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Drug Forgiveness Is About Depth, Not Duration: A Pharmacokinetic Simulation of Missed Doses across Half-Lives

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ABSTRACT

Background. Patients miss doses, and the pharmacological consequence differs enormously between medicines. The property is usually described as forgiveness and is usually attributed to half-life, on the reasoning that a drug eliminated slowly will still be present when the next dose is late. That reasoning is correct about the concentration reached and incomplete about whether it matters.

Objective. To quantify how half-life, dosing interval, adherence pattern and the position of the therapeutic threshold jointly determine the consequence of missed doses, and to test the common advice to double the next dose.

Methods. A one-compartment oral model with first-order absorption was simulated over 180 days of once-daily dosing for half-lives of 6 to 96 hours. Concentrations were expressed relative to the steady-state trough achieved under perfect adherence, so results are independent of dose. Random missed doses at adherence of 70–100 %, a three-day interruption every month, alternative dosing intervals, and doubling the next dose after a miss were examined, with the therapeutic threshold placed at 1.0, 0.8, 0.5 and 0.25 times the perfect-adherence trough.

Results. At 80 % adherence the lowest concentration reached fell to 0.2 % of the trough for a 6-hour half-life and 48.3 % for a 96-hour half-life, a more than two-hundredfold difference in depth. The consequence for time below threshold depended entirely on where the threshold sat. Measured against the perfect-adherence trough itself, the long half-life performed worst — 83.0 % of time below threshold against 20.8 % for the short half-life. With the threshold at half the trough the ranking reversed completely: 0.6 % against 15.8 %. After a three-day interruption the 96-hour drug never fell below 59 % of its trough but took 145 hours to recover, whereas the 6-hour drug reached effectively zero and recovered within 12 minutes of the next dose. Doubling the next dose after a miss reduced time below the trough from 83.0 % to 25.8 % for the longest half-life but raised the peak concentration from 12.0 to 22.4 times the trough for the shortest.

Conclusions. Half-life determines how far concentrations fall, not whether that fall matters. Forgiveness is a joint property of the half-life and the headroom between the trough and the minimum effective concentration, and advice about missed doses should follow from both.

1. Introduction

Adherence to long-term medication is around half in most studies, and the clinical consequence of imperfect adherence varies enormously between drugs [1–3]. Missing a dose of a long-acting antihypertensive is usually inconsequential; missing a dose of a short-acting antiretroviral or anticoagulant may not be. The property that distinguishes them is often called forgiveness, and it is routinely attributed to half-life [4–6].

That attribution is right as far as it goes and stops short of the useful part. A drug with a long half-life certainly falls less far when a dose is missed, because less is eliminated in the interval. Whether the concentration it falls to is still effective depends on where it started relative to the concentration needed, and that relationship is a property of the therapeutic window rather than of the elimination rate [7,8].

The two can point in opposite directions, and this is not widely appreciated [9]. A drug with a very long half-life has a flat concentration profile, so its steady-state trough sits close to its average concentration and there is little room between them; when a dose is missed the concentration falls slowly but from a starting point with no spare capacity, and it takes a long time to climb back. A drug with a short half-life falls precipitously but is restored almost immediately by the next dose. Which of those is more forgiving cannot be answered without knowing what concentration the patient actually needs.

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This study quantifies the relationship. Four questions are addressed. How far do concentrations fall under realistic patterns of missed dosing, by half-life? How long do they stay below a therapeutic threshold, and how does that depend on where the threshold is? What happens after a deliberate interruption of several days, the pattern usually called a drug holiday? And does the common advice to double the next dose help or harm?

2. Methods

2.1 Model

A one-compartment model with first-order absorption and elimination was simulated by superposition of successive doses [7,10]. For a dose given at time zero the concentration at time t is proportional to

$$C(t) \propto \left(\frac{k_a}{k_a - k_e} \right) \left(e^{-k_e t} - e^{-k_a t} \right) \quad (1)$$

with $k_e = \ln 2 / t_{½}$ and an absorption rate constant k_a of 1.5 per hour throughout, representing reasonably rapid absorption. Regimens were simulated for 180 days and the first 30 days discarded so that all results describe steady-state behaviour.

