Journal of Medical Pharmacology and Therapeutics
Vol. 01, Issue 01, July–December 2026, pp. 10–20

OPEN ACCESS
jmpt.corvusmedpress.com

What an Interaction Can Possibly Be: The Fraction-Metabolised Ceiling and the Limits of Categorical Drug Interaction Severity Labels

Makbul Hussain Choudhury[1*]

[1]*Assistant Professor, Rahman Institute of Pharmaceutical Sciences and Research, Guwahati, Assam, India.*
***Corresponding author:** Makbul Hussain Choudhury, makbulchy200@gmail.com

ARTICLE INFO

Article history
Received: 03 June 2026
Revised: 14 July 2026
Accepted: 10 August 2026
Published: 01 September 2026

Keywords
Drug interactions
Cytochrome P450
Fraction metabolised
Static mechanistic model
Clinical decision support
Alert fatigue

Cite this article
Choudhury MH. What an Interaction Can Possibly Be: The Fraction-Metabolised Ceiling and the Limits of Categorical Drug Interaction Severity Labels. *Journal of Medical Pharmacology and Therapeutics*. 2026;1(1):10–20.

Copyright and licence
© 2026 The Author(s). Open access under the Creative Commons Attribution 4.0 International licence (CC BY 4.0).

ABSTRACT

Background. Drug interaction alerts are delivered as categories — contraindicated, major, moderate, minor — while the underlying pharmacology is continuous. We examined how far those categories survive realistic uncertainty in the parameters that generate them.

Methods. Using the standard static mechanistic model for reversible enzyme inhibition, we computed the area-under-the-curve ratio across a grid of fraction metabolised by the inhibited pathway (f_m) and inhibitor exposure relative to potency ($[I]/K_i$). We derived the ceiling achievable at complete inhibition, then ran 20,000-draw Monte Carlo analyses with uncertainty in f_m and in K_i, and assessed how often the severity band implied by the point estimate was reproduced.

Results. At complete inhibition the AUC ratio collapses to $1/(1 - f_m)$, so the achievable magnitude is bounded by f_m alone. A substrate with f_m 0.50 cannot exceed 2.0-fold and one with f_m 0.60 cannot exceed 2.5-fold, however potent the inhibitor; f_m 0.90 permits 10-fold and f_m 0.95 permits 20-fold. Uncertainty in f_m dominated uncertainty in K_i: with f_m known to a standard deviation of 0.15 and K_i known exactly, the 5th-to-95th percentile interval for the AUC ratio spanned 16.4-fold, whereas a tenfold uncertainty in K_i with f_m known exactly produced only 2.6-fold. Categorical labels were least reproducible near band boundaries: the point-estimate band was reproduced in 56 % of draws at f_m 0.50, 57 % at f_m 0.80 and 55 % at f_m 0.85.

Conclusions. A severity category assigned without reference to f_m can be pharmacologically impossible. The parameter that dominates the prediction is the one least often reported, and near band boundaries a category approximates a coin toss. Interaction resources should publish f_m and an interval rather than a label alone.

1. Introduction

A prescriber adding a drug to an existing regimen is warned by a category. The interaction is contraindicated, or major, or moderate, or minor; the alert fires, the prescriber judges whether to proceed, and in the great majority of cases overrides it [1–3]. The categorical vocabulary is so established that it is rarely examined, and the resources that assign the categories disagree with one another to a degree that has been repeatedly documented [4–6].

The underlying pharmacology is not categorical. For reversible inhibition of a metabolic pathway, the change in systemic exposure of the victim drug is a continuous function of two quantities: how much of that drug's clearance runs through the inhibited pathway, and how thoroughly the inhibitor shuts that pathway down. The relationship between them is given by a static equation that has been in use for decades and underpins regulatory interaction guidance [7–10].

That equation has a property which we think deserves more attention in clinical practice than it receives. As inhibition becomes complete, the predicted exposure change does not grow without limit; it approaches a ceiling determined entirely by the fraction metabolised. A drug cleared only half by the inhibited enzyme cannot increase in exposure by more than twofold no matter what is co-prescribed, because the other half of its clearance is untouched.

© 2026 The Author(s). Published by Corvus Medical Press under CC BY 4.0.

If that is so, then some severity labels are not merely uncertain but impossible: a category implying a large exposure change assigned to a substrate whose ceiling forbids one is wrong on arithmetic grounds before any clinical evidence is considered. And the parameter that decides this — f_m — is, unlike inhibitor potency, poorly characterised for many drugs and almost never shown to the prescriber.

We therefore computed the ceiling across the plausible range of f_m, examined how the predicted interaction magnitude responds to uncertainty in each parameter separately, and asked how reproducible a categorical label is once that uncertainty is admitted.

1.1 Objectives

We aimed to characterise the maximum achievable exposure change as a function of f_m; to compute the AUC ratio across a grid of f_m and inhibitor potency; to determine whether uncertainty in f_m or in K_i contributes more to prediction uncertainty; and to quantify how often a categorical severity assignment is reproduced under realistic parameter uncertainty.

