

ORIGINAL RESEARCH

Escalating a Dose the Patient Is Not Taking: Misattribution of Subtherapeutic Concentrations and the Exposure Stored for Later

Dr. T Rajendran

Assistant Professor Tamil Nadu Agricultural University, Department of Agricultural Economics

VOC Agricultural College and Research Institute

Killikulam -628 252

rajendran.t@tnau.ac.in

Abstract

Background. A subtherapeutic drug concentration admits two explanations: high clearance, or doses not taken. The usual response is to increase the dose, which is correct for the first and creates a latent hazard for the second, because the larger dose is eventually taken. We quantified how often escalation is applied to the wrong cause.

Methods. We simulated 40,000 patients on a narrow-therapeutic-index drug with lognormal clearance and bimodal adherence, in which erratic intake produced both lower and more variable concentrations. Adherence improved partially or fully after the clinic visit. We compared no escalation, escalation of every subtherapeutic level, and escalation only where two levels agreed, and tested whether repeated measurement could separate the two causes.

Results. 27.5 per cent of patients had a subtherapeutic level at the first visit, of whom 72.0 per cent would have been within range at full adherence. Escalating every subtherapeutic level raised target attainment from 67.5 to 75.6 per cent and toxic concentrations from 0.7 to 1.2 per cent; among escalated patients 1.9 per cent became toxic, comprising 2.7 per cent of those escalated for non-adherence and 0.0 per cent of those escalated for genuinely high clearance. Patients escalated who subsequently became fully adherent experienced a median 2.45-fold and ninetieth-percentile 15.2-fold rise in exposure from a dose increased by half, with 35.0 per cent ending above the therapeutic range. No measurement strategy separated the causes well:

a single level gave an area under the curve of 0.669 and between-visit variability 0.667. Escalating only where two levels agreed halved escalations and reduced toxic concentrations to 0.8 per cent at a cost of 1.8 percentage points of target attainment.

Conclusion. Most subtherapeutic concentrations in this model were adherence failures, and dose escalation converts them into stored exposure. Concentration measurement alone did not identify them.

Keywords: medication adherence; therapeutic drug monitoring; dose escalation; narrow therapeutic index; drug toxicity; clinical pharmacology.

1. Introduction

Therapeutic drug monitoring exists because the relationship between dose and concentration varies between patients. When a measured concentration falls below the target range, the inference drawn is usually pharmacokinetic: this patient clears the drug faster than average, and the dose should be increased [1,2].

There is a second explanation, and for many drugs it is the more common one. Adherence to long-term therapy averages around half in chronic disease, and a patient who takes a substantial proportion of prescribed doses will have a concentration below target at any dose [3-5]. The measurement cannot distinguish the two, because it reports the product of dose, intake and the inverse of clearance.

The consequences of misattribution are asymmetric. Escalating the dose of a patient with genuinely high clearance is the correct action. Escalating the dose of a patient who is not taking their medication does nothing while the doses continue to be missed, and creates a hazard that is realised at the moment adherence improves — after counselling, after a dosing aid is supplied, after a hospital admission, or simply after the attention that a clinic visit brings [6,7].

That timing is the feature that makes the problem hard to see. The harm does not appear at the visit where the decision is made, and when it appears it presents as a toxic concentration in a patient taking the prescribed dose, which looks like a pharmacokinetic event rather than the consequence of a decision taken months earlier.

We therefore simulated the sequence explicitly: a cohort in which both causes are present and known, a clinic visit at which only the concentration is observed, and a subsequent period in which adherence changes.

1.1 Objectives

We aimed to determine what proportion of subtherapeutic concentrations are attributable to non-adherence rather than clearance; to quantify the exposure change experienced by patients escalated for the wrong reason; to compare escalation policies on target attainment and toxicity; and to test whether repeated concentration measurement can separate the two causes.

2. Methods

2.1 Cohort and pharmacokinetics

We simulated 40,000 patients. Relative clearance was lognormal with a geometric mean of 1 and a geometric standard deviation of 1.35, giving the several-fold between-patient range typical of hepatically cleared drugs.

Adherence was bimodal: 30 per cent of patients were poor adherers taking a mean of 46 per cent of doses, and the remainder took nearly all. Mean adherence across the cohort was 79 per cent.

Erratic intake was modelled as part of what non-adherence is: the variability of intake between measurement windows scales with the shortfall from full adherence, so a fully adherent patient is also a consistent one and a patient taking half their doses does so unevenly. This is the feature that gives repeated measurement any prospect of discriminating.

A proportion of patients were additionally modelled as improving intake in the days before a scheduled visit, so that the concentration measured overstates their usual exposure.

