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

Dr. Makbul Hussain Choudhury

Assistant Professor, Rahman Institute of Pharmaceutical Sciences and Research, Guwahati, Assam, India.

Corresponding author: makbulchy200@gmail.com

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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 (fm) and inhibitor exposure relative to potency ([I]/Ki). We derived the ceiling achievable at complete inhibition, then ran 20,000-draw Monte Carlo analyses with uncertainty in fm and in Ki, 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−fm), so the achievable magnitude is bounded by fm alone. A substrate with fm 0.50 cannot exceed 2.0-fold and one with fm 0.60 cannot exceed 2.5-fold, however potent the inhibitor; fm 0.90 permits 10-fold and fm 0.95 permits 20-fold. Uncertainty in fm dominated uncertainty in Ki: with fm known to a standard deviation of 0.15 and Ki known exactly, the 5th-to-95th interval for the AUC ratio spanned 16.4-fold, whereas a tenfold uncertainty in Ki with fm 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 fm 0.50, 57% at fm 0.80 and 55% at fm 0.85.

Conclusion: A severity category assigned without reference to fm 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 fm and an interval rather than a label alone.

Keywords: Drug Interactions, Cytochrome P450; Fraction Metabolised, Static Mechanistic Model, Clinical Decision Support, Alert Fatigue.

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 [1,2]. 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 [3–5].

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 [6–8].

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 double in exposure by more than twofold no matter what is co-prescribed, because the other half of its clearance is untouched.

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 — fm — 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 fm, 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 fm; to compute the AUC ratio across a grid of fm and inhibitor potency; to determine whether uncertainty in fm or in Ki 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, in which the ratio of victim-drug exposure with and without the inhibitor is

$$AUCR = 1 / [\, fm / (1 + [I]/Ki) + (1 - fm) \,] \qquad (1)$$

where fm 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 Ki 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 fm alone:

$$AUCR(max) = 1 / (1 - fm) \qquad (2)$$

Equation 2 is elementary and well known to pharmacokineticists [6,9]. 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.

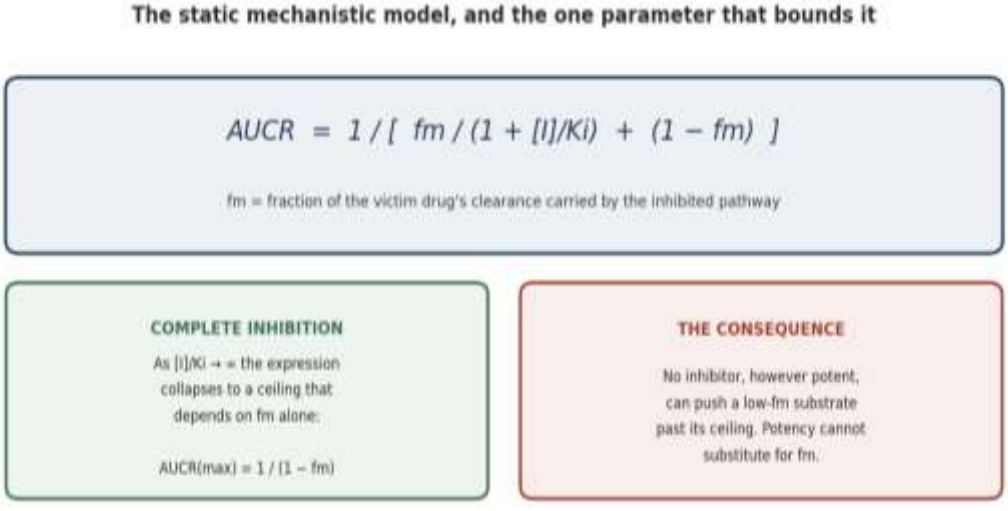

Figure 1. The static mechanistic model and the ceiling that follows from it at complete inhibition.

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 [7,8]. 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. fm 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 Ki values and the uncertainty in the appropriate concentration to use at the enzyme [9,10].

