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DRUG INTERACTIONS (1): GENERAL PRINCIPLES

- **Drugs interactions are an important cause of adverse drug reactions which can lead to an increased risk of morbidity and mortality**
- **Increasing age and polypharmacy are major risk factors for drug interactions**
- **The most clinically relevant drug interactions include those involving drugs with a narrow therapeutic index**
- **The most important way to reduce the risk of patient harm is to recognise the potential for a drug interaction in an individual patient and to take appropriate action to avoid harm occurring**

INTRODUCTION

A drug interaction occurs when the effects of a medicine are altered by the presence of other factors such as another medicine (including an over-the-counter medicine or herbal medicine), food or drink.[1-3] **Drug-drug interactions (DDIs) are an important cause of adverse drug reactions (ADRs) which can lead to an increased risk of morbidity and mortality.**[2-8] Knowledge of the pharmacodynamic and pharmacokinetic properties of a medicine can help to reduce the risk of a serious adverse outcome from a DDI.[9] This is the first of 2 bulletins which will outline the principles of DDIs and suggest ways to minimise the risk associated with them. The second bulletin will review some frequently asked questions on drug interactions received by the NMIC.

EPIDEMIOLOGY

The number of potential DDIs far outweighs the number of ADRs they cause in clinical practice; the number of clinically relevant DDIs ranges from 3 to 20% in various studies.[3] Clinically relevant DDIs are associated with an increased risk of hospitalisation and of prolonging hospitalisation; a large study found that up to 7% of hospitalisations were related to an ADR, of which 1 in 6 were due to a DDI.[8] **Drug combinations which have been associated with hospitalisations include: 1) warfarin and aspirin; 2) non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin; 3) warfarin and other interacting drugs; 4) diuretic combinations; 5) diuretics and angiotensin-converting enzyme inhibitors (ACEIs); and 6) digoxin and interacting drugs.**[2,3] Drug interactions have also been associated with the withdrawal of some medicines from the market (e.g. terfenadine, cisapride and cerivastatin).[10-13]

Clinically relevant DDIs may result in toxicity (e.g. increased risk of rhabdomyolysis with co-administration of statins and azole antifungals) or loss of efficacy of a drug (e.g. co-administration of oral contraceptives with rifampicin).[1,9,10,14] DDIs may also have advantageous effects in clinical practice, such as the use of ritonavir to boost the effects of other protease inhibitors in the treatment of human immunodeficiency virus.[1] **It is important to be able to predict when a potential DDI is likely to have significant adverse clinical consequences for the patient and take appropriate action.**[15] The clinical consequence of a DDI can be difficult to predict and varies between individual patients.[1,9] A number of drug and patient characteristics are associated with an increased risk of clinically significant DDIs occurring as shown in Table 1. Increasing age and polypharmacy (the use of ≥5 medicines) are major risk factors for a DDI occurring.[9,14,16-18] A study of older adults with polypharmacy found that the probability of ≥ 1 DDI occurring was 50% for persons taking 5 to 9 drugs, 81% with 10 to 14 drugs, 92% with 15 to 19 drugs and 100% with ≥ 20 drugs (**the addition of each drug was associated with a 12% increased risk of a potential DDI).**[19] The incidence of polypharmacy increases with age;[19-21] an Irish study (2019) found that the proportion of patients aged 45 to 54 years with polypharmacy was 38.6%, which increased to 82.6% in those aged ≥75 years.[21]

Table 1: Drug and patient characteristics associated with clinically significant drug interactions[17]

Drug factors include:	Patient factors include:

• Narrow therapeutic index
  ○ e.g. digoxin, warfarin, ciclosporin, lithium
• Steep dose-response curve
  ○ e.g. sulphonylureas, verapamil, levodopa
• Saturable hepatic metabolism
  ○ e.g. phenytoin, theophylline
• Dose dependent on patient response
  ○ e.g. antiepileptics, immunosuppressants
	• Polypharmacy
	• Increasing age
	• Genetic predisposition
	• Multiple comorbidities
	• Renal impairment
	• Hepatic impairment
	• Diet
	• Number of prescribing physicians

MECHANISMS OF DRUG INTERACTIONS

DDIs occur by a number of mechanisms including pharmacodynamic (PD), pharmacokinetic (PK) and a combination of both.[1,15,16] A knowledge of the mechanism by which a DDI occurs may help to prevent or reduce the risk of an adverse reaction occurring.[15,16]