2. Methods

2.1 Model

We used the standard static mechanistic model for reversible competitive inhibition of a single elimination pathway [11–13], in which the ratio of victim-drug exposure with and without the inhibitor is

$$AUCR = \frac{1}{\frac{f_m}{1+[I]/K_i} + (1 - f_m)} \quad (1)$$

where f_m is the fraction of the victim drug's total clearance carried by the inhibited pathway, [I] is the inhibitor concentration available to the enzyme and K_i is its inhibition constant. The two terms in the denominator are the inhibited and uninhibited portions of clearance; only the first is modifiable.

Letting inhibition become complete, the first term vanishes and the expression reduces to a ceiling that depends on f_m alone:

$$AUCR_{max} = \frac{1}{1 - f_m} \quad (2)$$

Equation 2 is elementary and well known to pharmacokineticists [7,14]. Our purpose is not to derive it but to work out what it implies for categorical alerting, which we do not think has been set out quantitatively for a clinical readership.

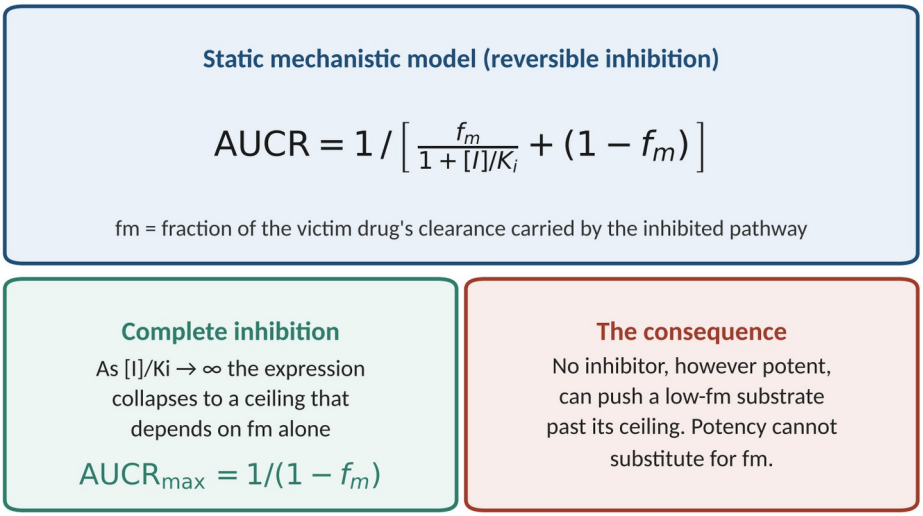

Figure 1. The static mechanistic model and the ceiling that follows from it at complete inhibition.

2.2 Severity bands

We adopted the exposure-based bands used in regulatory interaction guidance: an AUC ratio below 1.25 as no meaningful change, 1.25 to below 2 as weak, 2 to below 5 as moderate, and 5 or above as strong [8,9]. These thresholds are conventional rather than clinical, and a change of a given size matters more for a drug with a narrow therapeutic index; that is a separate axis we do not model here.

2.3 Uncertainty analysis

Monte Carlo analyses drew 20,000 parameter sets per scenario. f_m was perturbed on the logit scale so that draws remained within (0, 1), with a standard deviation on the natural scale of 0.12 in the base case. Inhibitor exposure relative to potency was perturbed lognormally with a threefold range, reflecting the well-documented variability in reported K_i values and the uncertainty in the appropriate concentration to use at the enzyme [14,15].

Two one-at-a-time analyses then varied f_m uncertainty from 0 to 0.20 with K_i fixed, and K_i uncertainty from 1- to 10-fold with f_m fixed, to establish which parameter dominates. A final analysis swept f_m from 0.40 to 0.95 under a potent inhibitor and recorded the proportion of draws falling in the same severity band as the point estimate.

Analyses used Python with NumPy [16,17]; the complete script, with all random seeds, is available from the corresponding author. No human participants, tissue or patient records were used, and institutional review board approval and informed consent were not applicable.

Table 1. Model parameters and their treatment

Parameter	Role	Uncertainty applied
f_m	Fraction of victim-drug clearance through the inhibited pathway	Logit-scale perturbation, base-case SD 0.12; varied 0 to 0.20
$[I]/K_i$	Inhibitor exposure relative to potency at the enzyme	Lognormal, base-case threefold range; varied 1- to 10-fold
Severity bands	AUCR < 1.25, 1.25–2, 2–5, ≥ 5	Fixed; conventional regulatory thresholds
Model form	Reversible competitive inhibition, single pathway	Fixed; see Section 4.4 for what this excludes

3. Results

3.1 The ceiling

Figure 2 and Table 2 give the maximum achievable AUC ratio as a function of f_m. A substrate with f_m 0.30 cannot exceed 1.43-fold. One with f_m 0.50 cannot exceed 2.0-fold, and one with f_m 0.60 cannot exceed 2.5-fold. At f_m 0.80 the ceiling is 5-fold, at 0.90 it is 10-fold, and at 0.95 it is 20-fold.

The clinical consequence is a set of impossibility statements. A substrate with f_m below 0.50 cannot reach the moderate band at all. One with f_m below 0.80 cannot reach the strong band. Assigning a severe categorical label to such a pair is not a conservative choice made under uncertainty; it asserts an exposure change the pharmacology forbids, and no inhibitor, at any dose, can produce it.

