k_e}(e^{-k_e t} - e^{-k_a t}) & \text{if } t \geq 0, \\ 0 & \text{if } t < 0. \end{cases} \quad (5)$$

We assume $k_a \neq k_e$ throughout this paper (our analysis is valid for both $k_a > k_e$ and $k_e > k_a$).

We note that the formulation above is flexible to model the case that the patient has been taking the drug for a time long enough so that steady-state has been reached or the case that the patient takes the drug over a finite time period. For the latter, one merely sets $f_n = 0$ for $n \leq N_0$ and/or $n \geq N_1$, where $N_0 < N_1$ are any finite indices.

Perfect adherence

Suppose the patient is instructed to take a dose of size $D > 0$ every $\tau > 0$ units of time. In the case of perfect adherence over a long time, we have that

$$f_n = 1, \quad t_n = n\tau, \quad n \in \mathbb{Z},$$

and the corresponding drug concentration time course for perfect adherence is

$$c^{\text{perf}}(t) = \sum_{n \in \mathbb{Z}} c_0(t - n\tau). \quad (6)$$

We denote the long-term average drug concentration for perfect adherence by

$$\langle c^{\text{perf}} \rangle := \lim_{T \to \infty} \frac{1}{T} \int_0^T c^{\text{perf}}(t)\, dt = \frac{1}{\tau} \int_0^\infty c_0(t)\, dt = \frac{DF}{V}\frac{1}{k_e \tau}. \quad (7)$$

The second equality in (7) reflects the well-known fact that for perfect adherence, the steady state "area under the curve" over one dosing interval is the long-term "area under the curve" for a single dose [14]. The final equality in (7) follows from merely integrating (5).

Analyzing a late dose

To analyze the effects of a dose delayed by time $d \geq 0$, define the difference

$$\delta(t, d) := c_0(t - d) - c_0(t), \quad t \in \mathbb{R}. \quad (8)$$

To see the utility of the function $\delta(t, d)$, suppose the patient is instructed to take a dose of size D at (without loss of generality) time $t = t_0 = 0$. Let $\{c(t)\}_{t \in \mathbb{R}}$ denote the drug concentration time course in the case that the patient takes this dose as directed,

$$c(t) = \sum_{n \leq -1} f_n c_0(t - t_n) + c_0(t) + \sum_{n \geq 1} f_n c_0(t - t_n), \quad (9)$$

where $\{f_n\}_{n \in \mathbb{Z}}$ is an arbitrary nonnegative sequence and $\{t_n\}_{n \in \mathbb{Z}}$ is any increasing sequence with $t_0 = 0$ (note that (9) is the same as (4), except (9) fixes $t_0 = 0$ and $f_0 = 1$). Letting $\{c^d(t)\}_{t \in \mathbb{R}}$ denote the same time course, except that the patient delays the dose scheduled for time $t = 0$ and instead takes it at time $d \geq 0$, we have that

$$c^d(t) = \sum_{n \leq -1} f_n c_0(t - t_n) + c_0(t - d) + \sum_{n \geq 1} f_n c_0(t - t_n).$$

Therefore,

$$\delta(t, d) = c^d(t) - c(t), \quad t \in \mathbb{R}. \quad (10)$$

Summarizing, $\delta(t, d)$ is the difference in drug concentration between the case that the patient delays a dose by time d and the case that the patient takes this dose as directed. Further, $\delta(t, d)$ is independent of the patient's behavior before and after this dose.

Skipping versus taking a late dose

The following metric

$$\rho := \frac{1}{\tau \langle c^{\text{perf}} \rangle} \int_{-\infty}^{\infty} \left| c^d(t) - c(t) \right| dt \quad (11)$$

measures how taking the late dose causes the patient's drug concentration to deviate from the case that they took the dose on time. It is instructive to decompose ρ into the following sum,

$$\rho = \rho_- + \rho_+, \quad (12)$$

where ρ_- is the area between c^d and c when c^d is below c,

$$\rho_- := \frac{1}{\tau \langle c^{\text{perf}} \rangle} \int_{-\infty}^{\infty} \max\{c(t) - c^d(t), 0\}\, dt, \quad (13)$$

and ρ_+ is the area between c^d and c when c^d is above c,

$$\rho_+ := \frac{1}{\tau \langle c^{\text{perf}} \rangle} \int_{-\infty}^{\infty} \max\{c^d(t) - c(t), 0\}\, dt. \quad (14)$$

That is, if the patient takes a late dose, ρ_- is the deviation "below," ρ_+ is the deviation "above," and $\rho = \rho_- + \rho_+$ is the "total" deviation. See the left panel of Fig. 1 for an illustration in the case that the patient has perfect adherence for a long time before and after this late dose.

Let $\{c^{\text{skip}}(t)\}_{t \geq 0}$ denote the same time course as $c^d(t)$, except in the case that the patient skips this late dose. Define

$$\rho^{\text{skip}} := \frac{1}{\tau \langle c^{\text{perf}} \rangle} \int_{-\infty}^{\infty} \left| c^{\text{skip}}(t) - c(t) \right| dt \quad (15)$$

to measure how skipping the dose causes the patient's drug concentration to deviate from the case that they took the dose on time. We note that c^{skip} is always less than c, and

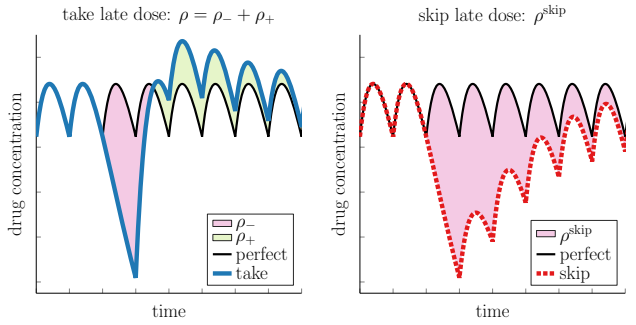

Fig. 1 Taking a late dose (left panel) versus skipping a late dose (right panel). The black curve in each panel is the drug concentration time course in the case of perfect adherence (denoted c^{perf}). The thick blue curve in the left panel is the drug concentration time course in the case that the patient takes a late dose (denoted c^d), and the dashed red curve in the right panel is the same time course except in the case that the patient skips the late dose (denoted c^{skip}). In the left panel, ρ_- is the area between c^d and c^{perf} when $c^d < c^{\text{perf}}$ (pink region) and ρ_+ is the area between c^d and c^{perf} when $c^d > c^{\text{perf}}$ (green region). In the right panel, $c^{\text{skip}} \leq c^{\text{perf}}$ for all time and ρ^{skip} is the area between these two curves (pink region). Though the plot illustrates the case of perfect adherence before and after the late dose, the value of ρ is independent of the adherence before and after the late dose (Color figure online)

thus ρ^{skip} is always a deviation "below." See the right panel of Fig. 1 for an illustration.

We emphasize that the statistics ρ, ρ_-, ρ_+, and ρ^{skip} are independent of the patient's adherence before and after this single late dose. Further, ρ, ρ_-, ρ_+, and ρ^{skip} are dimensionless, since they are normalized by the dosing interval τ and the long-term average drug concentration for perfect adherence $\langle c^{\text{perf}} \rangle$ in (7) (i.e. these statistics are independent of the units used to measure concentration, time, etc).

We are interested in understanding the scenarios in which $\rho < \rho^{\text{skip}}$ versus $\rho > \rho^{\text{skip}}$. We show in the Appendix that the deviation in (15) for skipping the late dose is always unity,

$$\rho^{\text{skip}} = 1. \tag{16}$$

We further show in the Appendix that if the patient takes the late dose, then the deviation above and the deviation below are always equal and are given by the following exact formula,

$$\rho_- = \rho_+ = f(k_a d, k_e d), \tag{17}$$

where f is the following function,

$$f(x,y) := (e^x - 1)^{y/(y-x)}(e^y - 1)^{x/(x-y)}. \tag{18}$$

Hence, (12) implies that the total deviation is

$$\rho = 2f(k_a d, k_e d). \tag{19}$$

The formula (19) shows that ρ depends only on the two dimensionless parameters $k_a d$ and $k_e d$, which compare the rates of absorption and elimination to the delay. Furthermore, ρ is a symmetric function of $k_a d$ and $k_e d$ since f is a symmetric function of x and y (meaning $f(x,y) = f(y,x)$). Formula (19) also implies that $0 < \rho < 2$ since $0 < f < 1$. Further, we show in the Appendix that for any value of k_a, k_e, and d,

$$\frac{\partial}{\partial k_a}\rho > 0, \quad \frac{\partial}{\partial k_e}\rho > 0, \quad \frac{\partial}{\partial d}\rho > 0. \tag{20}$$

That is, ρ is an increasing function of k_a, k_e, and d.