Concentrations are reported not in absolute units but as multiples of the steady-state trough that the same regimen achieves under perfect adherence. This normalisation removes dose, volume of distribution and bioavailability from the comparison, so that what remains is the property under study — how the shape of the concentration profile responds to missed doses — and makes half-lives directly comparable.

2.2 Scenarios

The simulated scenarios are summarised in Table 1. Non-adherence was represented by two of the dosing-history patterns described in the adherence literature: random omission of individual doses and a regular multi-day interruption [11,12].

Table 1. Simulation parameters and scenarios

Parameter or scenario	Values
Half-life	6, 12, 24, 48, 96 hours
Dosing interval	24 hours (primary); 8 and 12 hours in a secondary analysis
Absorption rate constant	1.5 per hour
Simulated duration	180 days, first 30 discarded
Random non-adherence	Each dose independently taken with probability 1.00, 0.90, 0.80 or 0.70
Drug holiday	Three consecutive days of doses missed every 30 days, otherwise perfect
Catch-up strategy	Skip the missed dose, or double the next dose
Therapeutic threshold	1.00, 0.80, 0.50 or 0.25 times the perfect-adherence trough
Replicates	20 per random-adherence scenario

The therapeutic threshold is the parameter that carries the argument of this paper, and it is deliberately expressed relative to the trough rather than in absolute terms. A threshold of 1.00 describes a drug dosed with no margin, where the trough of a perfectly adherent patient is exactly the minimum effective concentration. A threshold of 0.25 describes a drug dosed with fourfold headroom. Real drugs sit across that range and the position is rarely stated explicitly in prescribing information, which is part of the problem this analysis exposes.

2.3 Outcomes

Three outcomes were recorded: the proportion of time spent below the therapeutic threshold, the lowest concentration reached, and the time taken to regain the trough after an interruption. All simulation was performed in Python with a fixed random seed and reproduces exactly.

3. Results

3.1 What a missed dose does

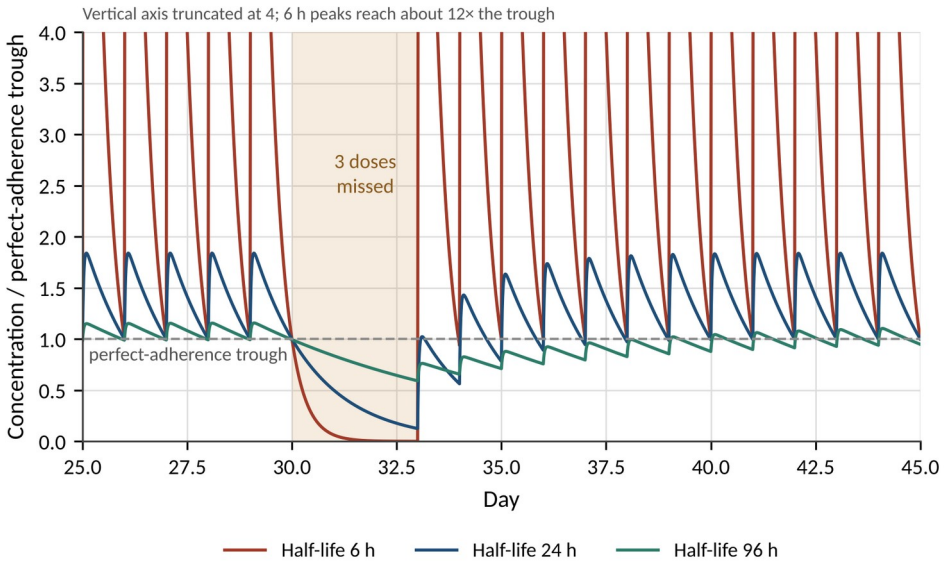

Figure 1. Concentration profiles through a three-day interruption, for three half-lives. Concentrations are expressed relative to the perfect-adherence trough.

Figure 1 shows the two behaviours that the rest of the paper quantifies. The 6-hour drug oscillates widely between doses, falls essentially to zero during the interruption, and is restored by the first dose taken afterwards. The 96-hour drug barely fluctuates, declines gently during the interruption and then climbs slowly back over several days. Both patterns are entirely expected from the half-life; what is not obvious is which is worse for the patient.