The curve also explains why interaction magnitude is so unevenly distributed across drugs. The ceiling is flat and unremarkable across most of the f_m range and then rises very steeply above about 0.85, so the drugs capable of large interactions are a small set with near-exclusive dependence on one pathway. For those drugs, small differences in f_m produce large differences in consequence, which is precisely where f_m is hardest to measure.

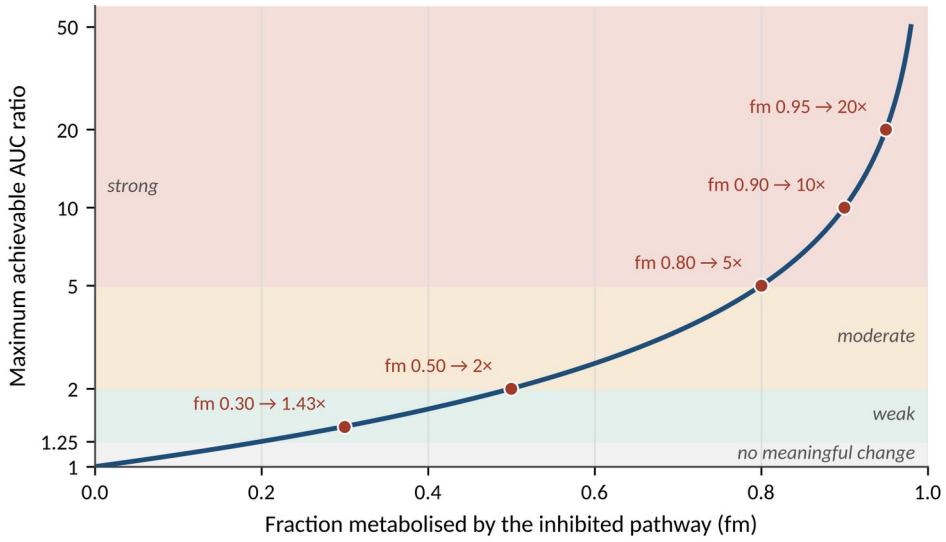

Figure 2. Maximum achievable AUC ratio as a function of fraction metabolised, against conventional severity bands.

Table 2. The ceiling by fraction metabolised

f_m	Maximum AUC ratio	Highest band reachable	Bands that are impossible
0.30	1.43	weak	moderate, strong
0.50	2.00	moderate	strong
0.60	2.50	moderate	strong
0.70	3.33	moderate	strong
0.80	5.00	strong	none
0.85	6.67	strong	none
0.90	10.00	strong	none
0.95	20.00	strong	none
0.98	50.00	strong	none

Note. *The ceiling is reached only at complete inhibition of the pathway; achievable values at finite inhibitor exposure are lower.*

3.2 The full surface

Figure 3 and Table 3 give the AUC ratio across f_m and inhibitor exposure. Reading across a row shows what increasing inhibitor potency buys: at f_m 0.50, moving from $[I]/K_i$ of 1 to 100 raises the AUC ratio only from 1.33 to 1.98. Reading down a column shows what f_m contributes: at $[I]/K_i$ of 30, the AUC ratio rises from 1.94 at f_m 0.50 to 7.75 at f_m 0.90 and 19.37 at f_m 0.98.

The asymmetry is the point. Along the potency axis the function saturates; along the f_m axis it does not. A clinician comparing two candidate co-prescriptions gains more from knowing which victim drug has the higher f_m than from knowing which inhibitor is the more potent, once the inhibitor is reasonably strong.

Table 3. AUC ratio by f_m and inhibitor exposure relative to potency

f_m	$[I]/K_i$ = 0.1	$[I]/K_i$ = 0.3	$[I]/K_i$ = 1	$[I]/K_i$ = 3	$[I]/K_i$ = 10	$[I]/K_i$ = 30	$[I]/K_i$ = 100
0.30	1.03	1.07	1.18	1.29	1.38	1.41	1.42
0.50	1.05	1.13	1.33	1.60	1.83	1.94	1.98
0.60	1.06	1.16	1.43	1.82	2.20	2.38	2.46
0.70	1.07	1.19	1.54	2.11	2.75	3.10	3.26
0.80	1.08	1.23	1.67	2.50	3.67	4.43	4.81
0.85	1.08	1.24	1.74	2.76	4.40	5.64	6.31
0.90	1.09	1.26	1.82	3.08	5.50	7.75	9.18
0.95	1.09	1.28	1.90	3.48	7.33	12.40	16.83
0.98	1.10	1.29	1.96	3.77	9.17	19.37	33.67