Furthermore, (20) implies the following relatively simple upper bound for ρ,

$$\begin{aligned} \rho &< \min\left\{ \lim_{k_a \to \infty} \rho, \lim_{k_e \to \infty} \rho \right\} \\ &= \min\left\{ 2(1 - e^{-k_e d}), 2(1 - e^{-k_a d}) \right\}. \end{aligned} \tag{21}$$

The upper bound in (21) and the value in (16) imply that if

$$\min\{k_a d, k_e d\} < \ln 2 \approx 0.69, \tag{22}$$

then $\rho < \rho^{\text{skip}}$. That is, (22) is a sufficient (but not necessary) condition to ensure that $\rho < \rho^{\text{skip}}$. If we define the respective absorption and elimination half-lives,

$$t_{a,\text{half}} = \frac{\ln 2}{k_a}, \quad t_{e,\text{half}} = \frac{\ln 2}{k_e},$$

then the sufficient condition in (22) has the following convenient and rather intuitive form,

$$d < \max\{t_{a,\text{half}}, t_{e,\text{half}}\}. \tag{23}$$

In words, (23) means that if the delay is less than the absorption and/or elimination half-life, then taking the late dose causes less deviation than skipping the late dose (i.e. $\rho < \rho^{\text{skip}}$).

Maximum increase in concentration and exposure

Define

$$v := \frac{1}{\langle c^{\text{perf}} \rangle} \max_{t \in \mathbb{R}} \left(c^d(t) - c(t) \right), \tag{24}$$

which measures how taking a late dose causes the drug concentration to rise above the drug concentration for the case that the dose is taken on time. Similarly, define

$$\gamma := \frac{1}{\langle c^{\text{perf}} \rangle} \max_{t \in \mathbb{R}} \frac{1}{\tau} \int_t^{t+\tau} \left(c^d(s) - c(s) \right) \mathrm{d}s, \tag{25}$$

which measures how taking a late dose causes the drug exposure over a single dosing interval to exceed the exposure for taking the dose on time. Note that v and γ are dimensionless since they are defined relative to the average concentration for perfect adherence ($\langle c^{\text{perf}} \rangle$ in (7)).

In the Appendix, we derive the following exact formulas for v and γ,

$$v = g(k_a\tau, k_e\tau)f(k_a d, k_e d), \tag{26}$$

$$\gamma = f(k_a\tau, k_e\tau)f(k_a d, k_e d), \tag{27}$$

where f is defined in (18) and

$$g(x, y) := x^{y/(y-x)}y^{x/(x-y)}. \tag{28}$$

We again emphasize that, like ρ, the metrics v and γ are independent of the patient's adherence before and after the late dose. In the Appendix, we derive another metric which yields more detailed information about the maximum concentration in the case that the patient has perfect adherence before and after the late dose.

Results

Consider a patient who is prescribed to take a dose of medication at intervals of time τ. Suppose the patient realizes after time $d > 0$ has elapsed since their last prescribed dose was scheduled to be taken that they did not take this last prescribed dose. Should the patient take this late dose or skip it?

We now use the metrics derived in Methods to address this question. In Sect. 3.1, we briefly summarize these three metrics. In Sect. 3.2, we outline some general implications of these metrics and illustrate these points for four specific drugs. In Sect. 3.3, we apply the metrics to a more detailed study of these four specific drugs. In Sect. 3.4, we show how this analysis extends to population pharmacokinetic models.

Metrics to quantify the pharmacokinetic effects of a late dose

In Methods, we derived three metrics to quantify the pharmacokinetic effects of taking versus skipping a late dose of medication. The purpose of this section is to briefly summarize these metrics and setup the analysis below.

The three metrics are

$$\rho := \frac{1}{\tau\langle c^{\text{perf}}\rangle}\int_{-\infty}^{\infty}\left|c^d(t) - c(t)\right|\,\mathrm{d}t, \tag{29}$$

$$v := \frac{1}{\langle c^{\text{perf}}\rangle}\max_{t\in\mathbb{R}}\left(c^d(t) - c(t)\right), \tag{30}$$

$$\gamma := \frac{1}{\langle c^{\text{perf}}\rangle}\max_{t\in\mathbb{R}}\frac{1}{\tau}\int_t^{t+\tau}\left(c^d(s) - c(s)\right)\,\mathrm{d}s, \tag{31}$$

where $\langle c^{\text{perf}}\rangle$ is the average drug concentration in a patient with perfect adherence (see (7)). The drug concentration time courses, $c^d(t)$ and $c(t)$, are identical, except that $c^d(t)$ has a dose delayed by time $d > 0$ and $c(t)$ has that particular dose taken at the prescribed time (no assumptions are made on the patient's adherence before or after this particular dose). In words, ρ measures how taking a late dose causes the drug concentration time course to deviate from the case that that particular dose was taken on time. We note that if the patient were to skip a dose rather than take it late, then we found that the corresponding metric is $\rho^{\text{skip}} = 1$ (see (15)-(16)). The metrics v and γ measure how taking a late dose causes the concentration and exposure to increase compared to the case that that particular dose was taken on time.

We obtained explicit mathematical formulas for ρ, v, and γ in Methods (see (19), (26), and (27)). These formulas depend only on the absorption rate k_a, the elimination rate k_e, the prescribed dosing interval τ, and the delay d. We emphasize that the metrics are dimensionless since they are normalized by $\langle c^{\text{perf}}\rangle$. In particular, the metrics do not depend on parameters such as the dose size, bioavailability fraction, volume of distribution, etc. We further emphasize that the metrics are independent of the patient's adherence before and after the late dose (see Sect. 2.3).

The effects of a late dose depend on absorption, elimination, and dosing interval

In Fig. 2, we plot a heat map of the metric ρ in (29) using the formula (19). Since $\rho^{\text{skip}} = 1$ for any choice of parameters, the blue region in Fig. 2 is where $\rho < \rho^{\text{skip}}$ and the red region is where $\rho > \rho^{\text{skip}}$. That is, the blue region is where the deviation caused by taking a late dose is less than the deviation caused by skipping a dose.

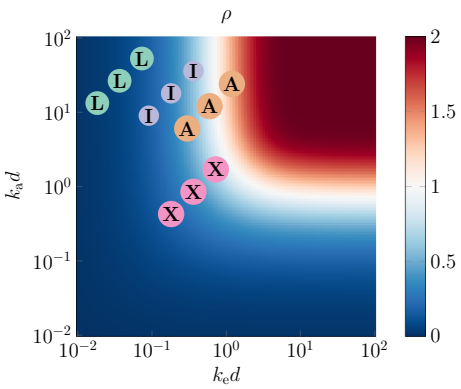

Fig. 2 Heat map of the deviation $\rho \in (0, 2)$ in (11) caused by taking a dose delayed by time $d > 0$. In the blue region, $\rho < \rho^{\text{skip}}$, meaning the deviation caused by taking the late dose is less than the deviation caused by skipping the late dose. In the red region, $\rho > \rho^{\text{skip}}$. The circles mark levothyroxine (L), atorvastatin (A), and lamotrigine in IR (I) and XR (X) formulations for different values of the delay d. See the text for details

Figure 2 shows that ρ increases if k_a, k_e, and/or d increases. Indeed, we show in the Appendix that for any value of k_a, k_e, and d,

$$\frac{\partial}{\partial k_a}\rho > 0, \quad \frac{\partial}{\partial k_e}\rho > 0, \quad \frac{\partial}{\partial d}\rho > 0. \tag{32}$$

In words, (32) means that faster absorption, faster elimination, and/or longer delays always increase the deviation caused by taking a late dose. We note that ρ is independent of the dosing interval τ.