Table 2. Lowest concentration reached at 80 % adherence

Half-life	6 h	12 h	24 h	48 h	96 h
Nadir, as a fraction of the trough	0.002	0.030	0.140	0.314	0.483

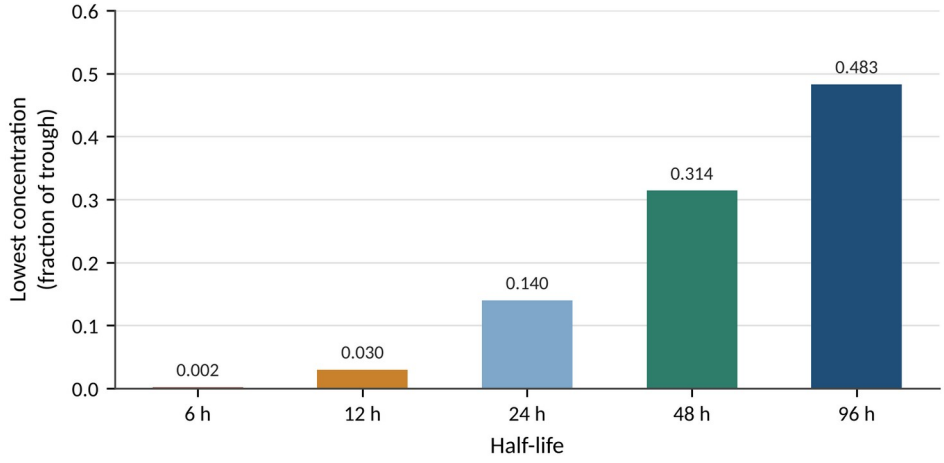

Figure 2. Lowest concentration reached at 80 % adherence, by half-life.

On the measure that forgiveness is usually taken to mean — how far the concentration falls — the conventional account is confirmed emphatically. At 80 % adherence the 96-hour drug never fell below 48.3 % of its trough while the 6-hour drug reached 0.2 %, a more than two-hundredfold difference. If the question is whether a patient is ever left with essentially no drug in the body, half-life answers it.

3.2 Time below threshold, and why the answer depends on the threshold

Table 3. Time below the perfect-adherence trough (%), by adherence and half-life

Half-life	Adherence 100 %	90 %	80 %	70 %
6 h	0.0	10.6	20.8	30.5
12 h	0.0	12.2	23.4	34.0
24 h	0.2	17.6	33.7	47.9
48 h	0.5	30.2	55.3	73.2
96 h	1.1	53.0	83.0	94.8

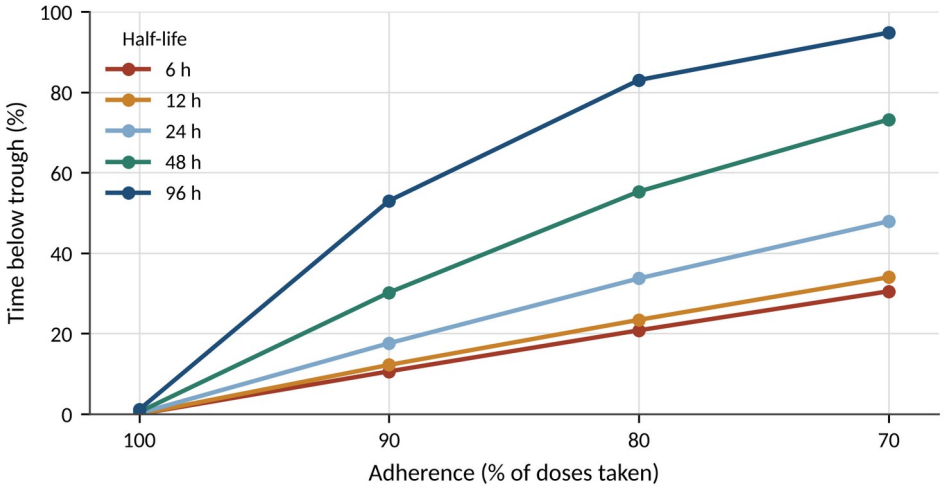

Figure 3. Time below the perfect-adherence trough, by adherence and half-life.

