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DRUG-DRUG INTERACTIONS IN INTENSIVE CARE UNIT PRESCRIPTIONS: PREVALENCE AND SEVERITY

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1. INTRODUCTION

Patients in an intensive care unit (ICU) rarely take fewer than a dozen drugs at the same time. Sedatives, analgesics, vasoactive infusions, antimicrobials, stress-ulcer prophylaxis, anticoagulants and insulin are layered on top of whatever the patient arrived with, and the list is rewritten almost daily as organ function shifts. Every added agent increases the number of possible pairs, and the number of pairs grows much faster than the number of drugs. Early work on medication safety showed that critically ill

Abstract

Patients in intensive care units receive many drugs at once, often through several infusion lines and under rapidly changing organ function, so interacting combinations are almost unavoidable. This narrative review draws on published surveys, cohort studies, consensus work and guidelines to describe how often potential drug-drug interactions are found in critical care prescriptions and how severe they are judged to be. It reports no new patient data. The literature shows that most patients are exposed to at least one potential interaction, yet only a minority are clinically important. Severity ratings differ between compendia, outcome data are sparse, and context-aware screening tools are still needed.

patients suffer more preventable adverse drug events than patients on general wards, largely because they receive more drugs and in more hazardous forms [1, 2]. Drug-drug interactions (DDIs) are one recognised route

to that harm, though far from the only one. Intensive care also compresses the time available to catch an error: a drug started at midnight can reach steady state, and start interacting, well before the morning review.

A DDI occurs when one drug changes the amount, the action or the tolerability of another. Pharmacokinetic interactions alter absorption, distribution, metabolism or excretion, while pharmacodynamic interactions arise when two drugs act on the same or opposing physiological targets. The distinction matters in practice, because the first kind can often be predicted from enzyme or transporter data and the second from the pharmacology of the drug classes involved [3]. Most hospital screening systems do not separate them well. They simply report that a pair of drugs is on a list, and leave the prescriber to judge whether this particular patient, on this particular day, is at risk. Two further terms recur in the literature. A potential interaction is one that a reference source lists for a pair of drugs given together, while a clinically manifest one is an interaction that has actually changed the patient's course. Most ICU studies can only count the first.

This review asks two plain questions about ICU prescriptions: how common are potential interactions, and how serious are they when graded by the tools clinicians actually use? It then looks at the combinations that recur in the literature, the way they are detected, and what pharmacists and prescribers can do about them. The review reports no new patient data and does not claim to be a systematic search. It collects what published surveys, cohort studies, consensus documents and regulatory guidance say, and it is candid about where that evidence is thin [4, 5]. Where figures are quoted they come from the cited papers, and where the studies disagree the text says so instead of choosing a winner.

2. ICU PRESCRIBING AND VULNERABILITY

Critical illness changes how the body handles drugs. Fluid resuscitation and capillary leak enlarge the volume of distribution of hydrophilic agents, hypoalbuminaemia raises the free fraction of highly protein-bound ones,

and altered hepatic blood flow changes the clearance of drugs with high extraction ratios [6, 7]. Kidney function may be reduced by acute injury or, less obviously, increased in young trauma and sepsis patients, so that the same dose is too much in one bed and too little in the next. Pharmacokinetic reviews in critically ill adults stress that standard dosing derived from healthy volunteers is a starting point, not a guarantee [6, 7]. Protein binding, tissue penetration and renal replacement therapy add yet more variability, so two patients with the same diagnosis can need very different doses of the same drug.

Metabolic interactions are shaped by the same disturbances. Systemic inflammation is known to suppress the expression of several cytochrome P450 enzymes, and organ dysfunction narrows the reserve that normally absorbs an inhibitor's effect. A patient with sepsis who is given an azole antifungal on top of a benzodiazepine may therefore show a greater and longer-lasting rise in sedative exposure than the interaction label would suggest [6]. The reverse also happens: enzyme inducers such as rifampicin or phenytoin can lower concentrations of other drugs sharply, and the effect lingers after the inducer is stopped. Neither situation is easy to see from the prescription chart alone. Gut oedema, vomiting and continuous enteral feeding can also make oral absorption erratic, which complicates interactions that depend on binding in the gut, such as chelation of fluoroquinolones by cations in feeds [6, 7].