Two one-at-a-time analyses then varied fm uncertainty from 0 to 0.20 with Ki fixed, and Ki uncertainty from 1- to 10-fold with fm fixed, to establish which parameter dominates. A final analysis swept fm 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; the complete script with all seeds accompanies this paper. 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
fm	Fraction of victim-drug clearance through the inhibited pathway	Logit-scale perturbation, base-case SD 0.12; varied 0 to 0.20
[I]/Ki	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 fm. A substrate with fm 0.30 cannot exceed 1.43-fold. One with fm 0.50 cannot exceed 2.0-fold, and one with fm 0.60 cannot exceed 2.5-fold. At fm 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 fm below 0.50 cannot reach the moderate band at all. One with fm 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 fm 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 fm produce large differences in consequence, which is precisely where fm 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.

fm	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

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

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

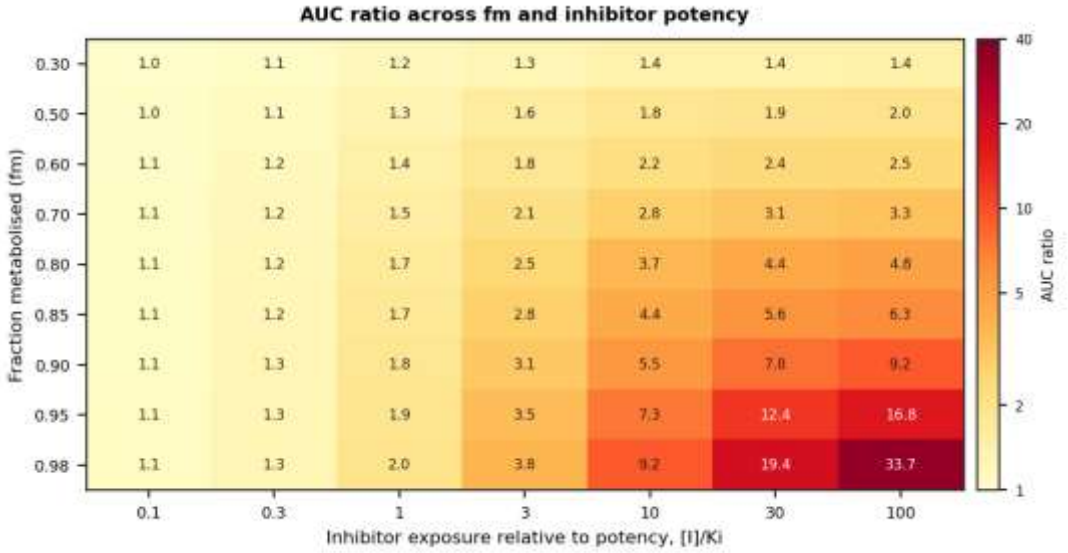

Figure 3. AUC ratio across fraction metabolised and inhibitor exposure relative to potency.

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

fm	[I]/Ki = 0.1	[I]/Ki = 0.3	[I]/Ki = 1	[I]/Ki = 3	[I]/Ki = 10	[I]/Ki = 30	[I]/Ki = 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

3.3 Which uncertainty matters

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

At the base-case settings the contrast is stark: fm uncertainty of 0.15 alone produced an interval of 1.56 to 25.56 — spanning three severity bands — while threefold Ki 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. Fraction metabolised is inferred, often indirectly, frequently from a single clinical study, and is rarely quoted at all in the resources a prescriber consults. The better-characterised parameter is the less consequential one.