Measured this way the conventional account inverts. At 80 % adherence the 96-hour drug spent 83.0 % of its time below the concentration a perfectly adherent patient would maintain, against 20.8 % for the 6-hour drug. The long half-life looks four times worse.

The explanation is that this measure has smuggled in an assumption. A drug with a long half-life has a nearly flat profile, so its trough is close to its mean and almost any perturbation drops it below. A drug with a short half-life spends most of each interval well above its trough, because the trough is the bottom of a large oscillation, so it has room to fall before crossing that line. Comparing each drug against its own trough therefore rewards drugs with large peak-to-trough fluctuation, which is not a clinically meaningful criterion.

Table 4. Time below threshold (%) at 80 % adherence, by where the threshold sits

Threshold	6 h	12 h	24 h	48 h	96 h	Direction
1.00 × trough	20.8	23.4	33.7	55.3	83.0	Long half-life worse
0.80 × trough	18.5	17.8	19.9	23.6	27.8	Nearly flat
0.50 × trough	15.8	12.3	6.3	2.7	0.6	Long half-life better
0.25 × trough	11.8	4.3	1.2	0.1	0.0	Long half-life far better

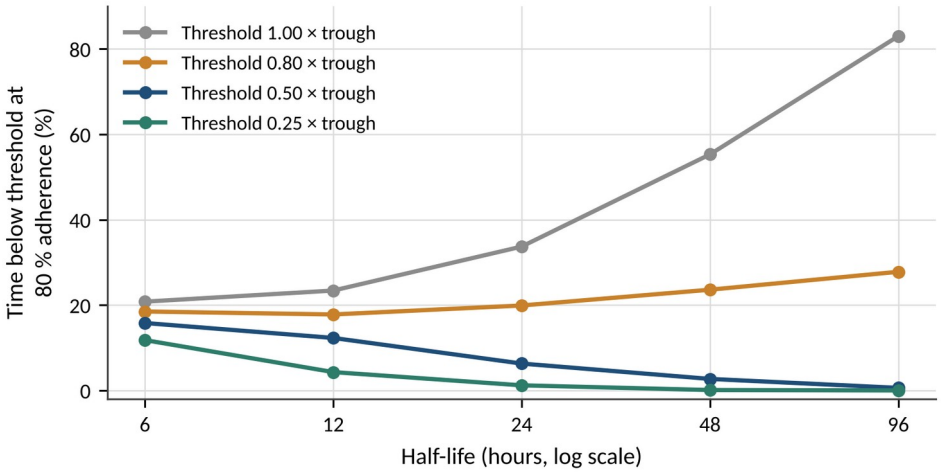

Figure 4. Time below threshold at 80 % adherence, across half-lives, for four positions of the therapeutic threshold.

Table 4 is the central result of this study. As the therapeutic threshold moves down from the trough, the ranking of half-lives reverses completely. With no headroom the 96-hour drug is four times worse than the 6-hour drug; with twofold headroom it is twenty-six times better; with fourfold headroom it never falls below threshold at all while the short half-life still does so 11.8 % of the time.

The crossover sits at about 0.8 times the trough, where all five half-lives perform within ten percentage points of each other. Above that line, fluctuation protects; below it, persistence protects. Since the position of the therapeutic threshold relative to the trough is a property of how the drug was dosed rather than of its pharmacokinetics, forgiveness is not a property of the molecule at all but of the molecule and its regimen together [6,9].

This resolves an apparent contradiction in how forgiveness is discussed. The claim that long half-life confers forgiveness is correct for drugs dosed with headroom, which is most drugs used for chronic conditions where the regimen was chosen to maintain effect comfortably. It is wrong for drugs dosed to the edge of their effective concentration, where the flat profile that protects against a deep fall also removes any reserve.