Steady-state concentration was taken as proportional to dose multiplied by intake and divided by clearance, with measurement subject to 12 per cent coefficient of variation representing assay and sampling-time imprecision:

$$C = \text{dose} \times \text{intake} / \text{clearance} \quad (1)$$

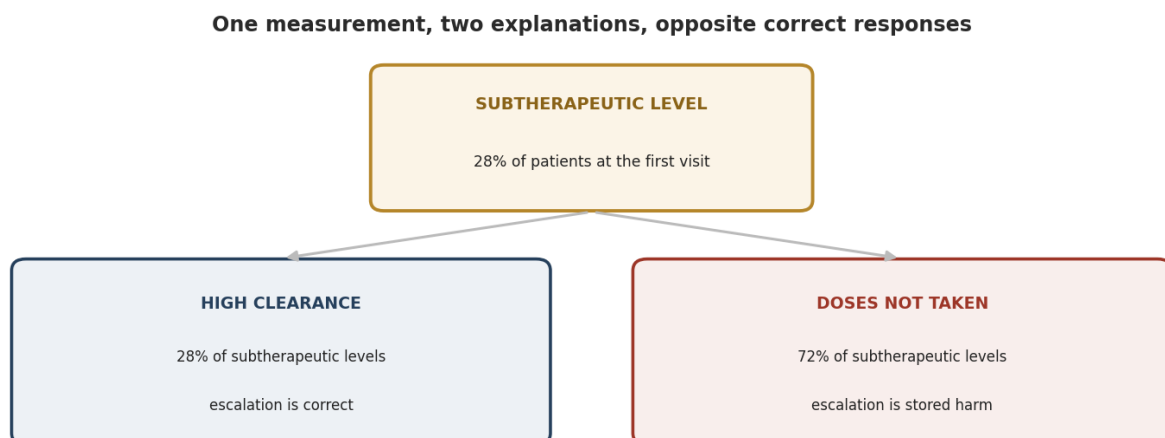


Figure 1. One measurement, two causes, and opposite correct responses.

2.2 Attribution and policies

A subtherapeutic concentration was classified as clearance-driven if the patient would still have been below target at full adherence, and as adherence-driven otherwise. This classification uses

information available only in the simulation and is the ground truth against which the policies are judged.

Three policies were compared: no escalation, escalation of every subtherapeutic level by 50 per cent, and escalation only where two separate levels were consistent with one another. After the visit, 35 per cent of patients became fully adherent and the remainder improved partially, representing the range of responses to counselling and renewed attention.

Parameters are given in Table 1. All are illustrative and represent a narrow-therapeutic-index oral drug rather than any specific agent.

Table 1. Model parameters.

Parameter	Value	Basis
Patients	40,000	Sufficient for stable subgroup estimates
Clearance	Lognormal, GSD 1.35	Several-fold between-patient range
Poor adherers	30% of cohort	Taking a mean of 46% of doses
Intake variability	Scales with shortfall from full adherence	Erratic intake is part of non-adherence
Therapeutic range	1.0 to 2.0	Normalised concentration
Toxic threshold	3.0	Concentration above which risk rises sharply
Escalation	50% dose increase	Applied to subtherapeutic levels
Post-visit adherence	35% fully adherent, rest partial	Counselling, dosing aids, renewed attention

3. Results

3.1 Most subtherapeutic levels are not pharmacokinetic

At the first visit 27.5 per cent of patients had a concentration below the therapeutic range. Of those, 28.0 per cent would have remained subtherapeutic at full adherence and were therefore genuinely clearance-driven; 72.0 per cent would have been within range had they taken their doses.

Table 2 and Figure 2 vary the prevalence of poor adherence in the population. The adherence-driven share rose from 58.4 per cent where 10 per cent of patients were poor adherers to 80.4 per cent where 60 per cent were.

In every population modelled, non-adherence was the more common cause of a subtherapeutic level. That ordering is not an artefact of a high assumed prevalence: even at the lowest prevalence tested, fewer than half of subtherapeutic concentrations reflected a genuine pharmacokinetic difference.

The reason is arithmetic. A patient must have unusual clearance to fall below the range while fully adherent, whereas any patient with ordinary clearance can fall below it by missing doses. The second route is available to everyone and the first only to the tail of the clearance distribution.