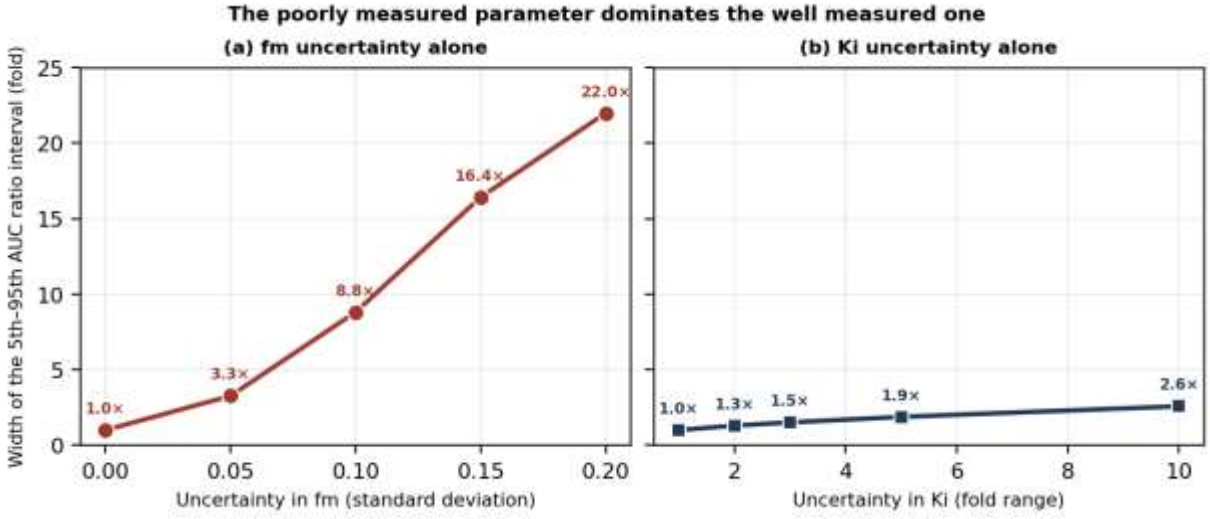

Figure 4. Width of the predicted AUC ratio interval attributable to uncertainty in fm alone and in Ki alone.

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

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

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 fm 0.50 and a potent inhibitor, the point estimate was 1.94 — weak — but 44% of draws fell in the moderate band. For fm 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 6 sweeps fm under a potent inhibitor and records how often the point-estimate band survives. Agreement was best where fm sat comfortably inside a band — 81% at fm 0.65 and 71% at fm 0.95 — and collapsed at the boundaries, to 56% at fm 0.50, 57% at fm 0.80 and 55% at fm 0.85.

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 fm 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 fm 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.

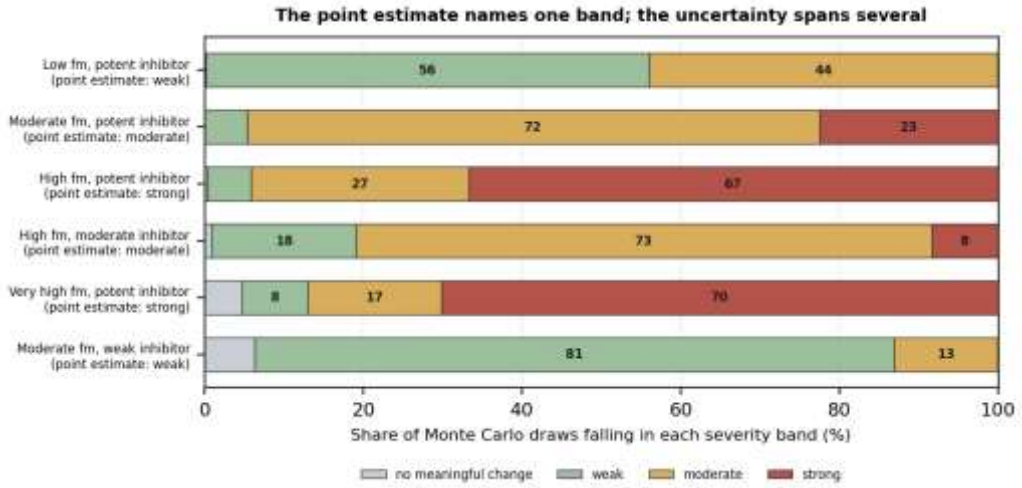

Figure 5. Distribution of Monte Carlo draws across severity bands for six worked scenarios, against the band named by the point estimate.