In Fig. 2, the letters correspond to different drugs, where "L" marks levothyroxine, "A" marks atorvastatin, and "I" and "X" mark lamotrigine in the IR and XR formulations, respectively. For each drug, the three circles correspond to delays equal to $d = \tau/4$, $d = \tau/2$, and $d = \tau$, where τ is the prescribed dosing interval for that particular drug (the circles move up and to the right as the delay increases). The values of k_a, k_e, and τ for these four drugs are given in Table 1.

Figure 2 shows that the deviation ρ depends critically on both the size of the delay, d, and the drug kinetics, k_a and k_e. In particular, notice that all four drugs in Fig. 2 have deviations $\rho \ll 1$ if $d = \tau/4$. However, if $d = \tau$, then $\rho \ll 1$ for levothyroxine, $\rho > 1$ for atorvastatin, and $\rho < 1$ for the IR and XR versions of lamotrigine. A detailed analysis of these particular drugs and the concentration time courses obtained by taking or skipping a late dose is given in Sect. 3.3 below.

Therefore, recommendations for taking or skipping a late dose should depend on the kinetics of the specific drug. To illustrate, a simple "halfway" rule which is sometimes recommended for late doses is to (a) take the late dose if it is delayed by less than half of the prescribed dosing interval and (b) skip the late dose if it is delayed by more than half of the dosing interval [10]. To compare this rule to our analysis, in Fig. 3 we show contour plots of ρ as a function of $k_e\tau$ and d/τ for different values of $k_a\tau$. The green dashed line in these plots is at $d/\tau = 1/2$, and thus the "halfway" rule recommends taking (skipping) the delayed if the parameters lie below (above) this green dashed line. However, there are blue regions above this line, which indicates that the "halfway" rule suggests skipping doses in scenarios when taking the dose would result in a smaller deviation. Conversely, there are red regions below this line, which indicates that the "halfway" rule suggests taking doses in scenarios when skipping the dose would result in a smaller deviation.

Table 1 Parameter values for some specific drugs. Parameter values for each drug were taken from the reference indicated in the table

Drug	k_a (1/hr)	k_e (1/hr)	τ (hr)	Ref.
Levothyroxine	2.2	0.003	24	[17, 18]
Atorvastatin	1	0.05	24	[19]
Lamotrigine IR	3	0.03	12	[20]
Lamotrigine XR	0.07	0.03	24	[20]

We do not make the blanket assertion that a late dose should always be taken if $\rho < 1$ and always skipped if $\rho > 1$. Indeed, our metrics ν and γ measure the increase in concentration and exposure caused by a taking a late dose, and such increases could be harmful for some drugs and acceptable for others. Of course, no single statistic depending on only a few pharmacokinetic parameters could serve as a definitive guide for skipping or taking late doses for all medications. However, the simple test of whether $\rho < 1$ or $\rho > 1$ can serve as a general principle to guide the development of appropriate ways to handle a late dose. Furthermore, situations in which $\rho \ll 1$ strongly suggest that a late dose should be taken, and conversely, taking a late dose should be strongly cautioned against if $\rho \gg 1$. In addition, comparing the values ρ for different drugs can be used to determine which drug is more "forgiving" of late doses (see Sect. 3.3 below) [21–28].

This analysis shows that, in many circumstances, a patient can minimize their deviation by taking rather than skipping a late dose. However, as mentioned above, one concern about taking a late dose is that it could cause the drug concentration or exposure to rise too high. The metrics ν and γ in (30)–(31) address this concern by measuring the respective largest increase in concentration and exposure caused by taking a late dose. In Fig. 4, we produce contour plots of ν and γ as functions of $k_e\tau$ and $k_a\tau$ for $d = \tau$ using (26)-(27). Since we set $d = \tau$ in Fig. 4, these plots correspond to the extreme case that a double dose is taken. Nevertheless, these plots show that the maximum increase in concentration or exposure is quite small for many parameter values. Hence, these plots show when a double dose could be taken without causing a significant increase in drug concentration or exposure. Analogous to Fig. 2, the circle markers in Fig. 4 correspond to the drugs in Table 1 with $d = \tau$.

Furthermore, the red dashed curve in Fig. 4 separates the region in which $\rho < 1$ (to the left of the red dashed curve) from the region in which $\rho > 1$ (to the right of the red dashed curve). We note that the red curve in which $\rho = 1$ corresponds to roughly $\nu \approx 0.3$ and exactly to $\gamma = 0.25$. Hence, if the patient takes a dose delayed by $d = \tau$ (i.e. they take a double dose) only if $\rho < 1$, then they could at most have an increase in concentration of approximately $0.3\langle c^{\text{perf}}\rangle$ and an increase in exposure over

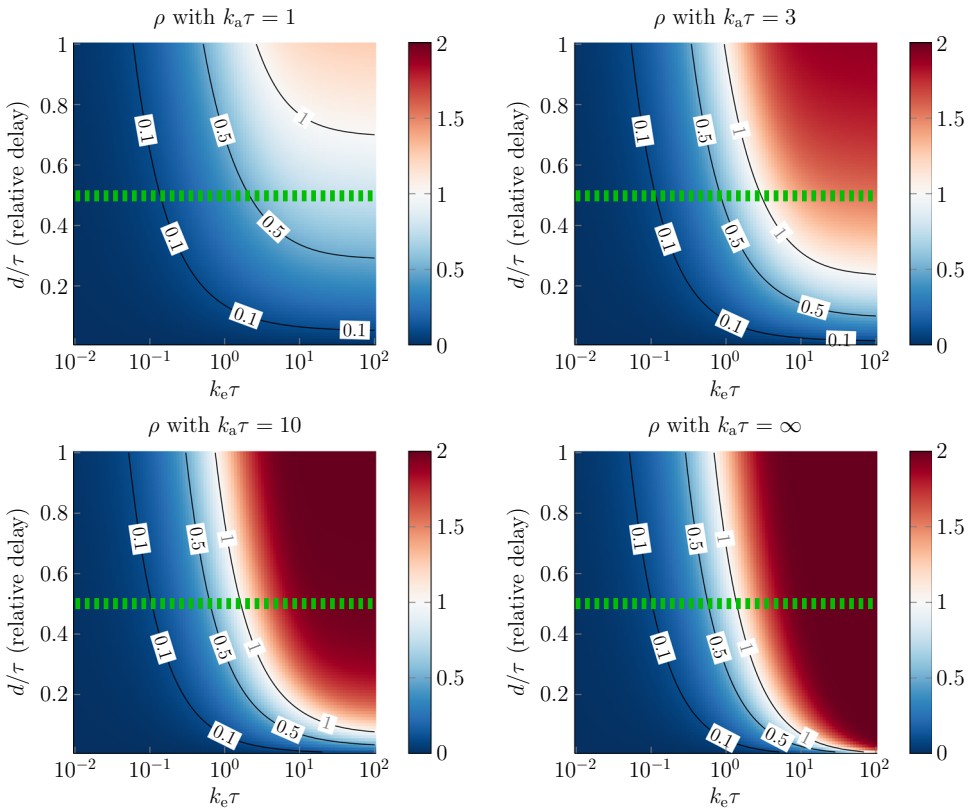

Fig. 3 Contour plots of $\rho \in (0, 2)$ in (11). The horizontal green dashed line marks a delay d equal to one half of the dosing interval τ. See the text for details (Color figure online)