Pharmacodynamic Drug Interactions

PD interactions are those where the pharmacological effects of one drug are altered by the presence of another drug;[1,14,16] this can result in additive or antagonistic pharmacological effects which may result in toxicity or reduced efficacy of the drug.[14] Additive or synergistic interactions occur when two drugs with the same pharmacological effect are co-administered, while antagonistic interactions occur when drugs with opposing effects are used together.[1] **PD DDIs are relatively common in clinical practice**; adverse effects may be reduced by anticipating the potential interaction and taking appropriate measures (e.g. dose reduction).[15] PD DDIs can be a particular problem in the elderly and in patients taking drugs affecting the central nervous system (CNS).[3] Table 2 provides some examples of PD DDIs which result in an increased risk of adverse effects or loss of efficacy. A PD DDI may also be desired in clinical practice such as with the co-administration of antihypertensive drugs, anti-infective drugs or analgesics.[16]

Table 2: Examples of pharmacodynamic interactions[1,10,16]

Drugs	Interacting drug	Result of interaction
Additive interactions		
Drug that can cause prolonged QT interval e.g. amiodarone, disopyramide	Drug that can cause prolonged QT interval e.g. fluoroquinolones and erythromycin	Additive prolongation of QT interval, increased risk of Torsades de Pointes
Antihypertensives	Drugs that cause hypotension e.g. phenothiazines, sildenafil	Increased antihypertensive effects; orthostatic hypotension
CNS depressants e.g. opioids	CNS depressants e.g. benzodiazepines	Increased risk of drowsiness, respiratory depression, death
Platelet-related interactions e.g. NSAIDs, anticoagulants, anti-platelets	SSRIs, anticoagulants, NSAIDs	Increased risk of bleeding
ACE inhibitors	Potassium sparing diuretics e.g. spironolactone	Increased risk of hyperkalaemia
Antagonistic interactions		
ACE inhibitors or loop diuretics	NSAIDs	Antidiuretic effects opposed
Levodopa	Antipsychotics (those with dopamine antagonist effects)	Antiparkinsonian effects opposed

CNS-central nervous system; NSAID- non-steroidal anti-inflammatory drug; SSRI-selective serotonin reuptake inhibitor; ACE-angiotensin converting enzyme

Pharmacokinetic Drug Interactions

PK DDIs are those that affect the absorption, distribution, metabolism and excretion (ADME) of drugs.[1] PK DDIs may result in increased or decreased exposure to one or other drug, which results in a potential risk of increased toxicity of a drug or loss of efficacy.[1,3,17] Drug transporter proteins, which transport drugs and endogenous substances across tissue membranes, also contribute to DDIs.[1,10] **There is often overlap between the different transporters and other clearance mechanisms (including cytochrome P450 isoenzymes [CYP]).[1]**

Drug Transporters: There are different types of drug transporters which include the adenosine triphosphate (ATP)-binding cassette (ABC) family, which are generally efflux transporters (transport drugs/substances out of cells) and the solute carrier superfamily (SLC), which are mainly uptake transporters.[1,22,23] Numerous drugs have been identified as substrates of these transporter families, and their kinetics may be altered as a result of induction or inhibition.[14] There is often overlapping substrate specificities between the ABC and SLC families.[23]

The drug transporter P-glycoprotein (P-gp) is the most well-known of the ABC family.[1,22,23] P-gp is an efflux transporter that is present in tissues including the intestine, liver, kidney and brain.[1,10,22] Potential for a DDI occurs due to inhibition or induction of P-gp. For example, in the intestine, P-gp inhibitors (e.g. verapamil, amiodarone, clarithromycin) can reduce the efflux transport of a P-gp substrate (e.g. digoxin, ciclosporin, dabigatran) into the intestine, resulting in an increased plasma concentration of the substrate, while P-gp inducers (e.g. rifampicin and St John's wort) can increase efflux transport leading to a reduction in substrate plasma concentration.[1,10,16]

Absorption: The absorption of a drug may be increased or decreased by other substances (e.g. drugs, food).[1,15] The most common absorption mechanisms which may result in potentially clinically significant DDIs include the formation of drug complexes, alterations in gastric pH, and inhibition or induction of the drug transporter proteins (e.g. P-gp) and intestinal cytochrome P450 (CYP) enzymes (e.g. CYP3A4).[9,14] Table 3 gives some examples of how a drug interaction affects absorption and management strategies.