Pharmacodynamic vulnerability is just as real. Haemodynamic instability, hypokalaemia, hypomagnesaemia and acidosis lower the threshold for arrhythmia, so that a modest QT-prolonging effect from one drug becomes dangerous when a second is added [8, 9]. Deep sedation removes the warning signs that a conscious patient would give, such as drowsiness, nausea or palpitations. Renal impairment amplifies potassium retention and the toxicity of renally cleared drugs. In short, the ICU concentrates physiological risk factors in the very setting where interacting drugs are most densely prescribed. Older patients are particularly exposed to these effects [10]. Glycaemic control offers another example: insulin infusions are tightly

protocolised, yet corticosteroids, vasopressors and some anti-infectives push glucose in either direction, so a drug that looks unrelated can quietly undo the target. Anticoagulated patients are a case in point: a small rise in INR that would be unremarkable on a ward can be hazardous when an invasive line is about to be placed or a drain removed.

Route of administration adds another layer of vulnerability. Many ICU patients receive drugs through enteral tubes while on continuous feeding, and critical illness commonly slows gastric emptying and alters gut perfusion, so absorption of oral agents can be delayed, reduced or erratic [6, 7]. Binding to feed components or to co-administered cations is a recognised concern for some drugs, which is why timing relative to feeding is often specified. The result is that a pharmacokinetic interaction of the chelation or adsorption type may be harder to predict in a tube-fed patient than in an ambulant one. Switching to the intravenous route avoids some of these problems but brings its own, such as compatibility in shared lines and the loss of an easy oral step-down later.

Older patients add a further layer. They arrive with long medication lists, reduced renal and hepatic reserve and, often, several prescribers who have never compared notes. Studies of elderly people hospitalised for drug toxicity found that a recently started interacting drug was a recurring feature of the admission, with combinations such as digoxin and clarithromycin standing out [11, 12]. When that patient is then admitted to intensive care, the home regimen is frequently continued alongside new acute-care drugs, and the interaction burden of the two lists is rarely reviewed together [10].

Working conditions also matter. ICU orders are frequently verbal, doses are titrated against targets rather than fixed, and several prescribers may touch the same chart across a single shift. Handovers introduce gaps. A review of the evidence from critical care units found that pharmacists who joined the clinical team were associated with fewer medication errors and adverse drug events, and with lower drug costs [13]. Current guidance on safe medication use in critical care builds on this finding and treats an ICU pharmacist as a

core member of the team rather than an optional extra [4]. Alert displays tuned for ordinary wards also behave poorly in a unit where nearly every patient triggers the same handful of warnings.

3. PREVALENCE AND SEVERITY

Published prevalence figures for potential DDIs in the ICU are high, but they vary more than the underlying practice probably does. Surveys of cardiothoracic, medical and mixed units in the United States and Europe consistently found that a majority of patients were exposed to at least one potential interaction during their stay, and that exposure rose with the number of drugs and the length of stay [14, 15, 16]. The exact percentage depends on which database was used, which pairs were counted, whether interactions were counted per patient or per prescription, and how long the observation window ran. Comparing one paper with another therefore needs care. Length of stay is itself a confounder, because a patient who remains for weeks accumulates more drugs and more opportunities to be counted.

A systematic review and meta-analysis of studies in adult ICUs confirmed that heterogeneity was the dominant feature of the evidence: pooled estimates of exposure were high, but the studies differed so much in design and screening tools that a single prevalence figure is hard to defend [17]. A large multicentre retrospective study from the Netherlands took a more clinical approach, asking which potential interactions were judged relevant for intensive care patients rather than simply listing all that a database could generate [18]. Its message was that filtering by clinical relevance shrinks the problem considerably, though it does not remove it. The two papers are complementary: one shows how large the numbers can look, the other how far they shrink once clinical judgement is applied.

Severity is the second difficulty. Different interaction compendia grade the same pair differently, sometimes by a full category. A comparison of four widely used compendia found low agreement on which interactions were severe [19], and a consensus panel that tried to agree on combinations that should not

be dispensed together produced a deliberately short list for that reason [20]. Even drugs carrying a boxed warning about contraindicated co-medication were not consistently flagged by the screening programmes that were compared [21]. Any statement that a given share of ICU interactions are severe is therefore tied to the database behind it. In practice, a unit that switches to a stricter compendium will report fewer severe pairs without any change in patient care. That is a statistical artefact, not an improvement.