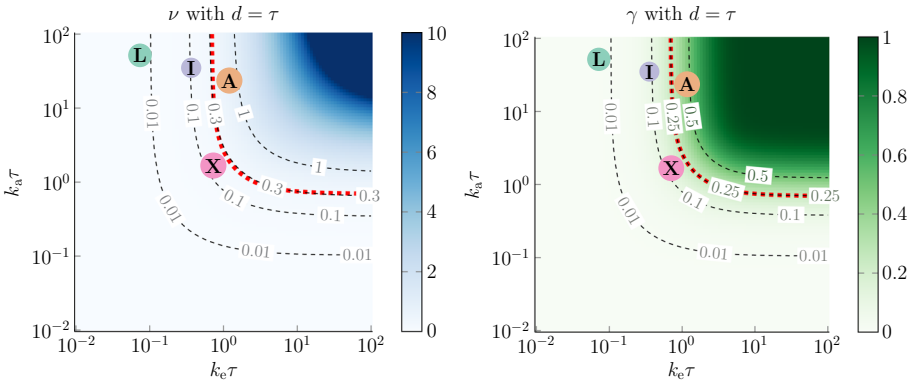

Fig. 4 The left panel plots the maximum relative increase in drug concentration ν in (24). The right panel plots the maximum relative increase in drug exposure γ in (25). In both plots, the red dashed curve marks where $\rho = \rho^{\text{skip}}$. The letters L, A, I and X correspond to the drugs in Table 1. See the text for details

any time interval of length τ of $0.25\langle c^{\text{perf}}\rangle\tau$ (these increases are compared to the case that the late dose was taken on time).

Finally, we note that Fig. 4 indicates that ν and γ increase if k_a or k_e increases. Indeed, we verify in the Appendix the more general result that

$$\frac{\partial}{\partial x}\nu > 0, \quad \frac{\partial}{\partial x}\gamma > 0, \quad \text{for any } x \in \{k_a, k_e, d, \tau\}. \tag{33}$$

That is, ν and γ are increasing functions of the absorption rate k_a, elimination rate k_e, delay d, and dosing interval τ.

Application to four common medications

We now apply the analysis above to some specific drugs. We note that we have created a simple web-based app [16] to allow pharmacometricians to use our metrics to study the consequences of late doses for other drugs and dosing scenarios. We consider levothyroxine, atorvastatin, and IR and XR formulations of lamotrigine. The absorption rate k_a, elimination rate k_e, and dosing interval τ for each of these drugs is given in Table 1. In Fig. 5, we plot ρ (left panel) and ν (right panel) as functions of the delay d for each of these four drugs. Plots of γ are similar to those of ν

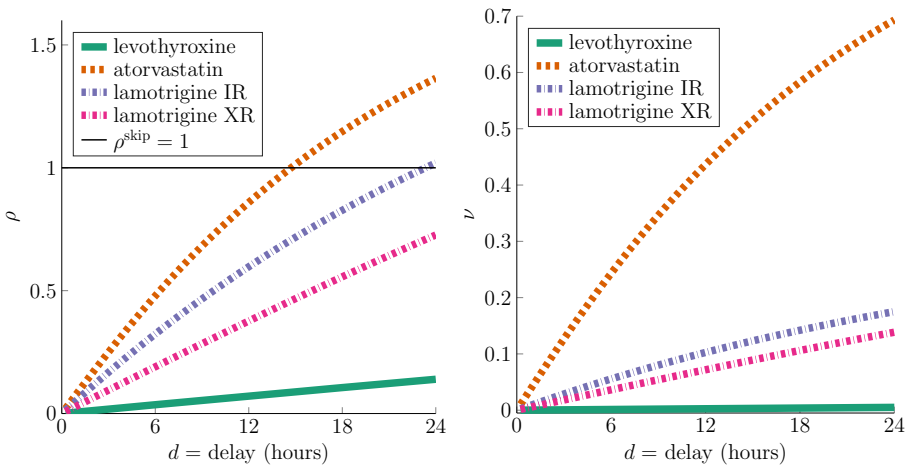

Fig. 5 Left: Plot of deviation caused by taking a late dose (ρ in (11) and (19)) for the four different drugs in Table 1. Right: Plot of maximum relative concentration increase (ν in (24) and (26)) for the four different drugs in Table 1

and are omitted. We now discuss each of these drugs in turn.

A daily dose of levothyroxine taken for the rest of a patient's life is the standard treatment for hypothyroidism, and levothyroxine is one of the most commonly prescribed drugs in the US [29] (common brand names are Synthroid, Tirosint, Levoxyl, Unithroid, and Levo-T). Owing to its very slow elimination rate of $k_e = 0.003\,\text{hr}^{-1}$ [17], Fig. 5 shows that the deviation from a late dose, ρ, and the maximum relative increase in drug concentration, ν, both rise very slowly as a function of the delay d. Indeed, even when the delay equals the dosing interval, $d = \tau = 24\,\text{hr}$, we have

$$\rho \approx 0.14, \quad \nu \approx 0.005, \quad \gamma \approx 0.005. \tag{34}$$

The values in (34) suggest that late doses of levothyroxine should be taken rather than skipped, even if that means taking a double dose. This is illustrated in the top left panel of Fig. 6, where we show the drug concentration time course for perfect adherence (thin black curve), a late dose (thick blue curve), and a skipped dose (dashed red curve). This suggestion (i) contradicts some existing recommendations to skip any dose of levothyroxine that is delayed by more than 12 hours [30–33] and (ii) agrees with recommendations of the American Thyroid Association [34].

Atorvastatin (brand name Lipitor) is another one of the most common prescription drugs in the US [35]. Atorvastatin is typically administered once daily to treat hyperlipidemia [35]. Compared to levothyroxine, Fig. 5 shows that ρ and ν rise much faster for atorvastatin as the delay d increases. Indeed, ρ surpasses $\rho^{\text{skip}} = 1$ for a delay d of slightly more than half of the dosing interval $\tau = 24\,\text{hr}$ (specifically, $\rho = 1$ if $d \approx 14.5\,\text{hr}$). For a delay equal to the dosing interval, $d = \tau = 24\,\text{hr}$, we have

$$\rho \approx 1.36, \quad \nu \approx 0.69, \quad \gamma \approx 0.47. \tag{35}$$

The values in (35) accord with common recommendations to avoid double doses of atorvastatin [36]. For a dose delayed by half the dosing interval, $d = \tau/2 = 12\,\text{hr}$, we have

$$\rho \approx 0.86, \quad \nu \approx 0.44, \quad \gamma \approx 0.29. \tag{36}$$

The values in (36) accord with the recommendations of some that late doses of altorvastatin can be taken as long as the delay is not more than 12 hours (half of the dosing interval) [37]. Time courses for atorvastatin which compare delaying a dose by 12 hours versus skipping a dose are shown in the upper right panel of Fig. 6.

Finally, we consider the antiepileptic drug lamotrigine in its IR and XR formulations. These formulations have identical elimination rates, but the XR formulation has a markedly slower absorption rate and is administered once daily rather than twice daily like its IR counterpart (see Table 1). Figure 5 shows that both formulations have fairly small values of ρ and ν for a delay d not more than the dosing interval. Indeed, for the IR version with a delay of $d = \tau = 12\,\text{hr}$, we have

$$\rho \approx 0.60, \quad \nu \approx 0.10, \quad \gamma \approx 0.09. \tag{37}$$

For the XR version with a delay of $d = \tau = 24\,\text{hr}$, we have that

$$\rho \approx 0.73, \quad \nu \approx 0.14, \quad \gamma \approx 0.13. \tag{38}$$

The values in (37)-(38) suggest that late doses of lamotrigine IR and XR should be taken, even if that means taking a double dose. This accords with recommendations of Chen et al. [20] but contradicts some existing recommendations [36].