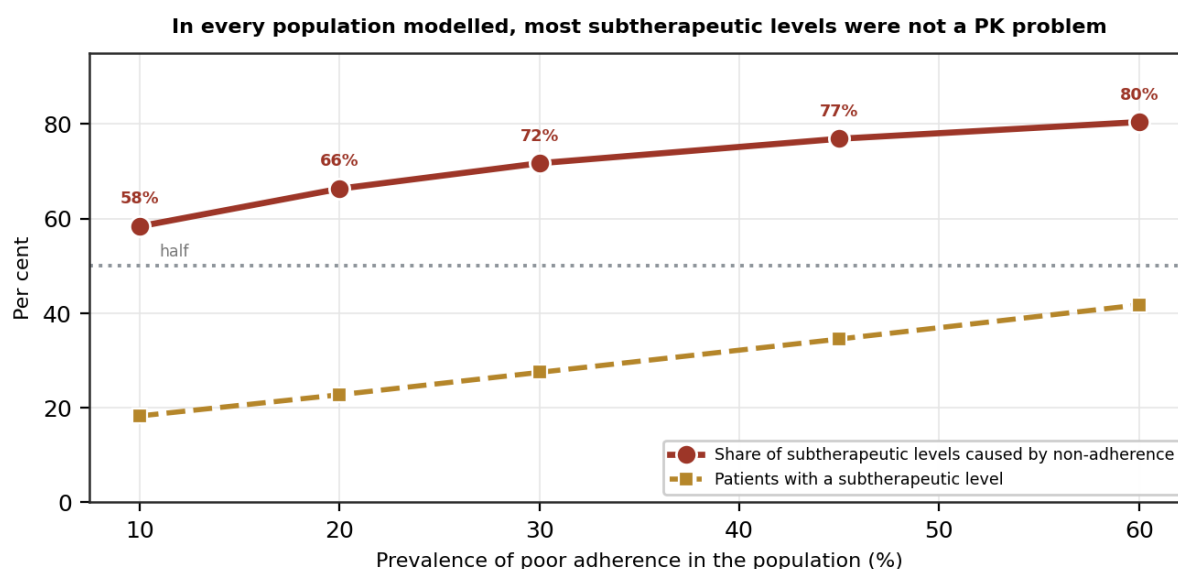


Figure 2. Cause of subtherapeutic levels against the prevalence of poor adherence.

Table 2. Attribution of subtherapeutic concentrations by population adherence.

Poor adherers in population	Patients subtherapeutic	Share attributable to non-adherence	Share attributable to clearance
10%	18.3%	58.4%	41.6%
20%	22.8%	66.3%	33.7%
30%	27.5%	71.7%	28.3%
45%	34.5%	76.9%	23.1%
60%	41.8%	80.4%	19.6%

3.2 Escalation stores exposure

Table 3 and Figure 3 report what happened to exposure. Across all escalated patients the concentration in the period after the visit was a median 1.76 times the measured level, with a ninetieth percentile of 9.8 times, from a dose raised by 50 per cent.

Among the 3,794 patients who were escalated and subsequently became fully adherent, the median rise was 2.45-fold and the ninetieth percentile 15.2-fold. 35.0 per cent of that group ended above the therapeutic range and 5.5 per cent above the toxic threshold.

The gap between the intended and realised exposure change is the finding. A clinician raising a dose by half expects a 1.5-fold change in exposure. Where the measured level was depressed by missed doses and those doses are subsequently taken, the realised change is the product of

the dose increase and the adherence increase, and the second factor can be several-fold on its own.

This is why the hazard is latent rather than immediate. At the visit, and for as long as adherence remains unchanged, the escalation appears to have had a modest effect or none. The exposure is realised only when the patient starts taking the medication as prescribed, which is the outcome every part of the consultation is trying to bring about.

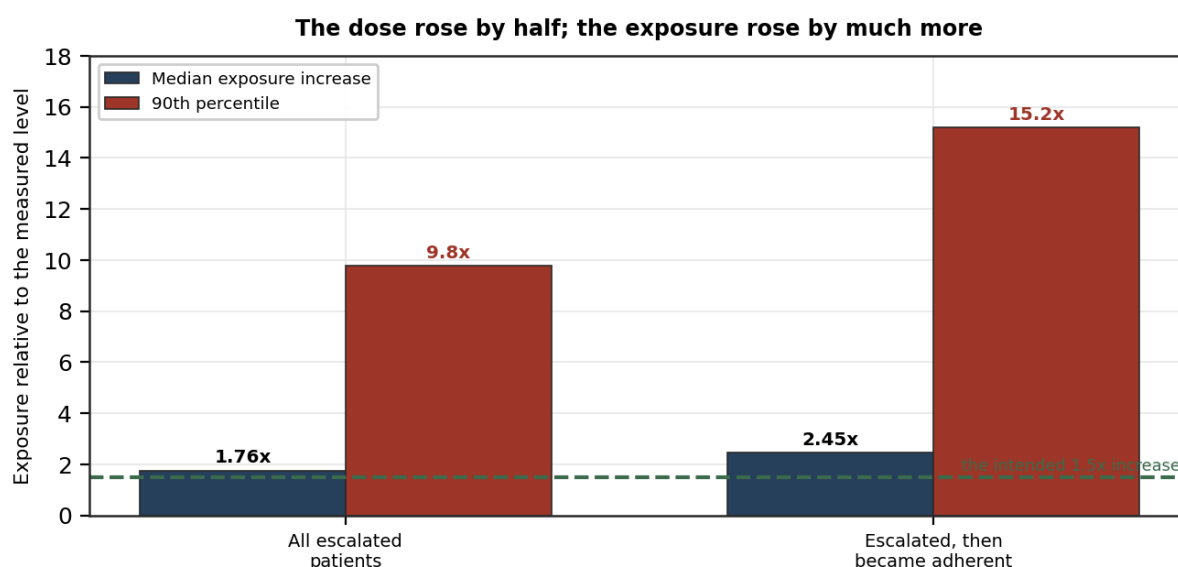


Figure 3. Realised exposure change relative to the measured concentration.