3.3 Drug holidays

Table 5. Effect of a three-day interruption every month

Half-life	Time below trough (%)	Nadir (fraction of trough)	Hours to regain the trough
6 h	10.5	0.000	0.2
12 h	11.8	0.016	0.5
24 h	16.1	0.125	2.0
48 h	25.5	0.354	49.2
96 h	45.6	0.591	145.2

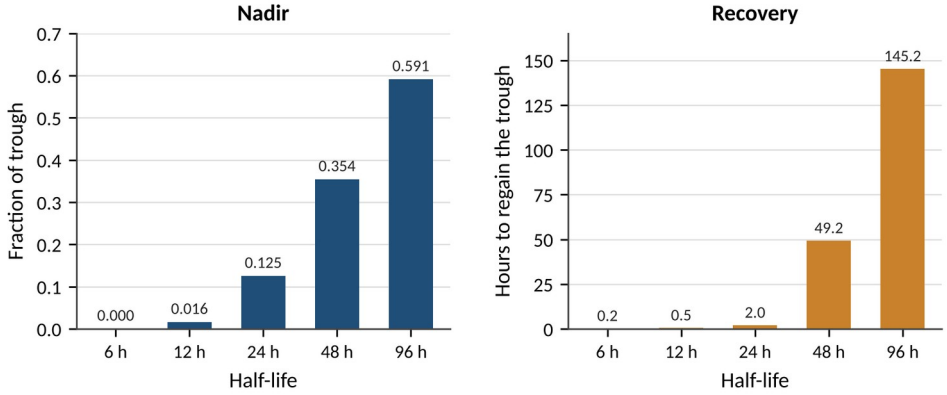

Figure 5. Nadir and recovery time after a three-day interruption.

The last two columns of Table 5 describe opposite failure modes, and this is the clearest practical finding in the paper. After a three-day interruption the 96-hour drug never fell below 59 % of its trough — the patient retained most of their drug exposure throughout — but took 145 hours, more than six days, to climb back. The 6-hour drug was effectively washed out, reaching zero, but was fully restored 12 minutes after the next dose was taken.

So the advice appropriate after an interruption differs by drug in a way that follows directly from this. For a short half-life drug the patient is unprotected during the gap and protected again as soon as they restart, so the message is simply to restart. For a long half-life drug the patient retains partial protection during the gap but will be below their usual concentration for the best part of a week after restarting, which is the window in which a clinician might reasonably consider whether additional cover is needed — and is a window that a patient who has simply restarted would not know about.

3.4 Dosing interval

Table 6. Time below the trough (%) at 80 % adherence, by dosing interval

Half-life	Every 8 h	Every 12 h	Every 24 h
12 h	48.3	35.1	23.4
24 h	74.9	57.1	33.7

Shortening the dosing interval made matters worse on this measure, not better, and the reason is the same normalisation effect as in Section 3.2: more frequent dosing raises the trough toward the mean, leaving less room to fall before crossing it. Expressed in absolute terms a more frequent regimen maintains higher concentrations throughout, so this is not an argument for less frequent dosing [10]. It is a further illustration that time below one's own trough is the wrong outcome measure, and that the meaningful comparison requires an externally defined therapeutic threshold.

3.5 Should the next dose be doubled?

Table 7. Skipping the missed dose against doubling the next, at 80 % adherence

Half-life	Time below trough, skip (%)	Time below trough, double (%)	Peak, skip	Peak, double
6 h	20.8	18.9	11.98	22.43
12 h	23.4	18.4	3.41	5.41
24 h	33.7	18.0	1.84	2.42
48 h	55.3	19.8	1.35	1.55
96 h	83.0	25.8	1.16	1.23