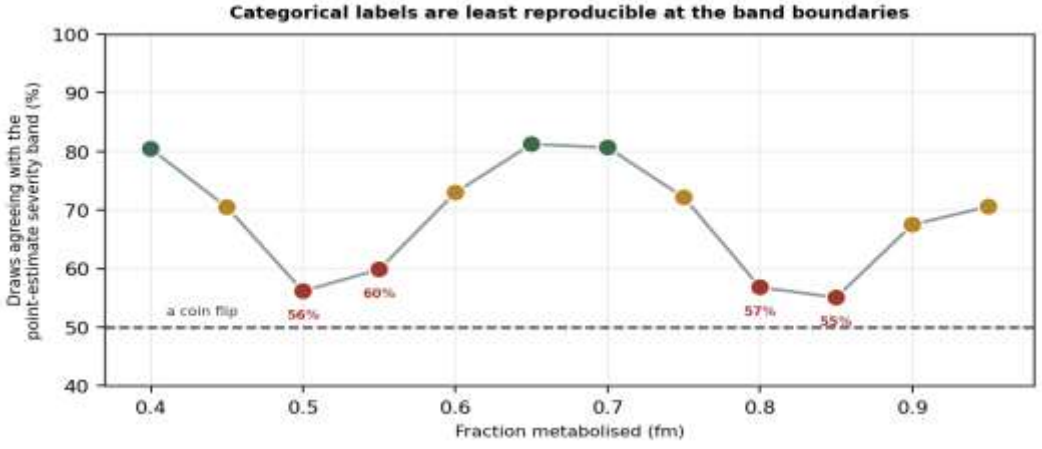

Figure 6. Proportion of draws agreeing with the point-estimate severity band, across fraction metabolised.

Table 5. Worked scenarios under joint uncertainty.

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

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

fm	Point-estimate band	Median AUCR	5th–95th	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

4. DISCUSSION

4.1 Principal findings

Three findings follow. The magnitude of a reversible metabolic interaction is bounded by the fraction metabolised: substrates with fm below 0.50 cannot reach the moderate band and those below 0.80 cannot reach the strong band, whatever the inhibitor. Uncertainty in fm dominates uncertainty in Ki 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 fm estimate that could as easily have produced moderate.

4.2 Relation to existing work

The static mechanistic model and the fm dependence are textbook clinical pharmacology and are embedded in regulatory guidance on interaction assessment [6–9]. The difficulty of estimating fm, and the sensitivity of interaction predictions to it, are recognised in the modelling literature [9,10]. Inconsistency

between interaction compendia in the severity assigned to the same pair has been documented repeatedly [3–5], and override rates for interaction alerts are high [1,2].

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 fm?

4.3 Implications

Figure 7 and Table 7 set out four recommendations. Two deserve comment.

Audit existing content against the ceiling. Equation 2 requires only fm, and for many widely warned-about substrates an fm 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.

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. A prescriber told major has a binary choice between overriding and not, which is why the override rate is what it is.

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

Table 7. Recommendations.

Recommendation	Addresses	Cost	Evidence here
Audit assigned severities against the fm ceiling	Categories the pharmacology forbids	One calculation per pair	Section 3.1
Publish fm 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 fm characterisation over further Ki 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

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. Physiologically based models handle these and are the appropriate tool for a specific prediction [11,12].

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 fm 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 fm and therefore raise the ceiling. A prescriber facing a patient who is a poor metaboliser by another route is dealing with a higher fm than the population value.

The uncertainty distributions are ours. An fm standard deviation of 0.12 and a threefold Ki 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 fm 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 $1/(1-fm)$. 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 fm 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 fm 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.

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Conflicts of interes: The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Makbul Hussain Choudhury	✓		✓	✓		✓				✓	✓	✓		✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

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