Table 3. Exposure change after escalation.

Group	Median exposure change	90th percentile	Ending above the therapeutic range
All escalated patients	1.76×	9.8×	—
Escalated and became fully adherent	2.45×	15.2×	35.0%
Intended effect of the dose change	1.50×	1.50×	—

3.3 The harm falls on the misattributed group

Table 4 and Figure 4 give the outcome by true cause. Escalating every subtherapeutic level raised the proportion of patients in the therapeutic range from 67.5 to 75.6 per cent and reduced subtherapeutic concentrations from 20.3 to 8.9 per cent, so the policy achieved its intended purpose.

It also raised toxic concentrations from 0.7 to 1.2 per cent. Among escalated patients, 1.9 per cent reached a toxic concentration: 2.7 per cent of those escalated for non-adherence and 0.0 per cent of those escalated for genuinely high clearance.

The entire increment in toxicity fell on the group for whom the escalation was the wrong action. That is not a coincidence of the parameterisation but a structural feature: a patient with genuinely high clearance is, by definition, less able to accumulate the drug, so escalation is both correct and comparatively safe in them. The patients who can become toxic on an escalated dose are those whose clearance was never the problem.

This asymmetry also explains why the aggregate toxicity increase is small while the individual hazard is not. Escalation selects against low-clearance patients, so most escalated patients cannot become toxic whatever their adherence. The risk is concentrated in a subgroup that the policy has no means of identifying.

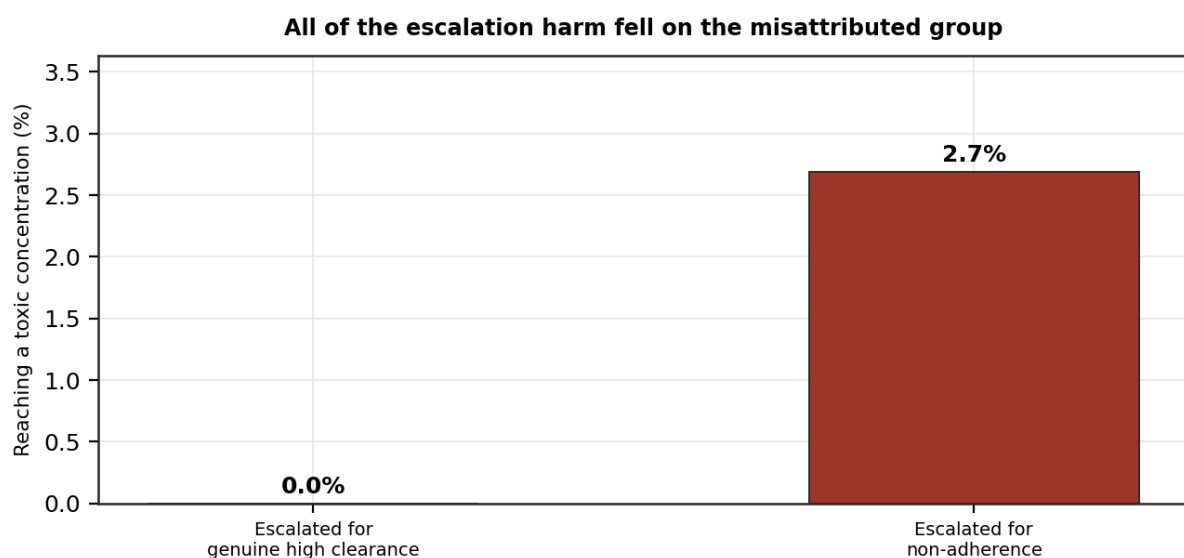


Figure 4. Toxic concentrations after escalation, by the true cause of the low level.

Table 4. Outcome by escalation policy.

Policy	Patients escalated	In therapeutic range	Subtherapeutic	Toxic
No escalation	0.0%	67.5%	20.3%	0.7%
Escalate every subtherapeutic level	27.5%	75.6%	8.9%	1.2%
Escalate only if two levels agree	13.8%	73.7%	13.1%	0.8%

3.4 Measurement did not separate the causes

Table 5 and Figure 5 test whether concentration measurement can identify the adherence-driven group. Among the 11,063 patients subtherapeutic at the first visit, a single concentration gave an area under the receiver operating characteristic curve of 0.669 for identifying non-adherence.