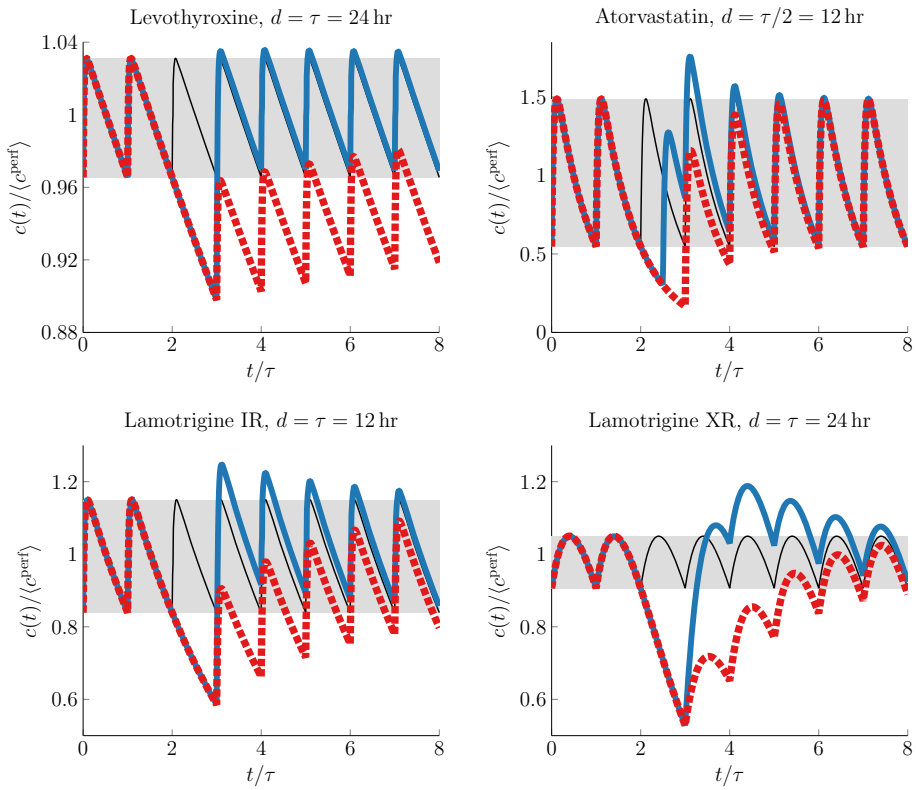

Fig. 6 Time courses comparing perfect adherence (thin black curve), taking a late dose (thick blue curve), and skipping a dose (dashed red curve) for four different drugs. The gray shaded region shows the area between the steady-state peaks and troughs of the concentration for perfect adherence (Color figure online)

Population pharmacokinetics

In the analysis above, for each drug we considered fixed values of the pharmacokinetic parameters. Hence, the results can be considered as concerning a single patient. However, these results can be immediately extended to a population of patients or "subjects" whose pharmacokinetic parameters vary according to any given probability distribution. The purposes of this section are to (i) demonstrate how to make this extension and (ii) investigate how such "between subject variability" modifies our results under typical pharmacological assumptions [38].

Consider a population of N patients indexed $i = 1, 2, \ldots, N$. Following pharmacological convention, we assume that the absorption and elimination rates of each individual patient in the population are drawn from a log-normal distribution [38]. That is, if $k_{\mathrm{a}}^{(i)}$ and $k_{\mathrm{e}}^{(i)}$ denote the absorption and elimination rates of the ith patient in the pop

$$k_{\mathrm{a}}^{(i)} = \frac{\overline{k_{\mathrm{a}}}}{\exp(\sigma_{\mathrm{a}}^2/2)}\exp(\sigma_{\mathrm{a}} Z_{\mathrm{a}}^{(i)}),$$
$$k_{\mathrm{e}}^{(i)} = \frac{\overline{k_{\mathrm{e}}}}{\exp(\sigma_{\mathrm{e}}^2/2)}\exp(\sigma_{\mathrm{e}} Z_{\mathrm{e}}^{(i)}), \tag{39}$$

where $\overline{k_{\mathrm{a}}}$, $\overline{k_{\mathrm{e}}}$ denote average absorption and elimination rates, σ_{a}, σ_{e} are positive parameters describing the variability in parameters, and $Z_{\mathrm{a}}^{(i)}$, $Z_{\mathrm{e}}^{(i)}$ are (possibly dependent) standard normal random variables.

If the ith patient delays a dose by time d, then using the values $k_{\mathrm{a}}^{(i)}$ and $k_{\mathrm{e}}^{(i)}$ in the formulas for the metrics derived above (ρ, ρ_-, ρ_+, ν, γ) makes these statistics specific to this ith patient. Simply computing these statistics for $k_{\mathrm{a}}^{(i)}$ and $k_{\mathrm{e}}^{(i)}$ as i varies from 1 to N then reveals how these statistics vary across the population.

In Fig. 7, we plot probability densities of ρ in (11) for $N = 10^6$ independent realizations of the pharmacokinetic parameters in (39), where the four panels correspond to taking $\overline{k_{\mathrm{a}}}$ and $\overline{k_{\mathrm{e}}}$ according to the four drugs in Table 1. We set $d = \tau$ or $d = \tau/2$ depending on the drug. In each panel, the three curves are for setting the coefficient of variation of $k_{\mathrm{a}}^{(i)}$ and $k_{\mathrm{e}}^{(i)}$ equal to 10%, 20%, and 30% (the coefficient of variation of a random variable is equal to the ratio of its standard deviation to its mean). Denoting these coefficients of variation by $\mathrm{CV}(k_{\mathrm{a}})$ and $\mathrm{CV}(k_{\mathrm{e}})$, the value of σ_{a} is defined by

$$\sigma_{\mathrm{a}} = \sqrt{\ln(1 + (\mathrm{CV}(k_{\mathrm{a}}))^2)} \approx \mathrm{CV}(k_{\mathrm{a}}),$$

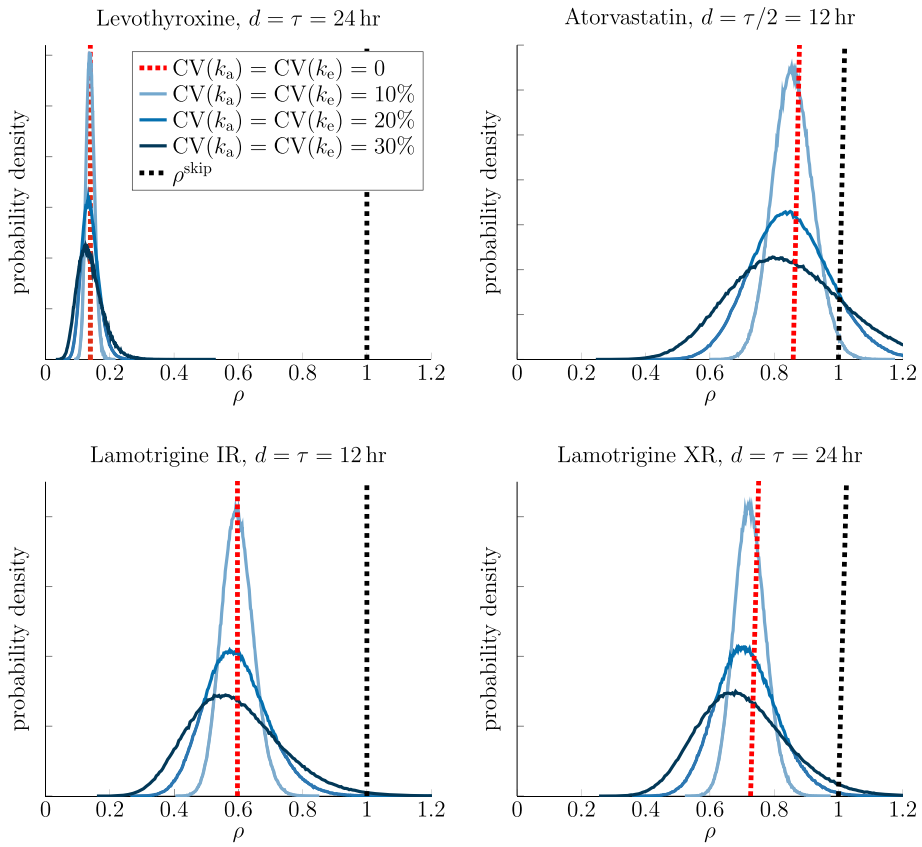

Fig. 7 Distributions of ρ across a population with log-normally distributed pharmacokinetic parameters. See the text for details

and analogously for σ_e. We also take $Z_a^{(i)}$ and $Z_e^{(i)}$ to be independent, though we found very similar results (not shown) when taking $Z_a^{(i)}$ and $Z_e^{(i)}$ to be positively or negatively correlated.