Table 3: Absorption type reactions[1,14,16]

Mechanism of effect	Examples	Result	Management
Chelation	Cation containing drugs (e.g. calcium, iron) and antacids with quinolones, tetracyclines, bisphosphonates	↓ absorption	Alter administration times
Changes in pH	PPI and H2-receptor antagonists with itraconazole capsules PPI and H2-receptor blockers with atazanavir	↓ absorption	Administer with acidic beverage PPI use with atazanavir not recommended

PPI-proton pump inhibitor; H2-receptor blockers-histamine type 2 receptor antagonists

Distribution: Following absorption, drugs are rapidly distributed around the body; factors influencing distribution include protein binding and drug transporters.[1,14] Most DDIs due to protein binding displacement are not thought to be clinically significant, as there is a transient increase in the concentration of the displaced drug which is cleared rapidly.[1,9,14,15,17]

Metabolism: Most clinically relevant DDIs are caused by cytochrome P450 (CYP) isoenzymes, which are located in tissues including the liver, intestine, kidney and lungs.[9,10,14] Their main role in drug metabolism is in Phase I reactions where they act as catalysts in the oxidation of drugs (substrates).[1,14,16] There are eight CYP isoenzymes which are recognised as being clinically relevant for drug metabolism; they have distinct but overlapping substrate specificities: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5.[14] CYP3A isoenzymes are involved in the metabolism of >50% of medicines.[3,10] Cytochrome activity may be affected by factors including other drugs, genetics (e.g. CYP2D6), food (e.g. grapefruit juice) and the environment (e.g. cigarette smoke).[9,10,14]

It is possible to predict potential DDIs by knowing which drugs are substrates and which drugs can inhibit or induce the CYP isoenzymes.[1,9,10] For example, midazolam is metabolised by CYP3A4; rifampicin is a known potent inducer of CYP3A4 (leading to reduced levels of midazolam) and itraconazole inhibits the activity of CYP3A4 (leading to increased levels of midazolam).[1]

Enzyme induction: Enzyme inducers may increase the metabolism of the substrate, thereby potentially resulting in a reduction in efficacy of the substrate.[9] For example, the plasma concentration of the direct oral anticoagulants (DOACs) apixaban and rivaroxaban is reduced by 50% when co-administered with carbamazepine, phenytoin or rifampicin, increasing the risk of thromboembolism.[3] **The onset of enzyme induction is gradual; DDIs can be delayed in onset (e.g. may take days or 2 to 3 weeks to develop fully) and are slow to resolve.[1,9]** it is important to note that stopping an interacting drug can also cause an adverse effect (e.g. an increase in warfarin's anticoagulant effect can occur on stopping carbamazepine).[1,3]

Enzyme inhibition of metabolism is the most important mechanism for DDIs, as it results in an increased drug concentration and exposure and an increased risk of toxicity.[1,9,15] Enzyme inhibition can occur rapidly (within 2 to 3 days); it begins within the first one or two doses of commencing the inhibitor and is maximal when steady state of the inhibitor has been reached.[1] **The most clinically relevant DDIs are those relating to drugs with a narrow therapeutic index.[1,9,10,16]** Small increases in exposure of drugs with a narrow therapeutic index (e.g. ciclosporin and warfarin), when co-administered with a weak inhibitor may be clinically relevant,[10,16] whereas for drugs with a wide therapeutic index (e.g. omeprazole), even a marked increase in exposure due to a potent inhibitor might not be clinically relevant.[1]

There is frequently overlap between CYP3A4 and P-gp substrates, inhibitors and inducers.[1] Table 4 provides examples of some common substrates, inducers and inhibitors of CYP isoenzymes. **Please note that this table is not exhaustive**; the Summary of Product Characteristics (SmPC) includes information on the potential for clinically relevant DDIs of individual drugs (available on www.hpra.ie or www.medicines.ie). The HIV interactions checker website is a useful resource when treating patients with medicines for human immunodeficiency virus (HIV).

Table 4: Examples of common substrates, inducers and inhibitors of different CYP isoenzymes[2,3]