Between-visit variability, which we expected to perform better because erratic intake produces erratic concentrations, gave 0.667 — no improvement. A second concentration considered

alone gave 0.370, which inverted is 0.630: a higher second level indicated non-adherence, consistent with erratic patients regressing upward from a low first measurement.

We report this as a negative result because it was the hypothesis the study set out to test. The variability signal is real in the model by construction, and it still did not discriminate usefully, because variability in measured concentration also arises from assay imprecision, sampling time and ordinary physiological variation, and because the clearance distribution overlaps heavily with the adherence distribution in its effect on the level.

The practical implication is that the information needed is not in the assay. Pharmacy refill records, electronic monitoring, directly observed dosing and a candid conversation are the instruments that bear on adherence, and none of them is a concentration.

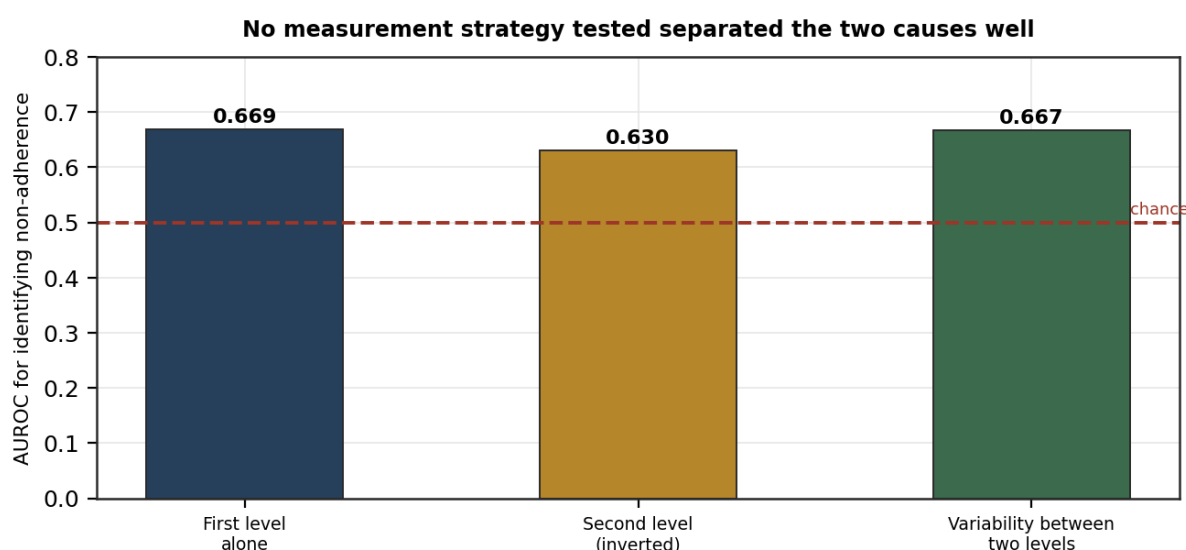


Figure 5. Discrimination between non-adherence and high clearance by three measurement strategies.

Table 5. Discrimination between causes among patients with a subtherapeutic level.

Strategy	AUROC	Interpretation	Useful?
Single concentration	0.669	Lower level weakly favours non-adherence	Marginal
Second concentration	0.370	Higher second level favours non-adherence	Marginal, inverted
Variability between two levels	0.667	Erratic levels favour non-adherence	No improvement

3.5 A more selective policy

Table 6 and Figure 6 evaluate escalating only where two concentrations were consistent with each other. That policy escalated 13.8 per cent of the cohort against 27.5 per cent, roughly halving the number of dose increases.

It achieved 73.7 per cent target attainment against 75.6 per cent, a loss of 1.8 percentage points, while reducing toxic concentrations from 1.2 to 0.8 per cent.

Given the weak discrimination reported in Section 3.4, the selective policy works less by identifying non-adherence than by escalating fewer people. It is closer to a precautionary rule than a diagnostic one, and it should be presented as such rather than as a test.

Whether the trade is worth making depends on the drug. For an agent where subtherapeutic exposure means treatment failure of a serious condition, a two-point loss in target attainment may be unacceptable. For one where the toxicity is severe and the underlying condition tolerates delay, it is clearly favourable. The model supplies the exchange rate; the drug determines the decision.