The red vertical dashed lines in Fig. 7 are for $\sigma_a = \sigma_e = 0$ (i.e. when $k_a^{(i)} = \overline{k_a}$ and $k_e^{(i)} = \overline{k_e}$ for all $i = 1, \ldots, N$). Naturally, the distribution of ρ spreads out as the variability in k_a and k_e increases. For the top left and bottom two panels in Fig. 7, the values of ρ for the vast majority of the population are below the value $\rho^{\text{skip}} = 1$ (marked by the black vertical dashed line), even in the highly variable case of $\text{CV}(k_e) = \text{CV}(k_e) = 30\%$. However, for a delay equal to half the dosing interval for atorvastatin in the upper right panel, we see that a sizable fraction of the population has ρ values larger than $\rho^{\text{skip}} = 1$.

Discussion

In this paper, we used mathematical analysis to study the pharmacokinetic effects of taking a late dose of medication. We derived several mathematical formulas which quantify the pharmacokinetic effects of taking a late dose. This analysis can be applied to any medication that can be described by a single compartment linear model, requiring only that the absorption rate k_a, elimination rate k_e, and dosing interval τ can be estimated. We applied our results to four common medications and also considered the effects of between subject variability in a population of patients. We have also created a simple web-based app [16] to allow pharmacometricians to use our metrics to study the consequences of late doses for other drugs and dosing scenarios.

One immediate implication of this work regards IR and XR drug formulations (we use XR interchangeably with slow release, sustained release, and controlled release [39]). Recall that XR drugs are identical to IR drugs, except that an XR formulation has a much slower absorption rate k_a and is sometimes prescribed with a larger dosing interval τ. The results in (32) and (33) show that the perturbations caused by a late dose decrease if k_a decreases and/or if τ decreases. Therefore, if a patient switches from an IR drug to its XR counterpart without increasing the dosing interval, then the pharmacokinetic effects of dosing irregularities are necessarily blunted. Hence, this analysis suggests that prescribing XR drugs dosed at the same frequencies as IR drugs is a promising strategy to ameliorate some aspects

of patient nonadherence. On the other hand, this analysis shows that switching from IR to XR formulations and increasing the dosing interval could ameliorate or could exacerbate the effects of dosing irregularities, depending on the changes in k_a and τ, and also the value of k_e.

There are several additional salient pharmacological implications of this work. First, this analysis highlights the importance of pharmacokinetic rates for determining appropriate remedial actions regarding a late dose. General rules which only involve the delay d and the dosing interval τ, such as "never take a double dose" or the "halfway" rule considered in Sect. 2.4, are not broadly applicable. Similarly, this work underscores the need for precise, drug-specific guidance regarding late doses. The appropriate remedial action for one drug may or may not be appropriate for another drug, and the appropriate action for a short delay (say, $d < \tau/4$) may differ from that of a long delay (say, $d > 3\tau/4$). Furthermore, this work demonstrates how the timing of doses can be quite unimportant for drugs with slow pharmacokinetic rates. For example, due to the very slow elimination rate of levothyroxine, perturbing the timing of doses (for instance, by delaying a dose 24 hours) causes only mild changes in the drug concentration time course compared to perfect adherence.

The fact that slow absorption and/or elimination rates dampen the pharmacokinetic effects of dosing irregularities can be understood intuitively in terms of simple concepts in dimensional analysis [40]. The timescales in the problem are the timescale of absorption $1/k_a$, the timescale of elimination $1/k_e$, the scheduled time between doses τ, and the delay d. If the timescale of absorption and/or elimination is much longer than the scheduled time between doses,

$$\max\{1/k_a, 1/k_e\} \gg \tau, \tag{40}$$

then any delay d that is not much larger than τ can only slightly affect the drug concentration time course. Levothyroxine satisfies (40), since using the parameter values in Table 1 yields

$$\max\{1/k_a, 1/k_e\} \approx 2\,\text{weeks} \gg \tau = 1\,\text{day}. \tag{41}$$

In fact, the values in (41) explain why the American Thyroid Association has advocated taking up to a week's worth of levothyroxine at one time [34]. In contrast, using the parameter values for atorvastatin in Table 1 yields

$$\max\{1/k_a, 1/k_e\} \approx 20\,\text{hours} < \tau = 24\,\text{hours},$$

which is compatible with our results indicating that delaying a dose of atorvastatin by 24 hours is likely inappropriate.

Many previous studies have used pharmacokinetic modeling to investigate the effects of a late dose and to test different remedial strategies [12, 20, 41–50]. The recent review paper [13] helpfully summarizes prior work in this area. The vast majority of prior work has used numerical simulations of computational models of specific examples of drugs and delay times, rather than the general mathematical analysis in the present work. A strength of numerical simulations is that they can be used on certain pharmacokinetic models which are too complicated for mathematical analysis. For example, numerical simulations are especially useful for analyzing nonlinear pharmacokinetic models, such as the study of valproic acid in [43]. In contrast, a strength of mathematical analysis is that it can reveal general principles which are broadly applicable across a range of drugs, dosing regimens, and late dosing scenarios.

Analysis of nonadherence is often complicated by the various patterns of nonadherence observed in actual patients. Indeed, missed doses, late doses, extra doses, extended "drug holidays," and other irregularities have been observed in electronically compiled dosing histories [51]. This has led to the development of various statistical models of adherence for use in computational analyses [26, 52]. However, our results are independent of the pattern of nonadherence before and after a given late dose. In particular, the values of our metrics ρ, v, and γ are unchanged if (a) the patient has perfect adherence before and after the late dose and (b) the patient has any pattern of nonadherence before and/or after the particular late dose in question. This is because our metrics are defined in terms of the difference in concentrations,

$$c^d(t) - c(t),$$

where $c^d(t)$ is the drug concentration time course in the case that the dose in question is taken time $d > 0$ after it was scheduled to be taken and $c(t)$ is the drug concentration time course in the case that the dose in question is taken at the scheduled time. The key point is that by considering the concentration difference $c^d(t) - c(t)$, the patient's adherence before and after the dose in question "cancel out," and thus does not affect the concentration difference $c^d(t) - c(t)$ and thus does not affect the metrics ρ, v, and γ (see Sect. 2.3 for details).

Naturally, this theoretical study neglects certain pharmacological details and incorporates various simplifying assumptions. For one, we have used a one-compartment linear pharmacokinetic model, but the pharmacokinetics of some drugs are much better described by a more complicated model that includes more compartments or nonlinear kinetics. We have also ignored dosing restrictions, such as taking medications with or without food. For instance, the results in (32) and (33) show that the perturbations caused by a late dose always increase if the delay d increases. Hence, this mathematical result suggests that a late dose

should be taken as soon as possible, rather than, for instance, waiting to combine the dose with the next scheduled dose. However, this recommendation may need to be modified if, for example, the drug must be taken on an empty stomach. Another limitation is that we have not considered the possibility that the patient alters their future doses in order to deal with the late dose. For example, the patient could perhaps take a late dose and then delay the next scheduled dose. We have also not considered the possibility that rather than skipping or taking the late dose, the patient instead takes a fraction of the late dose. One can imagine that in some scenarios, taking half of a dose late may be preferable to both skipping and taking a full dose late.

A further limitation is that we have focused on pharmacokinetics rather than pharmacodynamics. This is in line with many previous theoretical investigations of nonadherence [12, 20, 41–47, 49, 50]. However, the importance of both pharmacokinetics and pharmacodynamics was recently emphasized in [53].

One of the simplest pharmacodynamic models is the so-called direct effect model [54], which models the effect $E(t)$ of the drug at time t by the following function of the drug concentration $c(t)$,

$$E(t) = \frac{E_{\max} c(t)}{\mathrm{EC}_{50} + c(t)}. \tag{42}$$

Here, $E_{\max}$ denotes the maximum possible effect of the drug and EC_{50} denotes the drug concentration which elicits one half of the maximum effect. The saturating nature of the concentration-effect relation in (42) implies that fluctuations in concentration cause the greatest effect fluctuations when

$$c(t) \ll \mathrm{EC}_{50}. \tag{43}$$

Mathematically, this stems from the fact that the second derivative of (42) with respect to c is negative. Indeed, the opposite scenario $c(t) \gg \mathrm{EC}_{50}$ implies $E(t) \approx E_{\max}$ and only major lapses in adherence modify the drug effect.