Potential harm is not the same as actual harm. Many flagged pairs are given without incident, because the dose is low, the exposure short, or monitoring is already in place. Still, signals exist. In a Brazilian teaching hospital, exposure to interacting drugs was associated with longer hospital stay and higher cost, although the link may partly reflect sicker patients receiving more drugs [22]. A study of a large outpatient insurance population found excess hospitalisation after exposure to known interacting combinations [23]. ICU data linking specific interactions to patient-level outcomes remain sparse, and causal attribution is hard in a setting where almost everything is happening at once. Comparison with general wards helps to set the scale. Studies of internal medicine inpatients and of regional prescription databases also report interactions in a sizeable fraction of patients, with the burden climbing as the number of prescribed drugs rises [24, 25]. The resource consequences are real, since an ICU day is among the costliest in hospital care [26].

Surveys also agree, broadly, on which drug groups appear most often. Sedatives and analgesics, anti-infectives, cardiovascular agents and anticoagulants dominate the lists, which fits their near-universal use in critical care [14, 15, 16]. Comparisons with general medical wards suggest that the ICU carries more potential interactions per patient, mostly because of the greater number of drugs, but that the proportion of high-severity pairs is not dramatically different [24, 25]. Intensive care is, in this respect, an amplifier of an ordinary hospital problem rather than a separate one. The pattern is unsurprising.

These classes are used in almost every unit, they are often given together, and several of them are metabolised by the same few enzymes, so overlap is built into routine practice.

Case mix changes the picture. Cardiothoracic units, with their heavy use of antiarrhythmics, anticoagulants and vasoactive drugs, tend to generate cardiovascular pairs, whereas medical units report relatively more combinations of sedatives, anti-infectives and acid-suppressing agents [14, 16]. Neither pattern is a defect of the unit. Each is the visible shadow of the drugs the patients need. The practical implication is that a screening rule set borrowed from another unit may spend much of its effort on pairs that are rare locally and miss the ones that matter, so a periodic look at a unit's own interaction data is a sensible investment [15, 17].

There is an economic side too. An ICU day is among the most expensive days in hospital care, and any interaction that prolongs sedation, delays weaning or triggers renal injury adds days at that rate [26]. The costs are hard to isolate, since ICU stays are multifactorial, but the logic is straightforward: an interaction that costs even a few hours of ventilator time carries a price, and one that causes a serious bleed or arrhythmia carries a far larger one. Hospital managers sometimes read such figures as an argument for blanket restriction of drug combinations, but clinicians know that a rigid ban would also block therapy that patients need.

4. COMMON HIGH-RISK COMBINATIONS

Across the surveys, a fairly stable set of combinations recurs. They are summarised in table 1, grouped by the main mechanism of concern, and the number of entries in each group is shown in fig. 1. The table is a synthesis of examples described in the literature and in interaction guidance rather than a ranking by frequency, and it should not be read as a complete list [20, 27, 28]. Several of the pairs involve drugs that are hard to avoid in critical care, which is exactly why they keep appearing. Because the table collects examples instead of frequencies, it

works best as a prompt for review. Entries were chosen because they recur in surveys, appear in regulatory or consensus documents, or have a mechanism that can be monitored at the bedside.

Pharmacokinetic interactions through cytochrome P450 3A4 and 2C9 account for several of the best-known examples. Amiodarone inhibits warfarin metabolism and typically calls for a substantial reduction in the warfarin dose, with close INR monitoring over the following weeks because of the drug's long half-life [20, 27]. Macrolides such as clarithromycin raise exposure to simvastatin and certain other statins, with a risk of myopathy and rhabdomyolysis. Azole antifungals prolong the effect of midazolam by blocking its oxidation, an interaction that is easy to miss when sedation is already deep [6, 7]. Regulatory guidance describes how enzyme and transporter studies are designed to predict such effects before a drug is marketed [27, 28]. Induction is the less discussed direction. Rifampicin, carbamazepine and phenytoin can lower exposure to anticoagulants, azoles and many other drugs, sometimes for weeks after the inducer has been stopped [20, 27].