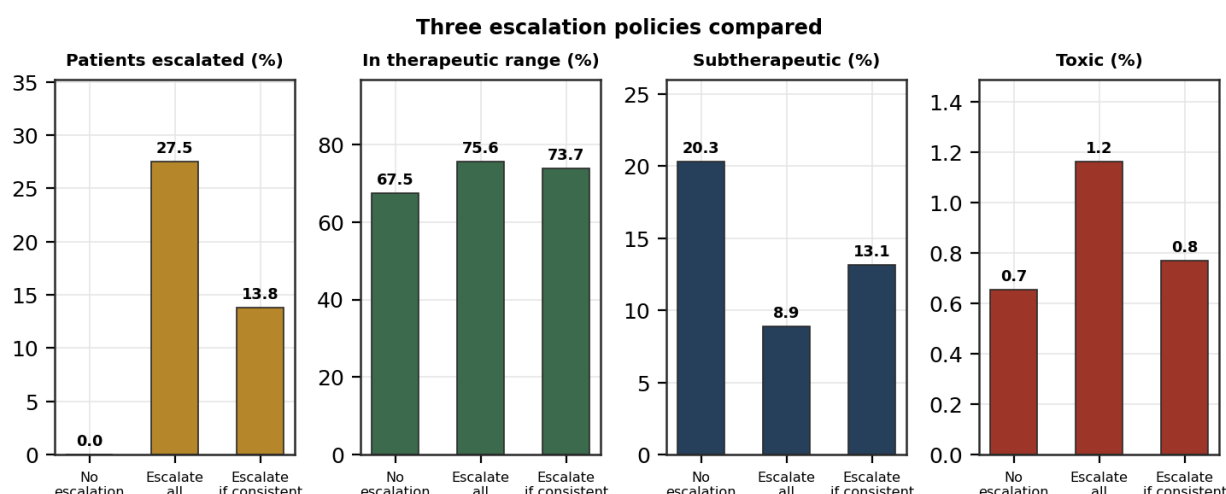


Figure 6. Three escalation policies compared on four outcomes.

Table 6. Trade-off between the two active policies.

Measure	Escalate all	Escalate if consistent	Difference
Patients escalated	27.5%	13.8%	-13.7 points
In therapeutic range	75.6%	73.7%	-1.8 points
Subtherapeutic	8.9%	13.1%	4.2 points
Toxic	1.2%	0.8%	-0.4 points

Table 7. Recommendations.

Recommendation	Addresses	Cost	Evidence here
Assess adherence before attributing a low level to clearance	The more common cause treated as the rarer one	A conversation and refill data	Section 3.1
Expect exposure to rise by more than the dose increment	Latent exposure realised when adherence improves	None	Section 3.2
Recheck the level after any adherence intervention	Toxicity appearing months after the decision	One additional level	Section 3.2
Do not rely on concentrations to detect non-adherence	Information the assay does not contain	None	Section 3.4

Recommendation	Addresses	Cost	Evidence here
Consider two consistent levels before escalating	Escalation applied to a transient low reading	One additional level	Section 3.5
Record the reason for each escalation in the notes	A decision whose consequence arrives later	One line	Section 3.3

4. Discussion

4.1 Principal findings

Four findings follow. 72 per cent of subtherapeutic concentrations were attributable to non-adherence rather than clearance, and the proportion exceeded half in every population modelled. Patients escalated who then became fully adherent experienced a median 2.4-fold rise in exposure from a dose raised by half, with 35 per cent ending above the therapeutic range. All of the additional toxicity fell on patients escalated for non-adherence, none on those escalated for genuine high clearance. And no concentration-based strategy separated the two causes usefully.

The unifying point is that a concentration is a product of three quantities and a single measurement cannot factor it. Clinical practice reads it as though the adherence term were one, and in the patients who most often trigger a dose change it is not.

4.2 Relation to existing work

Non-adherence to long-term therapy is extensively documented, with typical adherence around half in chronic conditions and substantial variation within patients over time [3-5,8]. The phenomenon of improved intake around scheduled visits is well described and complicates the interpretation of any measurement taken at a clinic [9,10]. The limitations of concentration measurement as an adherence measure, and the comparative performance of refill records and electronic monitoring, have been examined across several therapeutic areas [11-13].

The specific sequence modelled here — a low level, an escalation, an adherence intervention, and toxicity at the new dose — is described in the clinical literature as a recognised hazard, particularly for antiepileptics, immunosuppressants and anticoagulants [6,7,14]. What we add is a quantification of how often the misattribution occurs and how large the stored exposure is, together with the negative result that repeated concentration measurement does not resolve it.

4.3 Implications for practice

Table 7 sets out six recommendations. Two deserve comment.

Treat adherence as the leading hypothesis for a low level, not the residual one. On these figures it is the more common explanation in every population modelled, and it is the explanation for which the conventional response is actively harmful. Reversing the default costs a conversation and a look at dispensing records, and it identifies the group in whom escalation should not proceed.

