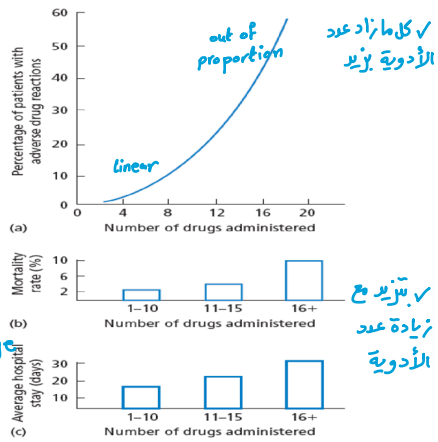
Drug Interactions

التداخلات الدوائية ← قد تكون إيجابية أو سلبية

- Are considered adverse drug reactions. → السلبية
- An interaction occurs when the effects of one drug are altered by the co-administration of another drug, herbal medicine, food, drink or other environmental agents.
- Increased in importance because of the widespread use of poly-pharmacy (multiple drug use) (especially in the elderly & chronically ill), non-prescription (OTC) use of herbal and complementary medicines, and food- and drink – drug interactions.

- Although rational use of more than one drug at a time can greatly benefit patients, adverse interactions are not uncommon, and may be catastrophic.
- Drug interactions are usually avoidable. ⇝ Type A
  - ↳ Intracranial Hemorrhage
  - ↳ GI Hemorrhage
- The greater the number of drugs taken, the more likely there will be an interaction.



✓ كل ما زاد عدد الأدوية يزيد
✓ يتزيد مع زيادة عدد الأدوية

Figure 13.1: Relationship of number of drugs administered to (a) adverse drug reactions, (b) mortality rate and (c) average duration of hospital stay. (Redrawn by permission of the British Medical Journal from Smith JW et al. *Annals of Internal Medicine* 1966; 65: 631.)

Epidemiology: →

مين الهدف منها حفظ الأرقام وإنما معرفة حجم المشكلة

- It is difficult to obtain an accurate estimate of the incidence of drug interactions, mainly because of unawareness[1] and under reporting[2].
- Hospital in-patients: the incidence of drug interactions range from 1-2 %.
- Out-pateints: incidence of interactions range from 2-4 %.
- Other studies reported much higher incidence rates (7% and 22%, respectively).

- The frequency of such interactions is probably underestimated.
- Epileptic patients suffer from much greater rejection rates of transplants than nonepileptics, due to induction of the metabolism of the immunosuppressants by antiepileptic drugs.

Susceptible patients:

1. Those with poly-pharmacy. ⇝ more than 4-6 medications
2. Those with hepatic or renal disease. ⇝ organs of elimination / dysfunction means: ↓ elimination + ↑ concentration of the drug in the body
3. Those with long-term therapy for chronic diseases: (epilepsy, diabetes, patients in intensive care, transplant patients, ..).
4. Those with more than one prescriber. يروح عند دكتورين أو ثلاث
5. Critically ill and elderly patients (altered homeostatic mechanisms). ↑ Age → ↓ body functions
6. Elderly patients. (that are not critically ill & have no poly-pharmacy)

Drug interactions can be: useful, of no consequence, or harmful.

Useful Interactions:

A. Increased therapeutic effect:

- Drugs can be used in combination to enhance their effectiveness.
- Disease is often caused by complex processes, and drugs that influence different components of the disease mechanism may have additive effects:

1. An antiplatelet drug with a fibrinolytic in treating myocardial infarction. + Anticoagulants → to prevent stent or coronary reocclusion
2. The use of a β2 agonist with a glucocorticoid in the treatment of bronchial asthma to cause bronchodilation and suppress inflammation, respectively. → there action has tolerance due to down regulation of its receptors → increase the # of β2 receptors → preventing the tolerance
3. Drug resistance via synthesis of a microbial enzyme that degrades an antibiotic (penicillinase-producing staphylococci) can be countered by using a combination of the antibiotic (amoxicillin) with an inhibitor of the enzyme (clavulanic acid). → has no anti-bacterial effect at all; but inhibit 'penicillinase'
4. Combinations of antimicrobial drugs are used to prevent the selection of drug-resistant organisms in tuberculosis. (in the alveoli / intracellular) population أكثر من tubercle bacilli في وجود ال سبب آخر : (in the gaseous material) ~> ما في ولا دواء بقتل كل هاي الأماكن لحالها
5. Imipenem is partly inactivated by a dipeptidase in the kidney. This inactivation can be overcome by administering imipenem in combination with cilastatin, a specific renal dipeptidase inhibitor. → for gram negative infection

B. Minimize adverse effects:

- Predictable adverse effects can sometimes be averted by the use of drug combinations.