Table 1: Examples of interacting combinations in critical care prescribing, as described in the literature

Combination	Reported concern	Ref.
Amiodarone with warfarin CYP2C9 inhibition	Higher INR and bleeding risk; warfarin dose usually needs a substantial reduction	[20, 27]
Clarithromycin with simvastatin CYP3A4 inhibition	Raised statin exposure, with myopathy and rhabdomyolysis	[20, 28]
Fluconazole with midazolam CYP3A4 inhibition	Prolonged sedation and delayed weaning from ventilation	[6, 7]
Haloperidol with amiodarone	Additive QT prolongation and risk of torsades de pointes	[8, 9]
Fluoroquinolone with ondansetron	Additive repolarisation delay, worse with low potassium or magnesium	[8, 9]
Fentanyl with midazolam	Deeper sedation and respiratory depression; hypotension in unstable patients	[4, 29]
Linezolid with vasopressors	Weak MAO inhibition may enhance the pressor response	[20, 28]

Combination	Reported concern	Ref.
ACE inhibitor with potassium supplement	Hyperkalaemia, especially with renal impairment	[11, 12]
Ketorolac with enoxaparin	Added bleeding risk from platelet and anticoagulant effects	[4, 20]
Aminoglycoside with loop diuretic	Added nephrotoxicity and ototoxicity	[20, 28]

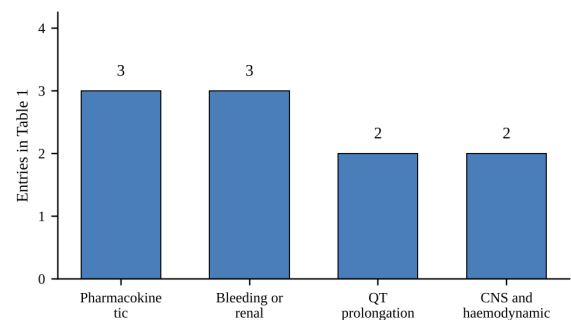


Fig. 1: Number of entries in table 1 by main mechanism of concern

QT prolongation is the pharmacodynamic interaction that attracts most attention. Haloperidol, ondansetron, several macrolides and fluoroquinolones, and amiodarone each lengthen repolarisation to some degree, and their effects add up [8]. The risk of torsades de pointes rises with female sex, structural heart disease, bradycardia and low potassium or magnesium, all common in the ICU. A validated score developed in hospitalised patients gives clinicians a way to count these risk factors and to decide where a baseline ECG and electrolyte correction are justified before a second QT-active drug is added [9]. Practical steps are modest: check the baseline ECG, correct potassium and magnesium, and review whether every QT-active drug on the chart is still needed [8, 9].

Additive central nervous system depression is the other everyday concern. Opioids combined with benzodiazepines deepen sedation and respiratory depression, and the guideline on pain, agitation and delirium recommends light sedation strategies with non-benzodiazepine agents in many ventilated adults, partly to avoid such stacking [29]. Nephrotoxic and electrolyte-active combinations, such as an ACE inhibitor with potassium supplements or a potassium-sparing diuretic in a patient with renal impairment, can cause hyperkalaemia within days [11, 12]. Anticoagulants

combined with ketorolac or other antiplatelet effects remain a familiar route to bleeding [4, 20]. Hypotension is a related worry. Propofol, dexmedetomidine and opioids all lower blood pressure, and when they are added to vasodilators or to antihypertensives continued from home, the vasopressor requirement can rise without any obvious change in the patient's illness. Prescribers sometimes treat that number as a disease signal rather than a drug effect, which is why a regular look at the infusion list is worthwhile [4, 29].

Transplant, haematology and infectious disease patients bring their own high-stakes pairs. Azole antifungals such as voriconazole raise exposure to the calcineurin inhibitors tacrolimus and ciclosporin to a degree that labelling advises a substantial reduction in the immunosuppressant dose when the azole is started, with drug-level monitoring afterwards [27, 28]. Rifampicin does the opposite and can drop calcineurin inhibitor levels enough to threaten a graft. These are examples where the interaction is predictable, large and measurable, and where therapeutic drug monitoring turns a hazard into a manageable adjustment. Where levels cannot be measured, the safer course is to pick a non-interacting antifungal or to agree the dose change with the transplant team beforehand.

A few combinations are less obvious. Linezolid is a weak, reversible monoamine oxidase inhibitor, and product information advises caution when it is used with adrenergic agents or serotonergic drugs. In practice that means watching blood pressure when vasopressors are running and being alert to agitation, clonus or fever that could signal serotonin toxicity. Aminoglycosides with loop diuretics add ototoxic and nephrotoxic risk. None of these is a reason to withhold a needed antimicrobial, but each is a reason to document why the combination was chosen and what is being watched [20, 28].