Recheck the concentration after any successful adherence intervention. The hazard created by an escalation is realised at the moment intake improves, so the point at which a dosing aid is supplied or a patient is counselled is precisely when a level is most informative and least often taken. This applies equally where no escalation occurred, since improving adherence on the original dose can itself move a patient through the range.

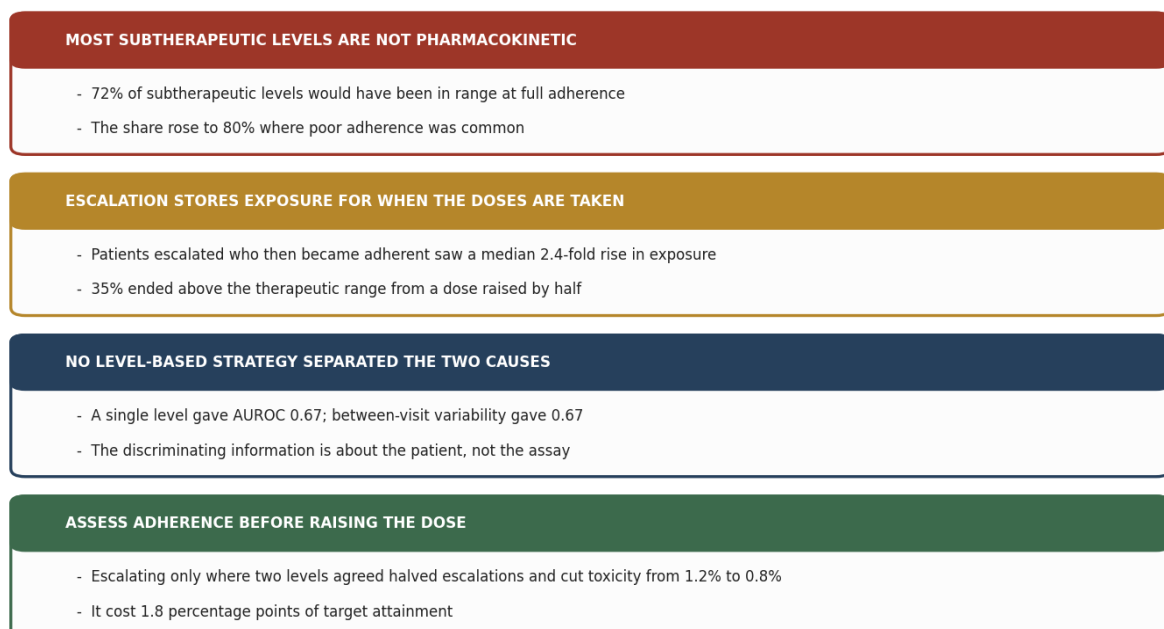


Figure 7. Proposed approach to a subtherapeutic concentration.

5. Limitations

Adherence is modelled as a proportion of doses taken with variability scaling from it, which omits the patterns that matter clinically: drug holidays, consistent omission of one daily dose, and timing errors that affect trough concentrations without changing the number of doses. Those patterns would alter both the concentration distribution and the discrimination results, plausibly in the direction of better discrimination for some of them.

The classification of cause is binary and defined by a counterfactual at full adherence. Real patients combine moderately elevated clearance with moderately reduced intake, and for them the correct action is genuinely mixed. Our two categories therefore sharpen a continuum.

We model a single escalation at a single visit with a fixed 50 per cent increment, and no subsequent monitoring or de-escalation. Real practice rechecks levels, and a follow-up measurement after the escalation would detect many of the overshoots we count as harm. Our toxicity figures are therefore an overestimate of what would be realised in a well-monitored service and a reasonable estimate for one where follow-up is unreliable.

Toxicity is represented by a single concentration threshold rather than a graded relationship, and no clinical outcome is modelled. The proportion above a threshold is a convenient index and not a rate of harm.

Finally, the post-visit adherence recovery is imposed rather than derived, and the proportion becoming fully adherent is the parameter to which the stored-exposure results are most sensitive. We did not vary it systematically, which would have been a useful addition.

6. Conclusion

In this model 28 per cent of patients had a subtherapeutic concentration, and 72 per cent of those would have been within range had they taken their doses. Escalating every subtherapeutic level improved target attainment from 67 to 76 per cent and raised toxic concentrations from 0.7 to 1.2 per cent, with the entire increment falling on patients escalated for non-adherence.

Those escalated who subsequently became fully adherent saw a median 2.4-fold rise in exposure, and 35 per cent ended above the therapeutic range, from a dose increased by half. The excess arrives not at the consultation where the decision is made but when the patient begins taking the medication as prescribed.

No concentration-based strategy we tested identified the misattributed group: a single level gave an area under the curve of 0.67 and between-visit variability 0.67. The information required is not in the assay, and a dose should not be raised on a concentration alone.