Note. *Peaks are expressed as multiples of the perfect-adherence trough.*

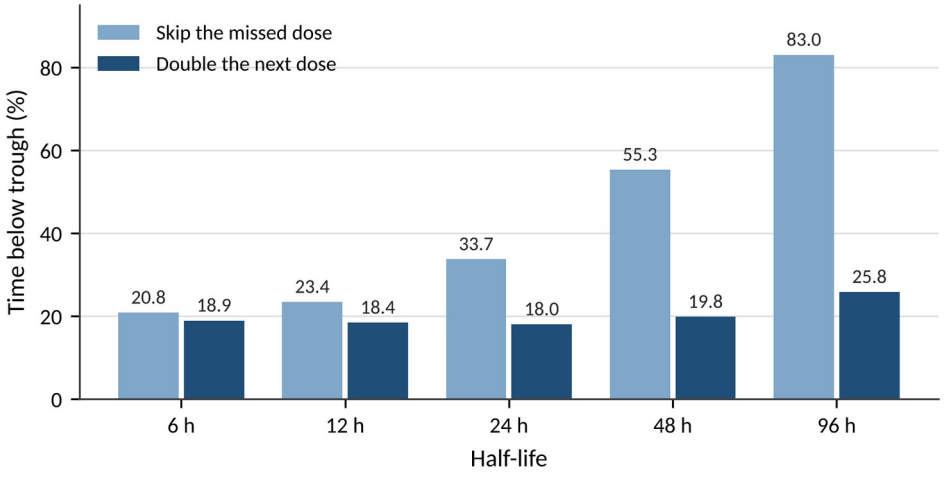

Figure 6. Time below the trough with and without doubling the next dose.

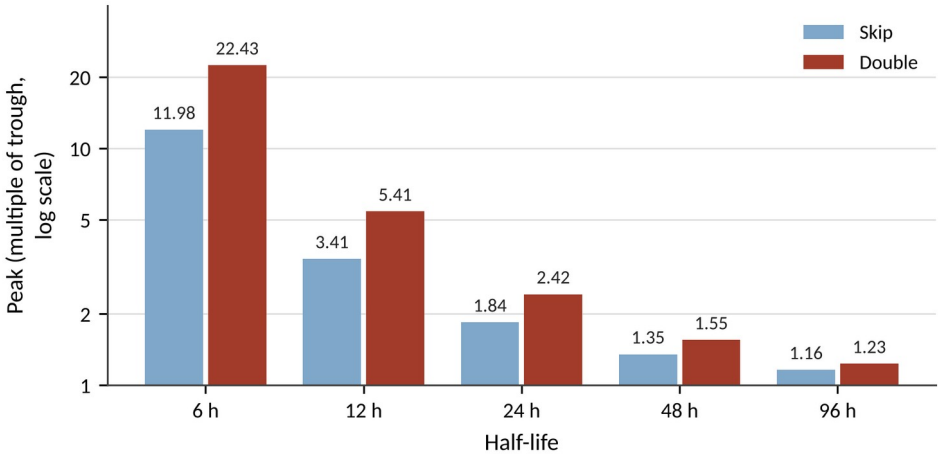

Figure 7. Highest concentration reached with and without doubling, as multiples of the trough. Vertical scale is logarithmic.

Doubling helps most where it is least needed in terms of depth and least where it is most tempting. For the 96-hour drug it cut time below the trough from 83.0 % to 25.8 % and raised the peak only from 1.16 to 1.23 times the trough, a negligible excursion. For the 6-hour drug it barely improved time below threshold, from 20.8 % to 18.9 %, and nearly doubled the peak from 12.0 to 22.4 times the trough.

The asymmetry follows from the shape of the profiles. A drug that oscillates widely already reaches high peaks, so an extra dose lands on top of a substantial residual concentration and produces a very high excursion while doing little to fill the gap, which has already been filled by the next ordinary dose. A drug with a flat profile has almost no peak, so an extra dose raises it trivially while making real progress toward restoring the concentration it lost.

The practical rule that follows is close to the opposite of how advice is usually phrased. Blanket instructions to take the missed dose as soon as remembered unless it is nearly time for the next are applied across all drugs; on these results the doubling strategy is reasonable for drugs with a long half-life relative to their dosing interval and inadvisable for drugs with a short one, where it buys almost nothing and roughly doubles the peak [5,8].

4. Discussion

4.1 Principal findings

Four results follow. Half-life determines the depth of the fall decisively — a two-hundredfold difference in nadir across the range examined — and is the right parameter for the question of whether a patient is ever left without drug. It does not by itself determine whether time is spent below an effective concentration: with the threshold at the trough the long half-life was four times worse, and with the threshold at half the trough it was twenty-six times better, the crossover falling at about 0.8 of the trough.

After an interruption the two behaviours are mirror images: shallow but slow for long half-lives, deep but immediately reversible for short ones. And doubling the next dose is a reasonable strategy for long half-life drugs and a poor one for short half-life drugs, where it adds peak without adding cover.