The same drug pair can be low risk in one patient and hazardous in another. Dose, route, duration, baseline renal and hepatic function, concurrent electrolyte disturbance and genetic variation in metabolising enzymes all modify the outcome. Static lists, such as table 1, tell the reader where to look. They cannot say how worried to be. That judgement belongs at

the bedside, supported by monitoring data and a clear idea of what the alternatives are [20, 27]. The trade-off is between sensitivity and usefulness: a list long enough to catch every hazard is too long to read, and a list short enough to read will miss some.

5. DETECTION AND MANAGEMENT

A regulatory perspective explains part of the difficulty. Pre-marketing interaction studies are usually carried out in healthy volunteers or in stable patients, using probe drugs chosen to represent enzyme or transporter pathways, and the resulting label statements are written for that population [27, 28]. Critically ill patients, with unstable organ function, multiple inhibitors and variable binding, sit well outside the studied range. Labelling is therefore a reasonable starting point and not a guarantee, and clinicians who manage ICU interactions often have to extrapolate from mechanism, case reports and monitoring data.

Most hospitals rely on electronic screening built into prescribing or pharmacy systems. Comparisons of commercial interaction software for ICU use have shown that the programmes differ in sensitivity and in how they grade severity, so the choice of product shapes what the unit sees [30]. A systematic review of interaction software in clinical practice found that these tools can reduce the prescribing of contraindicated pairs and improve detection, but that evidence of improved patient outcomes was limited [31]. Detection is necessary, but it is clearly not sufficient. Software also depends on accurate, complete medication records. If an infusion is charted as a free-text order, or a home medicine was never entered, the engine has nothing to compare, and a silent system can create false reassurance.

The main practical problem is alert volume. When a system flags every theoretical interaction, prescribers learn to click past the warnings, and the occasional important alert is lost among trivial ones. Evaluations of clinical decision support for DDI detection point to the same remedies again and again: restrict interruptive alerts to high-severity pairs, tailor them to the care setting, and give the prescriber an actionable alternative rather than just a warning [32]. Few ICUs have the

resources to do this thoroughly, and local tuning is often left to a pharmacist's spare time. Good practice here is as much about governance as about technology, since someone has to own the alert rules and review how they are performing.

Pharmacists have the best-documented record of success in this area. An ICU pharmacist who reviews orders daily can place an interaction in clinical context, which a screening engine cannot do. One study of a critical care pharmacist's work reported that a large share of identified interactions led to a change in therapy or to a monitoring plan [33], and a trial that combined an electronic decision support system with personal pharmacist intervention in an ICU reported fewer adverse drug reactions in the intervention period [34]. Broader work on pharmacist involvement in the direct care of critically ill patients describes favourable clinical and economic outcomes [35]. These studies are not randomised comparisons of every service model, and effects on mortality are harder to show than effects on error rates, so the strongest claims are about process and safety rather than survival.

When an interaction is found, the response usually follows a short ladder. First, ask whether both drugs are needed. Second, look for a non-interacting alternative in the same class, such as a different statin, antifungal or antiemetic. Third, adjust the dose or timing and set up monitoring that matches the mechanism: an ECG and electrolytes for QT-active pairs, INR or anti-Xa levels for anticoagulant combinations, potassium and creatinine for renin-angiotensin drugs, and sedation scores for combined depressants. Fourth, write the plan down so that the next shift does not reverse it [20, 29]. A short note in the chart, written in plain language, is usually enough, and it saves the pharmacist from being asked the same question at each handover.

Monitoring turns a flagged interaction into something that can be managed. When an enzyme inhibitor or inducer is started, its effect on a substrate drug develops over days rather than hours, and the effect fades just as slowly after withdrawal, so a stable concentration or laboratory value on day two

may not hold on day six [27, 28]. Warfarin is the familiar example, where the international normalised ratio is checked more often after any change in interacting therapy. Heparin dosing guided by anti-Xa activity follows the same logic. A useful habit is to record the start and stop dates of the perpetrator drug beside the monitoring plan, so that the review after discontinuation is not forgotten when the patient moves out of the unit.

Admission and transfer are natural checkpoints. Interaction exposure is already common at hospital entry, and the ICU stay then adds a fresh set of drugs on top of the home regimen [24, 25]. A structured reconciliation that asks which long-term drugs are still needed, which are being given in duplicate, and which should be held while the patient is unstable removes some pairs before they cause trouble. Deprescribing at ICU discharge matters too, because drugs started for acute indications, such as stress-ulcer prophylaxis or antipsychotics for delirium, have a habit of continuing on the ward without a clear stop date, carrying their interactions with them [10].