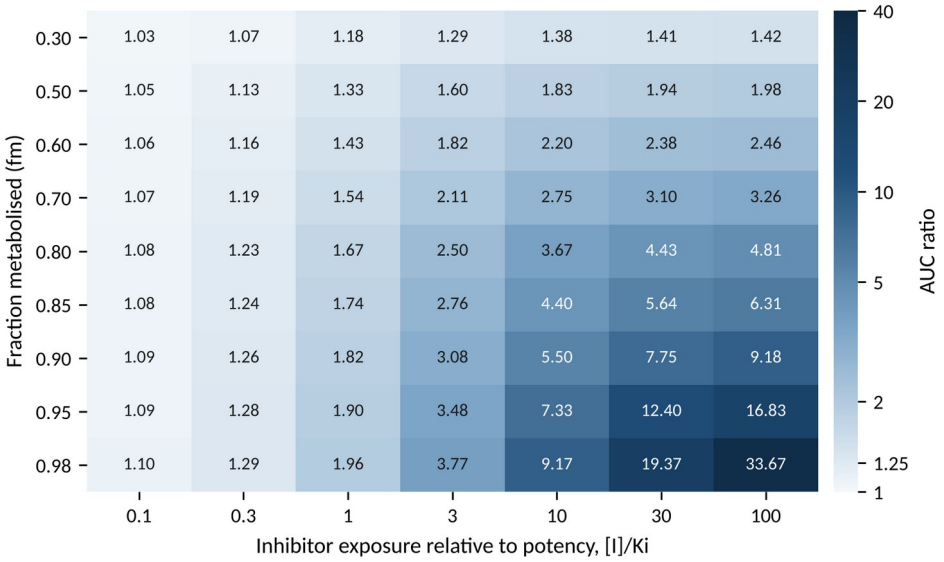

Figure 3. AUC ratio across fraction metabolised and inhibitor exposure relative to potency.

3.3 Which uncertainty matters

Figure 4 and Table 4 separate the two sources of uncertainty for a substrate with f_m 0.90 exposed to a potent inhibitor. With K_i known exactly, raising the uncertainty in f_m from a standard deviation of 0.05 to 0.20 widened the 5th-to-95th percentile interval for the AUC ratio from 3.3-fold to 22.0-fold. With f_m known exactly, a tenfold uncertainty in K_i widened it only to 2.6-fold.

The contrast is stark at an f_m standard deviation of 0.15 and the base-case threefold K_i range: f_m uncertainty alone produced an interval of 1.56 to 25.56 — spanning three severity bands — while threefold K_i uncertainty alone produced 5.93 to 8.95, entirely within one.

This is an inversion of where effort usually goes. Inhibitor potency is measured in vitro, reported in the literature, curated in databases and used to classify inhibitors as strong, moderate or weak [11,18,19]. Fraction metabolised is inferred, often indirectly, frequently from a single clinical study [9,20], and is rarely quoted at all in the resources a prescriber consults. The better-characterised parameter is the less consequential one.

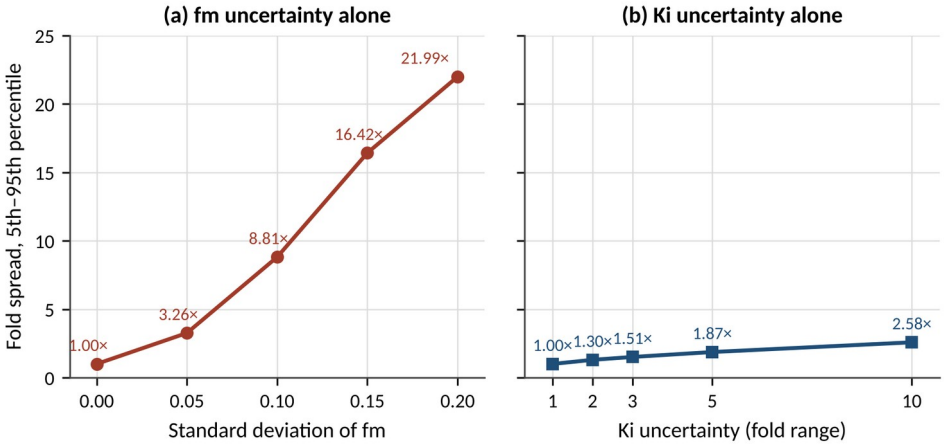

Figure 4. Width of the predicted AUC ratio interval attributable to uncertainty in f_m alone and in K_i alone.

Table 4. One-at-a-time uncertainty analysis, f_m 0.90 with a potent inhibitor

Source of uncertainty	5th percentile	95th percentile	Fold spread	Modal band retained (%)
f_m standard deviation 0.00	7.75	7.75	1.00	100.0
f_m standard deviation 0.05	4.15	13.54	3.26	87.1
f_m standard deviation 0.10	2.32	20.47	8.81	71.7
f_m standard deviation 0.15	1.56	25.56	16.42	64.7
f_m standard deviation 0.20	1.23	26.96	21.99	61.0
K_i uncertainty 1-fold	7.75	7.75	1.00	100.0
K_i uncertainty 2-fold	6.63	8.59	1.30	100.0
K_i uncertainty 3-fold	5.93	8.95	1.51	99.2
K_i uncertainty 5-fold	4.96	9.28	1.87	94.7
K_i uncertainty 10-fold	3.72	9.58	2.58	87.2

Note. *Each block varies one parameter with the other held exact. The two blocks are directly comparable.*

3.4 How reproducible is a category?

Table 5 and Figure 5 report the six worked scenarios under joint uncertainty. In every case the point estimate named a single band while the draws spanned two or three. For a substrate with f_m 0.50 and a potent inhibitor, the point estimate was 1.94 — weak — but 44 % of draws fell in the moderate band. For f_m 0.90 with a potent inhibitor, the point estimate of 7.75 sat in the strong band, with 27 % of draws moderate and 6 % weak.