Hence, adherence is most critical to treatment efficacy in the case of (43). In this regime, the drug effect is far from maximal and the nonlinear concentration-effect relation in (42) is well-approximated by the linear concentration-effect relation,

$$E(t) = \frac{E_{\max}}{\mathrm{EC}_{50}} c(t). \tag{44}$$

Assuming (44), our pharmacokinetic results immediately yield identical pharmacodynamic results. In particular, the values of the metrics ρ, v, and γ are unchanged if the concentrations in their definitions in (29)-(31) are replaced by the corresponding drug effects (i.e. the concentration for an on-time dose $c(t)$ is replaced by the effect for an on-time dose $E(t) = \frac{E_{\max}}{\mathrm{EC}_{50}} c(t)$, the concentration for a late dose $c^d(t)$ is replaced by the effect for a late dose $E^d(t) = \frac{E_{\max}}{\mathrm{EC}_{50}} c^d(t)$, and the average concentration for perfect adherence $\langle c^{\mathrm{perf}} \rangle$ is replaced by the average effect for perfect adherence $\langle E^{\mathrm{perf}} \rangle = \frac{E_{\max}}{\mathrm{EC}_{50}} \langle c^{\mathrm{perf}} \rangle$). Summarizing, our pharmacokinetic analysis is identical to a pharmacodynamic analysis in the case of a linear concentration-effect relation, which is a case in which adherence is especially critical to treatment efficacy. Investigating how more detailed pharmacodynamic considerations inform proper handling of late doses is an important area for future research.

Finally, as described in Sect. 2.4, the bare analysis in this paper is not intended to definitively tell a patient or clinician if a late dose of medication should be taken or skipped. Rather, our analysis should be combined with drug-specific information. For example, our analysis can predict whether or not taking a late dose will cause the drug concentration to rise above, say, 20% of the long-term average drug concentration for perfect adherence. However, our analysis of course does not say whether or not this 20% increase is clinically acceptable, as this depends on the particular drug. Nevertheless, the metrics derived in this paper can be used in conjunction with drug-specific information (such as the therapeutic range) to develop drug-specific remedial strategies to handle late doses.

Appendix

In this Appendix, we collect details of the mathematical analysis. We also present a fourth metric in Sect. 5.3 for studying the effects of a late dose.

Derivation of mathematical formulas

To calculate ρ^{skip} in (15), we note that

$$|c^{\mathrm{skip}}(t) - c(t)| = c_0(t), \tag{45}$$

where $c_0(t)$ is defined in (5). Integrating (45) yields (16).

To calculate ρ_- and ρ_+ defined in (13)-(14), we first use that (10) and (8) imply that ρ_- and ρ_+ can be written in terms of $\delta(t,d)$ in (8) as

$$\rho_- = \frac{-1}{\tau \langle c^{\mathrm{perf}} \rangle} \int_0^{s_0} \delta(t,d)\, \mathrm{d}t, \quad \rho_+ = \frac{1}{\tau \langle c^{\mathrm{perf}} \rangle} \int_{s_0}^{\infty} \delta(t,d)\, \mathrm{d}t, \tag{46}$$

where $s_0 > d > 0$ is such that $\delta(t,d) < 0$ for all $t \in (0, s_0)$ and $\delta(t,d) > 0$ for all $t > s_0$. Solving for s_0 yields

$$s_0 = \frac{1}{k_a - k_e} \ln\left(\frac{e^{k_a d} - 1}{e^{k_e d} - 1}\right) > d > 0. \tag{47}$$

Integrating (46) using (8) and (47) yields (17), which then yields (19) by (12).

To calculate v defined in (24), we first use (10) to obtain that v can be written in terms of δ as

$$v = \frac{1}{\langle c^{\text{perf}} \rangle} \max_{t \in \mathbb{R}} \delta(t, d). \tag{48}$$

A simple calculus exercise yields that $\delta(t, d)$ is maximized at $t = s_1$, where

$$s_1 = \frac{1}{k_a - k_e} \log\left[\frac{(e^{k_a d} - 1)k_a}{(e^{k_e d} - 1)k_e}\right]. \tag{49}$$

Plugging (49) into (48) yields the formula for v in (26).

To calculate γ in (25), we first use (10) to obtain that γ can be written in terms of δ as

$$\gamma = \frac{1}{\langle c^{\text{perf}} \rangle} \max_{t \in \mathbb{R}} \frac{1}{\tau} \int_t^{t+\tau} \delta(s, d)\, \mathrm{d}s. \tag{50}$$

Integrating (50) and performing a simple calculus exercise yields that the maximum in (50) occurs at $t = s_2$, where

$$s_2 = \frac{1}{k_a - k_e} \log\left(\frac{(e^{k_a \tau} - 1)(e^{k_a d} - 1)}{(e^{k_e \tau} - 1)(e^{k_e d} - 1)}\right) - \tau. \tag{51}$$

Plugging (51) into (50) yields the formula for γ in (27).

Monotonicity

We now prove (32) and (33). Applying the chain rule to (19) yields

$$\begin{aligned} &\frac{\partial}{\partial k_a}\rho = 2f_x(k_a d, k_e d)d, \quad \frac{\partial}{\partial k_e}\rho = 2f_y(k_a d, k_e d)d, \\ &\frac{\partial}{\partial d}\rho = 2f_x(k_a d, k_e d)k_a + 2f_x(k_a d, k_e d)k_e, \end{aligned} \tag{52}$$

where f_x and f_y denote the partial derivatives of f in (18) with respect to x and y, respectively. Specifically,

$$f_x(x, y) = \frac{y\left(\frac{e^y - 1}{e^x - 1}\right)^{\frac{x}{x-y}}(e^x(y - x) - (e^x - 1)\log(e^y - 1) + (e^x - 1)\log(e^x - 1))}{(x - y)^2}, \tag{53}$$

and the formula for $f_y(x, y)$ is obtained from (53) upon swapping x and y. Though (53) is a complicated expression, it is easy to plot as a function of $x > 0$ and $y > 0$ to obtain that

$$f_x(x, y) > 0, \quad f_y(x, y) > 0. \tag{54}$$

Hence, (54) and the expressions in (52) yield (32).

The sign of the partial derivatives of γ in (33) follow immediately from (27), the chain rule, and (54).

To obtain the sign of the partial derivatives of v in (33), we first note that the partial derivative of g in (28) with respect to x is

$$g_x(x, y) = \left(\frac{y(x\log(x) + y - x\log(y) - x)}{(x - y)^2}\right)\left(\frac{y}{x}\right)^{\frac{x}{x-y}}, \tag{55}$$

and the formula for $g_y(x, y)$ is obtained from (55) upon swapping x and y. Though (55) is a complicated expression, it is easy to plot as a function of $x > 0$ and $y > 0$ to obtain that

$$g_x(x, y) > 0, \quad g_y(x, y) > 0. \tag{56}$$

Hence, the sign of the partial derivatives of v in (33) follow immediately from using (26), the chain rule, and (54) and (56).