Education has a place as well, though it is not a substitute for system design. Experienced clinicians recognise a surprising number of interactions unaided, yet studies of pharmacists asked to identify interacting pairs showed that a sizeable proportion went unrecognised without a reference source [36]. In a crowded ICU, memory alone is not a reliable safeguard. Teaching works best when it targets the handful of combinations that recur in the unit's own data, and when it is paired with decision support that reinforces rather than contradicts it [32, 36]. A short laminated list at the nurses' station, or a standing item at the weekly unit meeting, costs little and can keep the highest-risk pairs in people's minds. Nursing staff deserve a place in that teaching, since they see the early effects of an interaction, such as oversedation, falling blood pressure or an abnormal rhythm, before anyone else does.

6. LIMITATIONS AND FUTURE DIRECTIONS

The literature has clear limits. Most studies are retrospective and count potential

interactions from prescription records, not harm that was actually observed. Screening tools differ, observation windows differ, and the case mix of an ICU in one country may bear little resemblance to that in another. Severity grading depends on the database, so the same prescription list can generate quite different totals [17, 19, 21]. Publication bias is also plausible, since units with unremarkable interaction rates have less reason to write them up. Randomised or well-matched comparative designs are almost absent, which means that estimates of the benefit of any specific intervention rest largely on before-and-after data. Language and database restrictions in the underlying reviews may also have left out units that publish in other settings or other languages.

Several directions look promising. Alerts that take account of renal function, electrolytes, ECG intervals and current doses would be far more specific than pair-based lists, and risk scores for QT prolongation point in that direction [9]. Pharmacogenetic information could refine predictions where metabolism is polymorphic. Prospective, outcome-oriented studies are needed to show which interactions in the ICU actually cause harm, and which interventions prevent it at an acceptable workload. Until then, the combination of tailored decision support and routine pharmacist review remains the best-supported approach [4, 33, 34]. Practical implementation matters as much as invention here. A tool that reduces alert volume by half and is used is worth more than a brilliant one that nobody opens, so usability testing with nurses, intensivists and pharmacists should be treated as part of the research. Computable phenotypes drawn from electronic records could also help to target the sickest patients first.

A last point concerns reporting. Studies of ICU interactions would be easier to compare if they stated the database, the version, the severity categories counted and the unit of analysis, and if they separated interactions that were acted upon from those that were merely displayed. Journals and reviewers could ask for that as a matter of course. Small changes of this kind would do more for the usefulness of the field than another set of

prevalence figures calculated in yet another way [17, 18]. Common data standards for medication records, shared across units, would allow pooled analyses that no single hospital could manage alone.

7. CONCLUSION

Potential drug-drug interactions are the rule rather than the exception in ICU prescribing. Published surveys agree that most patients are exposed to at least one, that exposure rises with the number of drugs and the length of stay, and that sedatives, anti-infectives, cardiovascular drugs and anticoagulants make up most of the pairs involved [14, 15, 16, 17]. Whether a given figure for severity is believable depends on the compendium that produced it, since agreement between databases is poor [19, 21]. Sources agree less on how much of this exposure translates into harm, and the answer almost certainly differs from unit to unit. That uncertainty should make units cautious about league tables of interaction rates, which can mislead when the underlying tool is not the same.

What helps is fairly consistent across the literature: filtered, context-aware alerts, routine review by an ICU pharmacist, monitoring matched to the mechanism of each interaction, and a habit of documenting the reasoning when a risky pair is unavoidable [4, 34, 35]. What is missing is outcome evidence. Until prospective studies link particular interactions to patient harm, units will do best to focus on the few combinations that are both frequent and dangerous, and to review them often. Regular review of a unit's own interaction data, shared with prescribers in plain terms, is a modest step that most services can afford. Where the evidence is thin, the safest assumption is that a flagged pair deserves a look and a documented decision, not automatic alarm and not automatic dismissal.

8. ABBREVIATIONS

ACE-Angiotensin-converting enzyme,
CYP-Cytochrome P450, DDI-Drug-drug
interaction, ECG-Electrocardiogram,
ICU-Intensive care unit, INR-International
normalised ratio, MAO-Monoamine oxidase,
QT-Interval between Q wave and end of T wave,
Anti-Xa-Anti-factor Xa activity

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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