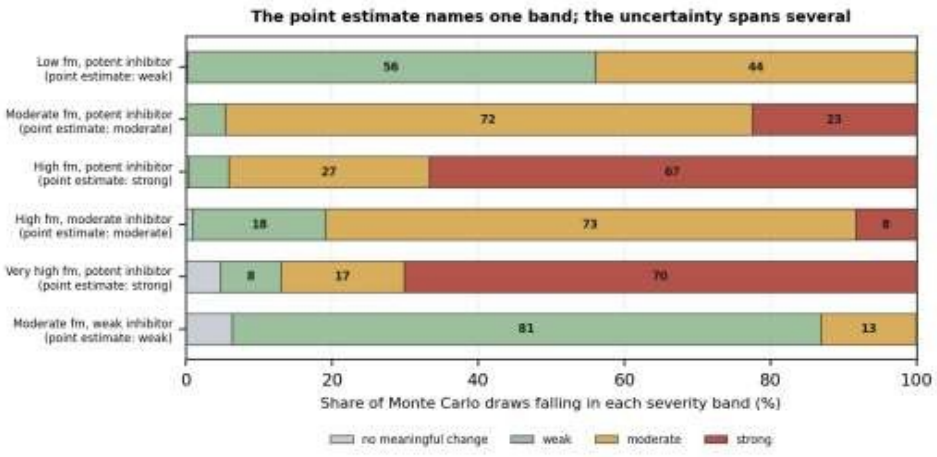

Figure 5. Distribution of Monte Carlo draws across severity bands for six worked scenarios, against the band named by the point estimate.

Table 5. Worked scenarios under joint uncertainty

Scenario	f_m	[I]/K_i	Point AUCR	5th–95th percentile	Point band	Modal band retained (%)
Low f_m, potent inhibitor	0.50	30	1.94	1.43–2.97	weak	55.8
Moderate f_m, potent inhibitor	0.75	30	3.65	1.98–7.44	moderate	72.1
High f_m, potent inhibitor	0.90	30	7.75	1.91–24.47	strong	66.7
High f_m, moderate inhibitor	0.90	3	3.08	1.53–5.65	moderate	72.5
Very high f_m, potent inhibitor	0.95	30	12.40	1.26–40.02	strong	70.2
Moderate f_m, weak inhibitor	0.75	1	1.60	1.23–2.27	weak	80.6

Figure 6 sweeps f_m under a potent inhibitor and records how often the point-estimate band survives (Table 6). Agreement was best where f_m sat comfortably inside a band — 81 % at f_m 0.65 and 71 % at f_m 0.95 — and collapsed at the boundaries, to 56 % at f_m 0.50, 57 % at f_m 0.80 and 55 % at f_m 0.85.

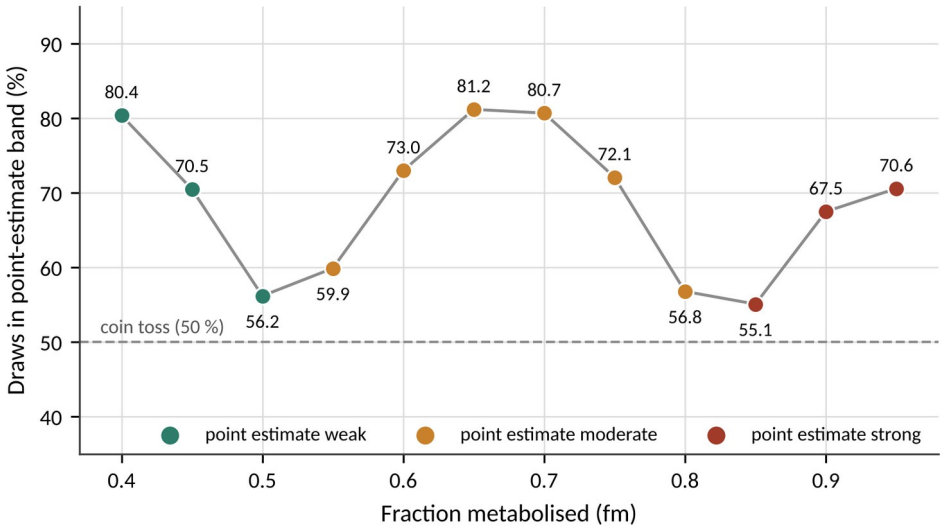

Figure 6. Proportion of draws agreeing with the point-estimate severity band, across fraction metabolised.

Table 6. Reproducibility of the categorical label across f_m, potent inhibitor

f_m	Point-estimate band	Median AUCR	5th–95th percentile	Agreement (%)
0.40	weak	1.62	1.28–2.39	80.4
0.45	weak	1.76	1.34–2.66	70.5
0.50	weak	1.93	1.43–2.97	56.2
0.55	moderate	2.13	1.52–3.38	59.9
0.60	moderate	2.37	1.62–3.95	73.0
0.65	moderate	2.68	1.72–4.73	81.2
0.70	moderate	3.06	1.84–5.81	80.7
0.75	moderate	3.59	1.96–7.36	72.1
0.80	moderate	4.33	2.08–10.09	56.8
0.85	strong	5.41	2.08–14.92	55.1
0.90	strong	7.40	1.97–24.83	67.5
0.95	strong	11.12	1.28–39.55	70.6

A label reproduced in 55 per cent of draws is close to a coin toss, and it is assigned with no visible indication that it is. The f_m values at which this happens — around 0.8 to 0.9 — are exactly where many clinically important substrates of a single major pathway are believed to sit, so the unreliable zone is not a corner case.