CYP isoform and Substrates	Inhibitor	Inducer
CYP1A2 Agomelatine, clozapine, duloxetine, pirfenidone, propranolol, theophylline, tizanidine	Aciclovir, cimetidine, ciprofloxacin, erythromycin, fluvoxamine	Carbamazepine, leflunomide, phenytoin, rifampicin, ritonavir, tobacco smoking
CYP2C9 Aspirin and most NSAIDs, diazepam, gliclazide, losartan, *(S)*-warfarin	Amiodarone, cranberry juice, fluconazole, fluvoxamine (other SSRIs weak), metronidazole, omeprazole, ritonavir, voriconazole	Bosentan, carbamazepine, enzalutamide, phenytoin, rifampicin
CYP2D6 Beta-adrenoceptor blockers (several), codeine, donepezil, flecainide, propafenone, risperidone, TCAs, tolterodine	Amiodarone, abiraterone, chlorphenamine, fluoxetine, haloperidol, ketoconazole, mirabegron, paroxetine, ritonavir, sertraline, TCAs, venlafaxine	Carbamazepine, rifampicin
CYP2C19 Citalopram, clopidogrel, diazepam, lansoprazole, omeprazole, voriconazole	Cannabidiol, esomeprazole, fluconazole, fluoxetine	Efavirenz, enzalutamide, rifampicin
CYP3A4 Apixaban, atorvastatin, calcium channel blockers, ciclosporin, codeine, colchicine, eplerenone, midazolam, oral contraceptives, rivaroxaban, sildenafil, simvastatin, sorafenib, sunitinib, ticagrelor, triazolam, verapamil, *(R)*-warfarin	Amiodarone, calcium channel blockers (especially diltiazem), cannabidiol, clarithromycin, ciclosporin, cimetidine, cobicistat, crizotinib, danazol, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, itraconazole, lansoprazole, ketoconazole, metronidazole, norfloxacin, omeprazole, quinine, ranolazine, ritonavir, saquinavir, sertraline, tacrolimus, tamoxifen, TCAs, venlafaxine, voriconazole, zafirlukast	Barbiturates, carbamazepine, dexamethasone, efavirenz, enzalutamide, phenytoin, rifampicin, St John's wort

NSAIDs-non-steroidal anti-inflammatory drugs; SSRI-selective serotonin reuptake inhibitor; TCAs- tricyclic antidepressants

Phase II metabolism of drugs, in particular glucuronidation, is also a factor in drug interactions.[14,15] The enzymes uridine diphosphate glucuronosyltransferases (UGTs) which are involved in glucuronidation of medicines can be inhibited or induced, and are recognised as playing a role in clinically significant DDIs.[1,14,15] For example, valproic acid which inhibits UGT2B7 increases the exposure to zidovudine and lamotrigine.[14]

Excretion: Most drugs are excreted in the urine or bile.[1] The renal excretion of drugs may be affected by co-administration of other drugs, especially in patients with reduced glomerular filtration rate (e.g. in elderly patients).[1,3,15] Drugs that are weak acids or weak bases may be influenced by other drugs that affect urinary pH, however in clinical practice only a few drugs may be affected (e.g. salicylates with antacids, methotrexate with urinary alkalinisers [e.g. sodium bicarbonate]).[1] Active secretion into the renal tubules by drug transporters is an important elimination pathway for some drugs; inhibition of these transporters can inhibit renal elimination with a resulting increase in serum drug concentrations.[1,15]

Other Types of Drug Interactions

Drug-gene interactions: The CYP isoenzymes and drug transporters are subject to genetic control; at least 1% of the population have genetic polymorphisms, which might result in important person-to-person variability in drug metabolism.[1,3,14] Poor metabolisers may have a greater response (and an increased risk of adverse effects) to the effects of drugs that are highly dependent on clearance of an inactive metabolite by the particular isoform, compared to extensive metabolisers (those with a functional gene).[9] Important genetic polymorphisms exist for CYP2C9, CYP2C19 and CYP2D6;[1,9,14,25,26] the distribution of each polymorphism differs according to ethnicity.[14] For example, approximately 10% of the white population and 1% of the Asian and black populations are poor metabolisers of CYP2D6.[1,14] Drugs that are most affected by CYP2D6 polymorphisms are those in which CYP2D6 represents a substantial metabolic pathway.[25,26] Pharmacogenetic variations can also occur in other drug-metabolising enzymes such as UGTs and P-gp.[1,9]

Drug-herb interactions can also occur. Patients should be asked about their use of herbal medicines and supplements, however the interacting constituent of the herbal preparation may not be known and the concentration may vary widely between products and batches of the same product.[1] St John's wort is a herbal medicine which is widely documented to interact with a variety of drugs.[1] Evidence has shown that St John's wort can induce CYP3A4 and P-gp, and as it also has serotonergic properties, there is also potential for a PD interaction with the SSRIs (i.e. serotonin syndrome).[1]

Drug-food interactions: Food can also cause clinically important changes in drug absorption.[1] For example, calcium ions in milk can reduce the absorption of bisphosphonates, calcium-containing foods or neutralising antacids (containing aluminium or magnesium) can reduce the absorption of tetracyclines, quinolones and levothyroxine. Also levothyroxine absorption, which mainly occurs in the small intestine, is reduced with food.[16,27] Tyramine (present in foodstuffs e.g. cheese, chocolate, red wine) might reach toxic concentrations in patients taking monoamine oxidase inhibitors.[1] Grapefruit juice causes the most clinically relevant food metabolism interaction; it inhibits intestinal CYP3A4 which may result in increased exposure of CYP3A4 substrates (e.g. simvastatin).[1,10] The effects of grapefruit juice can be variable and depend on factors including the source, brand and preparation procedure of the juice.[10]