4.2 Implications

Table 8. Implications for practice

Finding	Implication	Practice
Nadir varied 200-fold across half-lives	Half-life answers "is there any drug left"	Use it to judge the risk of complete loss of effect
Ranking reversed with the therapeutic threshold	Forgiveness is a property of drug and regimen together	State the headroom between trough and effective concentration
Crossover at about 0.8 of the trough	Drugs dosed to the edge lose the benefit of a long half-life	Treat narrow-margin long half-life drugs as unforgiving
Long half-life took 145 h to recover after an interruption	Restarting does not restore protection promptly	Counsel on the recovery window, not only on restarting
Short half-life restored within minutes of the next dose	The gap is the risk, not the aftermath	Emphasise not missing rather than what to do afterwards
Doubling helped long half-lives and not short ones	Blanket catch-up advice is wrong for some drugs	Make missed-dose advice drug-specific
Doubling doubled the peak at short half-life	Catch-up can cause toxicity without restoring cover	Avoid doubling for rapidly cleared narrow-index drugs

The second row is the one that would most improve prescribing information. Product labels state half-life routinely and almost never state where the steady-state trough sits relative to the minimum effective concentration, which this analysis shows is equally necessary to predict what a missed dose does. Where that quantity is known from dose-ranging work it could be reported, and where it is not, the label's implicit claim that a long half-life confers forgiveness is not supported.

4.3 Limitations

The model is one-compartment with first-order absorption and linear elimination, and treats the drug as acting instantaneously through its plasma concentration. Drugs with substantial distribution phases, saturable elimination, active metabolites, or effects that lag concentration through a receptor or downstream process will behave differently, and for several important classes — anticoagulants, antidepressants, immunosuppressants — the pharmacodynamic time course rather than the concentration determines the consequence of a missed dose [7,8]. The analysis characterises exposure, not effect.

Non-adherence was modelled either as independent random omission or as a fixed regular interruption. Real non-adherence is neither: omissions cluster, weekends and travel produce patterns, and adherence declines over time [1,2]. Clustered omission would produce deeper and longer gaps than the random model at the same overall adherence, so the random results here understate the consequences.

The therapeutic threshold was expressed as a fraction of the trough rather than taken from data, which is what permits the generalisation across drugs and also means no result here applies to a named medicine. The single absorption rate constant is a simplification that matters most for the short half-life drugs, where absorption and elimination are less clearly separated; drug-specific application would require parameter estimates from population pharmacokinetic analyses [13].

Finally, the analysis says nothing about why patients miss doses or about what improves adherence, which are the questions that determine how much any of this matters in practice [11,12]. Forgiveness is a reason to choose one drug over another and never a substitute for addressing adherence itself.

5. Conclusion

At 80 % adherence, a drug with a six-hour half-life fell to 0.2 % of its steady-state trough and a drug with a ninety-six-hour half-life to 48.3 %, which is the sense in which long half-life confers forgiveness, and it is real. Whether that depth matters depends on a second quantity that is rarely stated: the headroom between the trough and the concentration actually needed. With no headroom the long half-life drug spent 83 % of its time below threshold against 21 % for the short; with twofold headroom, 0.6 % against 15.8 %.

Two practical consequences follow. Missed-dose advice should be drug-specific rather than generic, because doubling the next dose restored cover for long half-life drugs at negligible cost while roughly doubling the peak of short half-life drugs for almost no benefit. And counselling after an interruption should differ by drug: a patient restarting a rapidly cleared medicine is protected again within the hour, while a patient restarting one with a four-day half-life will remain below their usual concentration for most of the following week without knowing it.

Declarations

Ethical approval. Not applicable. This is a pharmacokinetic simulation study; no human participants, animals, biological samples or identifiable data were involved.

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Conflicts of interest. The author declares no conflicts of interest, financial or non-financial, in relation to the subject matter of this manuscript.

Data availability. No empirical data were generated or analysed in this study. All results were produced by simulation from the model and parameters stated in the Methods and Table 1; the simulation code is available from the corresponding author upon reasonable request.

Author contributions. Abdul Mukit is the sole author of this work and was responsible for the conception and design of the study, development of the simulation model, formal analysis, preparation of the figures and tables, and drafting, revision and final approval of the manuscript. The author is accountable for all aspects of the work.

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