It also explains, without needing to invoke error, why interaction resources disagree. Two curators working from slightly different f_m estimates will assign different categories for the same pair while both applying the same thresholds correctly to their own inputs. The disagreement documented across databases may be less a quality problem than the visible consequence of forcing a continuous, uncertain quantity into four bins.

4. Discussion

4.1 Principal findings

Three findings follow. The magnitude of a reversible metabolic interaction is bounded by the fraction metabolised: substrates with f_m below 0.50 cannot reach the moderate band and those below 0.80 cannot reach the strong band, whatever the inhibitor. Uncertainty in f_m dominates uncertainty in K_i by roughly an order of magnitude in its effect on the predicted interval. And near band boundaries the categorical label is reproduced in little more than half of draws.

The three combine into a single practical claim. A severity category is a low-resolution summary of a quantity that is both bounded and uncertain, and it conceals both properties. It cannot tell a prescriber that a warned-about interaction is incapable of exceeding 1.5-fold, and it cannot tell them that a label of major rests on an f_m estimate that could as easily have produced moderate.

4.2 Relation to existing work

The static mechanistic model and the f_m dependence are textbook clinical pharmacology and are embedded in regulatory guidance on interaction assessment [7–10,14,21]. The difficulty of estimating f_m, and the sensitivity of interaction predictions to it, are recognised in the modelling literature [14,15,20]. Inconsistency between interaction compendia in the severity assigned to the same pair has been documented repeatedly [4–6], and override rates for interaction alerts are high [1,2]; consensus work on how interaction evidence should be generated, evaluated and selected for decision support has followed [22–24].

What we add is the link between them. The inconsistency across compendia and the unreliability of a category at band boundaries are the same phenomenon viewed from different sides, and the impossibility result gives a concrete, checkable test that any interaction resource could apply to its own content: does the assigned severity exceed the ceiling implied by the substrate's f_m?

4.3 Implications

Figure 7 summarises four principles and Table 7 sets out the corresponding recommendations. Two deserve comment.

Audit existing content against the ceiling. Equation 2 requires only f_m, and for many widely warned-about substrates an f_m estimate exists. Any pair whose assigned severity exceeds its ceiling is wrong on arithmetic grounds and can be corrected without new evidence. We would expect such an audit to reduce alert volume, because the impossible assignments will be disproportionately the severe ones [25].

Show the interval, and show fm. A prescriber told that exposure is predicted to rise between two- and eightfold, with the substrate 90 per cent dependent on the inhibited pathway, has information they can act on proportionately [26]. A prescriber told major has a binary choice between overriding and not, which is why the override rate is what it is.

Table 7. Recommendations

Recommendation	Addresses	Cost	Evidence here
Audit assigned severities against the f_m ceiling	Categories the pharmacology forbids	One calculation per pair	Section 3.1
Publish f_m with every substrate entry	The dominant parameter being invisible	Curation effort	Sections 3.1, 3.3
Report a predicted interval rather than a category	Uncertainty concealed by binning	Presentation change	Section 3.4
Flag pairs sitting near a band boundary	Labels reproduced in about half of draws	One calculation per pair	Section 3.4
Prioritise f_m characterisation over further K_i refinement	Effort spent on the less consequential parameter	Research prioritisation	Section 3.3
Treat cross-compendium disagreement as expected	Disagreement read as a quality failure	None	Section 3.4

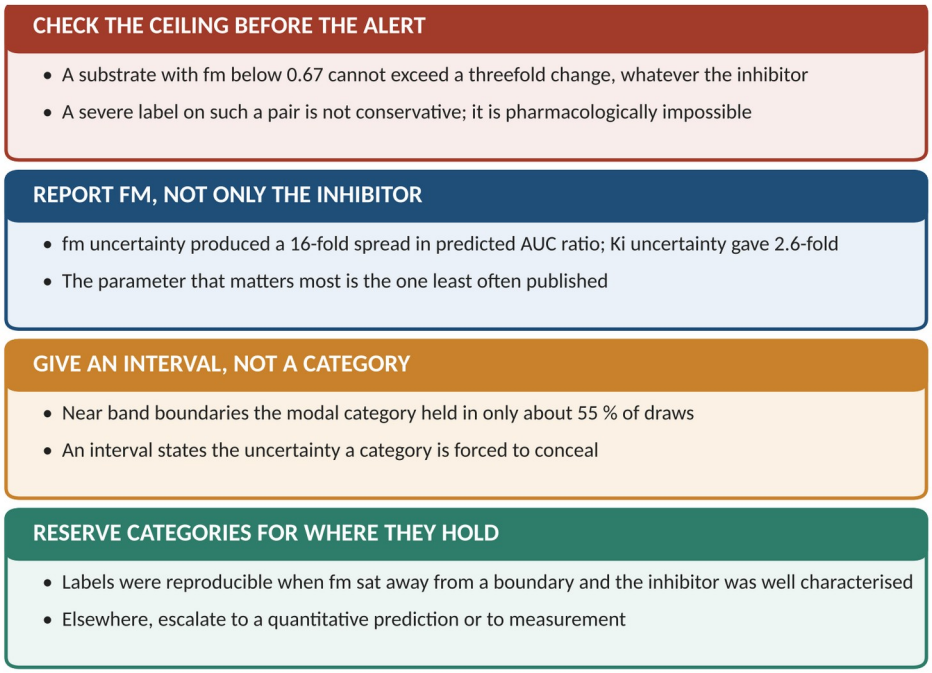

Figure 7. Proposed practice for interaction resources and for clinical decision support.