Declarations

Ethics approval and consent to participate. Not applicable. This study used entirely synthetic data generated by the authors. No human participants, patient records, samples or

prescribing data were involved. Institutional review board or ethics committee approval and informed consent were therefore not required.

Consent for publication. Not applicable.

Data availability statement. No real-world data were used. All results were generated by the simulation script described in Section 2, provided as supplementary material with all random seeds and every parameter stated in full in Table 1. Every figure and every value in Tables 2 to 6 can be regenerated exactly by executing it. The script will be deposited in a public repository with a permanent identifier on acceptance.

Conflict of interest. The authors declare that they have no competing interests, financial or non-financial, in relation to the subject matter of this manuscript. No author has any financial or advisory relationship with any manufacturer of therapeutic drug monitoring assays, adherence monitoring technology or the drug classes discussed.

Funding. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions. [AO] conceived the study, designed the model and drafted the manuscript. [AT] implemented the simulation, performed the analysis and verified all reported values. [ATh] contributed the medicines optimisation and adherence framing and the recommendations. All authors critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work in accordance with ICMJE criteria.

Acknowledgements. None declared.

Use of artificial intelligence. The authors should disclose here any use of AI-assisted tools in manuscript preparation, in accordance with the journal's policy.

References

1. Kang JS, Lee MH. Overview of therapeutic drug monitoring. Korean J Intern Med. 2009;24(1):1-10.
2. Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring: a systematic review. Ther Drug Monit. 2005;27(1):10-17.
3. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
4. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-97.

5. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppert T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705.
6. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs: best practice guidelines for therapeutic drug monitoring. *Epilepsia*. 2008;49(7):1239-76.
7. Nevins TE, Nickerson PW, Dew MA. Understanding medication nonadherence after kidney transplant. *J Am Soc Nephrol*. 2017;28(8):2290-301.
8. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol*. 2012;52:275-301.
9. Feinstein AR. On white-coat effects and the electronic monitoring of compliance. *Arch Intern Med*. 1990;150(7):1377-78.
10. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. *Arch Intern Med*. 1990;150(7):1509-10.
11. Hawkshead J, Krousel-Wood MA. Techniques for measuring medication adherence in hypertensive patients in outpatient settings: advantages and limitations. *Dis Manage Health Outcomes*. 2007;15(2):109-18.
12. Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int*. 2015;2015:217047.
13. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry urine analysis. *Heart*. 2014;100(11):855-61.
14. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342(5):314-19.
15. Urquhart J. The electronic medication event monitor: lessons for pharmacotherapy. *Clin Pharmacokinet*. 1997;32(5):345-56.
16. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health Econ*. 2001;10(7):601-15.
17. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. *Clin Pharmacol Ther*. 2014;95(6):617-26.
18. Gonzalez D, Rao GG, Bailey SC, Brouwer KLR, Cao Y, Crona DJ, et al. Precision dosing: public health need, proposed framework, and anticipated impact. *Clin Transl Sci*. 2017;10(6):443-54.
19. Darwich AS, Ogungbenro K, Vinks AA, Powell JR, Reny JL, Marsousi N, et al. Why has model-informed precision dosing not yet become common clinical reality? *Clin Pharmacol Ther*. 2017;101(5):646-56.
20. Keizer RJ, Ter Heine R, Frymoyer A, Lesko LJ, Mangat R, Goswami S. Model-informed precision dosing at the bedside: scientific challenges and opportunities. *CPT Pharmacometrics Syst Pharmacol*. 2018;7(12):785-87.
21. Peck RW. The right dose for every patient: a key step for precision medicine. *Nat Rev Drug Discov*. 2016;15(3):145-46.
22. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2008;(2):CD000011.

23. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keenanasseril A, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014;(11):CD000011.
24. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Tong AY, Khan NF, et al. Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. *JAMA Intern Med*. 2017;177(5):624-31.
25. Kini V, Ho PM. Interventions to improve medication adherence: a review. *JAMA*. 2018;320(23):2461-73.
26. Rotenstein LS, Huckman RS, Wagle NW. Making patients and doctors happier: the potential of patient-reported outcomes. *N Engl J Med*. 2017;377(14):1309-12.
27. Sheiner LB, Rosenberg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J Pharmacokinet Biopharm*. 1977;5(5):445-79.
28. Harris CR, Millman KJ, van der Walt SJ, Gommers R, Virtanen P, Cournapeau D, et al. Array programming with NumPy. *Nature*. 2020;585(7825):357-62.
29. Pedregosa F, Varoquaux G, Gramfort A, Michel V, Thirion B, Grisel O, et al. Scikit-learn: machine learning in Python. *J Mach Learn Res*. 2011;12:2825-30.
30. Hunter JD. Matplotlib: a 2D graphics environment. *Comput Sci Eng*. 2007;9(3):90-95.