HOW TO MINIMISE RISK FROM DRUG INTERACTIONS

The clinical significance of an interaction depends on patient (e.g. age and co-morbidities) and drug factors including the therapeutic index of the drug, the potency and concentration of the interacting drug and the clearance system of the drug (e.g. the number of PK pathways involved, the sensitivity of the substrate and the potency of the inhibitor or inducer).[1,9,10,14] The most important way to reduce the risk of patient harm from a DDI is to recognise the potential for a DDI to occur and to take appropriate action to avoid harm.[15] This includes the use of an alternative medicine (from the same class or different class) or a reduction in dose of one or more of the drugs with subsequent monitoring of the patient.[15,16] While DDIs can occur due to inappropriate prescribing, the prescribing of 2 potentially interacting drugs may be clinically indicated with appropriate precautions (e.g. monitoring of the patient and/or dose adjustment), when the benefits outweigh the risks.[1,3] Table 5 suggests ways to prevent harm occurring from DDIs.

Table 5: How to minimise drug interactions[1,17]

- Remember that the elderly, patients with polypharmacy and co-morbidities are at increased risk of drug interactions
- Ensure that you know ALL of the patient's medication including over-the-counter products, dietary supplements and special food products (including juices) before prescribing an additional drug
- Be alert for drugs that have a narrow therapeutic index and require monitoring (e.g. anticoagulants, antiepileptics, digoxin, antineoplastic cytotoxics, and immunosuppressants). Take care when initiating these drugs or co-prescribing other drugs
- Be familiar with the metabolism of the drugs that you prescribe frequently and of their potential to interfere with other drugs
- Be aware of some of the drugs that are key enzyme inducers (e.g. phenytoin, barbiturates, carbamazepine, rifampicin) or enzyme inhibitors (e.g. azole antifungals, HIV-protease inhibitors, erythromycin, SSRIs) (see table 3)
- Consider the pharmacology of the drugs in order to avoid potential pharmacodynamic interactions with other drugs (e.g. additive CNS depression) and when ≥2 drugs are used concomitantly that act on the same receptor
- Avoid using a combination of drugs if the potential hazards appear to outweigh the benefits
- If no alternative combination is possible, monitor the patient closely for signs of toxicity or lack of efficacy

USEFUL RESOURCES

In addition to the Summary of Product Characteristics (SmPC), the British National Formulary (BNF) provides information on drug interactions. **Another well-known UK reference resource is Stockley's Drug Interactions (subscription required; available on MedicinesComplete).** Table 6 includes some freely accessible online sources that may be useful.

Table 6: Freely available resources for information on drug interactions

Title	Content and notes	Website
HPRA	SmPCs* of the individual medicines contains information on pharmacodynamic and pharmacokinetic drug interactions	www.hpra.ie
CredibleMeds	This is a US database of medicines that prolong the QT interval and/or induce Torsades de Pointes. The drugs are categorised according to risk. This resource also provides commentary on CYP3A4 drug interaction issues	www.crediblemeds.org
Drugs.com interactions checker	To be used only after other approved sources have been checked. Useful for information not readily available in UK sources	http://www.drugs.com/drug_interactions.html
Medscape Drug Interaction checker	Caution must be exercised with the Medscape Drug Interaction Checker, which is widely used; to be used only after other approved sources have been checker. It is based primarily on drugs used in the USA and there may be some inconsistencies in terms of drug interactions information	www.medscape.com/druginfo/druginterchecker
HIV drug interactions checker	This website is maintained by the University of Liverpool; it provides useful information on interactions with HIV medicines	http://www.hiv-druginteractions.org
Hepatitis C drug interactions	This website is maintained by the University of Liverpool; it provides useful information on drug interactions with hepatitis C medicines	https://www.hep-druginteractions.org/
Cancer Drug Interactions	Published by Radboud University Medical Centre, Netherlands and University of Liverpool; provides a clinically useful, reliable, comprehensive, up-to-date, evidence-based drug-drug interaction resource	http://cancer-druginteractions.org/checker

HPRA- Health Products Regulatory Authority; SmPC-Summary of Product Characteristics; *also available on www.medicines.ie

List of references available on ePublication on www.nmic.ie. Date of publication: November 2020