4.4 Limitations

The static model is a simplification of a system the field now routinely models dynamically. It assumes a single inhibited pathway, reversible competitive inhibition, a single well-stirred compartment, no change in absorption or transport, and steady-state inhibitor exposure. Real interactions involve intestinal and hepatic first-pass contributions, transporters, multiple affected pathways, time-dependent and mechanism-based inhibition, induction, and active metabolites, none of which the equation carries [13,27]. Physiologically based models handle these and are the appropriate tool for a specific prediction [19,21,28].

The ceiling result, however, is robust to most of that. It follows from the existence of an uninhibited clearance route, so any mechanism that leaves part of clearance untouched imposes a ceiling of the same form. Where it fails is where f_m is itself modified — by a second interaction affecting the alternative pathway, by genetic loss of that pathway, or by organ impairment — and those situations raise the effective f_m and therefore raise the ceiling. A prescriber facing a patient who is a poor metaboliser by another route is dealing with a higher f_m than the population value.

The uncertainty distributions are ours. An f_m standard deviation of 0.12 and a threefold K_i range are plausible but not derived from a systematic assessment of how well these parameters are known across drugs, and the reproducibility percentages would change with different assumptions. The qualitative finding that f_m dominates follows from the functional form rather than from the specific spreads, and is the more robust part.

Exposure bands are not clinical bands. A twofold change is inconsequential for a drug with a wide therapeutic index and dangerous for one without, so an exposure-based severity scheme is at best an intermediate. We have deliberately not attempted to map exposure onto clinical severity, which would require a second model and a great deal more evidence.

Finally, nothing here concerns whether an alert should fire. We address what the number behind the alert can be, not whether the prescriber should be interrupted, which depends on workflow, on the patient and on the alternatives available.

5. Conclusion

The magnitude of a reversible metabolic drug interaction is bounded above by $1/(1 - f_m)$. A substrate half-cleared by the inhibited pathway cannot exceed a 2.0-fold change in exposure however potent the inhibitor, and one cleared 60 per cent by it cannot exceed 2.5-fold. Severity categories implying more than that are not cautious; they are arithmetically unavailable.

Within the ceiling, the prediction is governed by the parameter that is least well measured. Uncertainty in f_m of 0.15 produced a 16.4-fold spread in the predicted exposure ratio; a tenfold uncertainty in inhibitor potency produced 2.6-fold. Near the boundaries between severity bands the resulting category was reproduced in barely half of draws.

A category is therefore a lossy summary of a bounded, uncertain quantity, and it discards exactly the two facts a prescriber could use: how large the interaction could possibly be, and how confidently that has been established. Publishing f_m and an interval alongside the label would restore both, and auditing existing labels against the ceiling would correct the assignments that cannot be right.

Declarations

Ethical approval. Not applicable. This is a computational analysis of a published pharmacokinetic model; no human participants, tissue, patient records or identifiable data were involved.

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

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 clinical or experimental data were used in this study. All results were generated by the model described in Section 2 with the parameters listed in Table 1. The analysis script, including all random seeds, reproduces every reported value and is available from the corresponding author upon reasonable request.

Author contributions. Makbul Hussain Choudhury is the sole author of this work and was responsible for the conception and design of the study, development of the model and uncertainty analysis, software, analysis and interpretation of the results, 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.

References

1. van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc. 2006;13(2):138–147. https://doi.org/10.1197/jamia.M1809
2. Nanji KC, Slight SP, Seger DL, Cho I, Fiskio JM, Redden LM, et al. Overrides of medication-related clinical decision support alerts in outpatients. J Am Med Inform Assoc. 2014;21(3):487–491. https://doi.org/10.1136/amiajnl-2013-001813
3. Seidling HM, Phansalkar S, Seger DL, Paterno MD, Shaykevich S, Haefeli WE, et al. Factors influencing alert acceptance: a novel approach for predicting the success of clinical decision support. J Am Med Inform Assoc. 2011;18(4):479–484. https://doi.org/10.1136/amiajnl-2010-000039
4. Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, Van Bergen RC, et al. Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc. 2004;44(2):136–141. https://doi.org/10.1331/154434504773062582
5. Vitry AI. Comparative assessment of four drug interaction compendia. Br J Clin Pharmacol. 2007;63(6):709–714. https://doi.org/10.1111/j.1365-2125.2006.02809.x
6. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: a systematic review. Eur J Clin Pharmacol. 2015;71(2):131–142. https://doi.org/10.1007/s00228-014-1786-7
7. Rowland M, Matin SB. Kinetics of drug-drug interactions. J Pharmacokinet Biopharm. 1973;1(6):553–567. https://doi.org/10.1007/BF01059791
8. Ito K, Iwatsubo T, Kanamitsu S, Ueda K, Suzuki H, Sugiyama Y. Prediction of pharmacokinetic alterations caused by drug-drug interactions: metabolic interaction in the liver. Pharmacol Rev. 1998;50(3):387–412. https://doi.org/10.1016/S0031-6997(24)01372-3
9. Ohno Y, Hisaka A, Suzuki H. General framework for the quantitative prediction of CYP3A4-mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. Clin Pharmacokinet. 2007;46(8):681–696. https://doi.org/10.2165/00003088-200746080-00005
10. Zhang L, Reynolds KS, Zhao P, Huang SM. Drug interactions evaluation: an integrated part of risk assessment of therapeutics. Toxicol Appl Pharmacol. 2010;243(2):134–145. https://doi.org/10.1016/j.taap.2009.12.016