Maximum concentration

In the main text of the paper, the metric v measures the maximum amount that $c^d(t)$ can rise above $c(t)$. To obtain the value for the maximum of $c^d(t)$ rather than how the $c^d(t)$ rises above $c(t)$, we must make assumptions about the patient's adherence before and after the late dose. For simplicity, we assume that the patient has perfect adherence for a long time before and after the late dose. Letting $\{c^{\text{perf,d}}(t)\}_{t \in \mathbb{R}}$ denote this concentration time course, we prove below that

$$\max_{t \in \mathbb{R}} c^{\text{perf,d}}(t) = \max_{j \in \{j^* j^* + 1\}} \left(\delta(j\tau + t_j, d) + c^{\text{perf}}(t_j)\right), \tag{57}$$

where δ is defined in (8) and

$$j^* = \left\lfloor \frac{1}{k_a\tau - k_e\tau} \log\left(\frac{(e^{k_a\tau}-1)(e^{k_a d}-1)}{(e^{k_e\tau}-1)(e^{k_e d}-1)} \right) - 1 \right\rfloor, \tag{58}$$

$$t_j = \frac{1}{k_a - k_e} \log\left(\frac{k_a(e^{k_e\tau}-1)[(e^{k_a\tau}-1)(e^{k_a d}-1) + e^{(j+1)k_a\tau}]e^{j(k_e-k_a)\tau}}{k_e(e^{k_a\tau}-1)[(e^{k_e\tau}-1)(e^{k_e d}-1) + e^{(j+1)k_e\tau}]} \right). \tag{59}$$

In (58), we use the floor function notation, in which $\lfloor x \rfloor$ denotes the largest integer less than or equal to x.

While the complicated formulas in (57)-(59) do not offer much intuition, they can be easily plotted to investigate how the maximum concentration depends on the various parameters. In Fig. 8, we plot

$$\theta := \frac{\max_{t\in\mathbb{R}} c^{\text{perf,d}}(t) - \langle c^{\text{perf}} \rangle}{\langle c^{\text{perf}} \rangle}, \tag{60}$$

which is a dimensionless measure of how far $c^{\text{perf,d}}(t)$ rises above $\langle c^{\text{perf}} \rangle$, relative to $\langle c^{\text{perf}} \rangle$. The top left panel in Fig. 8 is for no delay ($d = 0$) to show how the concentration time courses rises above the average $\langle c^{\text{perf}} \rangle$ for perfect adherence. In this case of no delay, θ has a simpler formula which we denote by θ^{perf},

$$\theta^{\text{perf}} = \lim_{d\to 0} \theta = \frac{k_a k_e \tau}{k_a - k_e} \left(\frac{\left(\frac{k_e(e^{k_a\tau}-1)}{k_a(e^{k_e\tau}-1)} \right)^{\frac{k_e}{k_a-k_e}}}{e^{k_e\tau}-1} - \frac{\left(\frac{k_e(e^{k_a\tau}-1)}{k_a(e^{k_e\tau}-1)} \right)^{\frac{k_a}{k_a-k_e}}}{e^{k_a\tau}-1} \right) - 1. \tag{61}$$

The bottom right panel shows that even in the extreme case of a double dose ($d = \tau$), the drug concentration rises only slightly above the average if the absorption and/or elimination rate is sufficiently slow compared to $1/\tau$. Conversely, this plot shows that the drug concentration can rise far above the average if both the absorption and elimination rate is sufficiently fast compared to $1/\tau$. Analogous to Figs. 2 and 4, the letter markers in Fig. 8 are for the drugs in Table 1.

To obtain the formula for $\max_{t\in\mathbb{R}} c^{\text{perf,d}}(t)$ in (57), we first note that

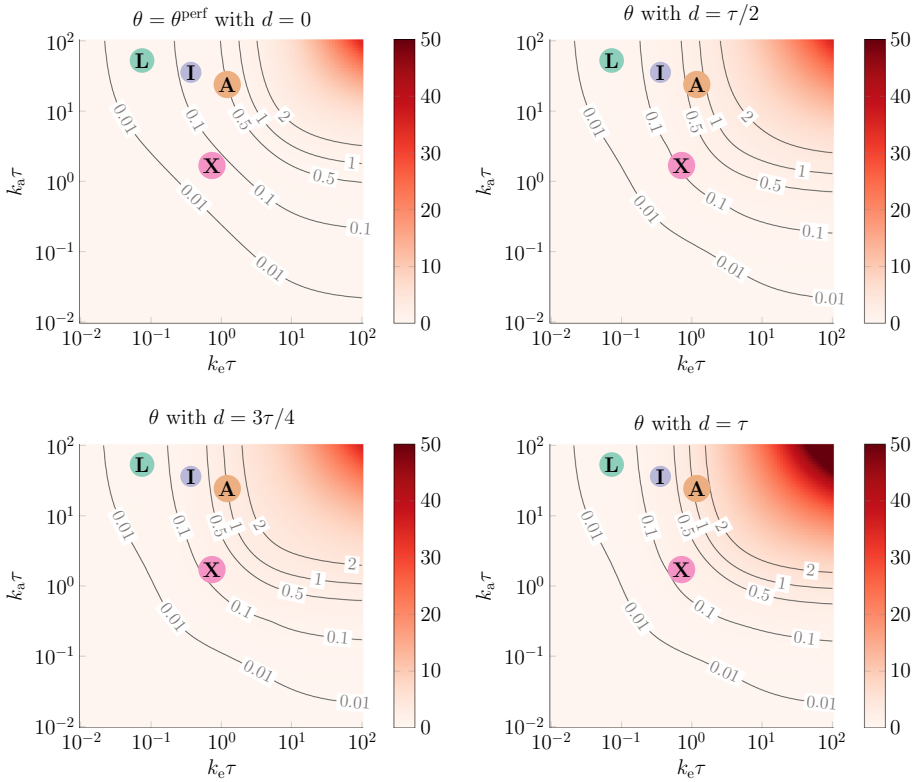

Fig. 8 Maximum relative increase in concentration θ in (60) for different values of the delay $d \in [0, \tau]$. Note that the top left panel is for $d = 0$ (see (61)). The letters L, A, I and X correspond to different drugs. See the text for details

$$c^{\text{perf,d}}(t) = c^{\text{perf}}(t) + c^{\text{perf,d}}(t) - c^{\text{perf}}(t) = c^{\text{perf}}(t) + \delta(t,d), \tag{62}$$

where $c^{\text{perf}}(t)$ is defined in (6). Now, $\delta(t,d)$ is strictly increasing for $t \in (s_0, s_1)$ and strictly decreasing for $t \in (s_1, \infty)$. It therefore follows that $s_2 \in (s_0, s_1)$ is such that $\delta(t_1,d) > \delta(t_0,d)$ if $t_1 \in (s_2, s_2+\tau)$ and $t_0 \notin (s_2, s_2+\tau)$. Since $c^{\text{perf}}(t)$ is periodic with period τ, it follows from (62) that the maximum of $c^{\text{perf,d}}(t)$ must occur at some $t \in [s_2, s_2+\tau]$. Now, since j^* in (58) satisfies $j^* = \lfloor s_2/\tau \rfloor$, it follows that the maximum of $c^{\text{perf,d}}(t)$ must occur at some $t \in [j^*\tau, (j^*+2)\tau]$ since $[s_2, s_2+\tau] \subset [j^*\tau, (j^*+2)\tau]$. If $t = j\tau + s$ for some fixed integer $j \in \mathbb{Z}$ and some time $s \in [0,\tau]$, then it follows immediately from (6) that

$$c^{\text{perf}}(j\tau+s) = \frac{DF}{V}\frac{k_a}{k_a-k_e} \left[e^{-k_e s}/(1-e^{-k_e\tau}) - e^{-k_a s}/(1-e^{-k_a\tau})\right]. \tag{63}$$

Hence, (62) implies $c^{\text{perf,d}}(j\tau+s) = C_j^d(s)$ where $C_j^d(s)$ is defined to be

$$C_j^d(s) := \frac{DF}{V}\frac{k_a}{k_a-k_e} \left[e^{-k_e s}/(1-e^{-k_e\tau}) - e^{-k_a s}/(1-e^{-k_a\tau})\right] + \delta(j\tau+s,d). \tag{64}$$

Differentiating (64) with respect to s shows that $\frac{\mathrm{d}}{\mathrm{d}s} C_j^d(s) = 0$ if $s = t_j$ where t_j is defined in (59). Hence, we have obtained (57).

To obtain $\max_{t\in\mathbb{R}} c^{\text{perf}}(t)$, we merely differentiate (63) with respect to s to find the maximum. Plugging the resulting expression into the definition of θ in (60) yields the formula for θ^{perf} in (61).

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