11. Obach RS, Walsky RL, Venkatakrishnan K, Gaman EA, Houston JB, Tremaine LM. The utility of in vitro cytochrome P450 inhibition data in the prediction of drug-drug interactions. J Pharmacol Exp Ther. 2006;316(1):336–348. https://doi.org/10.1124/jpet.105.093229
12. Einolf HJ. Comparison of different approaches to predict metabolic drug-drug interactions. Xenobiotica. 2007;37(10–11):1257–1294. https://doi.org/10.1080/00498250701620700
13. Fahmi OA, Hurst S, Plowchalk D, Cook J, Guo F, Youdim K, et al. Comparison of different algorithms for predicting clinical drug-drug interactions, based on the use of CYP3A4 in vitro data: predictions of compounds as precipitants of interaction. Drug Metab Dispos. 2009;37(8):1658–1666. https://doi.org/10.1124/dmd.108.026252
14. Zhao P, Zhang L, Grillo JA, Liu Q, Bullock JM, Moon YJ, et al. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. Clin Pharmacol Ther. 2011;89(2):259–267. https://doi.org/10.1038/clpt.2010.298
15. Wagner C, Zhao P, Pan Y, Hsu V, Grillo J, Huang SM, et al. Application of physiologically based pharmacokinetic (PBPK) modeling to support dose selection: report of an FDA public workshop on PBPK. CPT Pharmacometrics Syst Pharmacol. 2015;4(4):226–230. https://doi.org/10.1002/psp4.33
16. Harris CR, Millman KJ, van der Walt SJ, Gommers R, Virtanen P, Cournapeau D, et al. Array programming with NumPy. Nature. 2020;585(7825):357–362. https://doi.org/10.1038/s41586-020-2649-2
17. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. Nat Methods. 2020;17(3):261–272. https://doi.org/10.1038/s41592-020-0772-5
18. Wienkers LC, Heath TG. Predicting in vivo drug interactions from in vitro drug discovery data. Nat Rev Drug Discov. 2005;4(10):825–833. https://doi.org/10.1038/nrd1851
19. Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S, et al. The conduct of in vitro and in vivo drug-drug interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective. J Clin Pharmacol. 2003;43(5):443–469. https://doi.org/10.1177/0091270003043005001
20. Hisaka A, Ohno Y, Yamamoto T, Suzuki H. Prediction of pharmacokinetic drug-drug interaction caused by changes in cytochrome P450 activity using in vivo information. Pharmacol Ther. 2010;125(2):230–248. https://doi.org/10.1016/j.pharmthera.2009.10.011
21. Tucker GT, Houston JB, Huang SM. Optimizing drug development: strategies to assess drug metabolism/transporter interaction potential — toward a consensus. Clin Pharmacol Ther. 2001;70(2):103–114. https://doi.org/10.1067/mcp.2001.116891
22. Hines LE, Malone DC, Murphy JE. Recommendations for generating, evaluating, and implementing drug-drug interaction evidence. Pharmacotherapy. 2012;32(4):304–313. https://doi.org/10.1002/j.1875-9114.2012.01024.x
23. Scheife RT, Hines LE, Boyce RD, Chung SP, Momper JD, Sommer CD, et al. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. Drug Saf. 2015;38(2):197–206. https://doi.org/10.1007/s40264-014-0262-8
24. Tilson H, Hines LE, McEvoy G, Weinstein DM, Hansten PD, Matuszewski K, et al. Recommendations for selecting drug-drug interactions for clinical decision support. Am J Health Syst Pharm. 2016;73(8):576–585. https://doi.org/10.2146/ajhp150565
25. Phansalkar S, van der Sijs H, Tucker AD, Desai AA, Bell DS, Teich JM, et al. Drug-drug interactions that should be non-interruptive in order to reduce alert fatigue in electronic health records. J Am Med Inform Assoc. 2013;20(3):489–493. https://doi.org/10.1136/amiajnl-2012-001089
26. Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, et al. Recommendations to improve the usability of drug-drug interaction clinical decision support alerts. J Am Med Inform Assoc. 2015;22(6):1243–1250. https://doi.org/10.1093/jamia/ocv011
27. Varma MV, Pang KS, Isoherranen N, Zhao P. Dealing with the complex drug-drug interactions: towards mechanistic models. Biopharm Drug Dispos. 2015;36(2):71–92. https://doi.org/10.1002/bdd.1934
28. Grimstein M, Yang Y, Zhang X, Grillo J, Huang SM, Zineh I, et al. Physiologically based pharmacokinetic modeling in regulatory science: an update from the U.S. Food and Drug Administration's Office of Clinical Pharmacology. J Pharm Sci. 2019;108(1):21–25. https://doi.org/10.1016/j.xphs.2018.10.033