1. Isoniazid neuropathy is caused by pyridoxine deficiency, and is prevented by the prophylactic use of this vitamin. → Isoniazid & Pyridoxine are chemicaly similar so inhibits its activation (compititively) ~> we give pyridoxine with it to overcome the inhibition
2. The combination of a peripheral dopa decarboxylase inhibitor (carbidopa) with levodopa permits reduction of dose of levodopa, while reducing its dose-related peripheral adverse effects (nausea and vomiting ..). → for the treatment of parkinsonism

C. Block acutely an adverse effect:

- Drugs can be used to block an undesired or toxic effect:

1. A cholinesterase inhibitor to reverse neuromuscular blockade.
2. Naloxone to treat opioid overdose.
3. Vitamin K or fresh plasma to reverse the effect of warfarin. → clotting factors فيها reverse the action of warfarin

Harmful interactions:

- You should always check drug interactions among drugs that your patient is taking.

→ Some Severe adverse drug interactions:

1. Unwanted pregnancy, from failure of the contraceptive pill due to concomitant medication, usually enzyme inducers. → estrogen component of oral contraceptive ← يزيد ال metabolism ال ~> pregnancy
2. Stroke, from hypertensive crisis in patients on monoamine oxidase inhibitors. → one of the old anti-depressants (catecholamines & serotonin)
3. Gastrointestinal or cerebral hemorrhage, in patients receiving anticoagulants (warfarin). with antiplatelets or NSAIDs
4. Cardiac arrhythmias, secondary to interactions leading to electrolyte disturbances or prolongation of the QTc interval. → this may be fatal; due to polymorphic ventricular arrhythmias → may degenerate to ventricular fibrillation ~> No ejection of blood (خاصة البوتاسيوم والمغنيسيوم)
   https://southwest.devonformularyguidance.nhs.uk/formulary/ch apters/2.-cardiovascular/drugs-that-prolong-the-qt-interval ← ميّن داخلة بالامتحان
5. Blood dyscrasias, from interactions between allopurinol and azathioprine. → يزيد وإمكانيتها ← concentration يزيد ← metabolism يمنع ال

Mechanisms of drug interactions:

1. Chemical (Pharmaceutical) interactions
2. Pharmacodynamic interactions
3. Pharmacokinetic interactions

- A drug interaction can result from one or a combination of these mechanisms.

Chemical Interactions

- Mainly these interactions occur outside the body if the drugs are mixed together before injection:

1. Inactivation of heparin with gentamicin.
2. Inactivation of heparin with hydrocortisone.
3. Inactivation of gentamicin with hydrocortisone.
4. Inactivation of penicillin with hydrocortisone.
5. Aminoglycosides and penicillins inactivate each other. → don't mix them together / خلي بينهم مثلاً ساعتين
6. Diazepam can be precipitated by infusion fluids, and adsorbs to the plastic of intravenous bags and tubing. ↳ it will not act
   - Normal Saline -
   Glucose 5% or Sodium Chloride 0.9% Intravenous Infusion of minimum volume 250 mL should be used.
7. Phenytoin can be precipitated by infusion fluids.
   Injection of phenytoin is often diluted with infusion fluids before administration, which may lead to precipitation of the drug due to changes in pH and/or vehicle.

Pharmacodynamic Interactions

- Are Common.

1. Drowsiness caused by an H1-blocking antihistamine and alcohol.
   - Patients must be warned of the dangers of consuming alcohol concurrently when antihistamines are prescribed, especially if they drive or operate machinery.
   - Such interactions can be produced also by antidepressants, hypnotics, and some antiepileptics leading to excessive drowsiness.
2. β-blockers and verapamil may precipitate heart failure in patients with supra-ventricular tachycardia, because both have negative inotropic effects. The combination may also cause heart block and asystole.
3. Antihypertensive drugs may be less effective by concurrent use of non-steroidal antiinflammatory drugs, because of inhibition of biosynthesis of vasodilator prostaglandins in the kidney, and because of sodium and water retention.
4. Warfarin inhibits the coagulation cascade, whereas aspirin influences hemostasis by inhibiting platelet function.
   - Therefore, the concomitant use of these drugs may cause excessive bleeding.
   - Aspirin also predisposes to gastric bleeding by direct irritation and by inhibition of prostaglandin E2 biosynthesis in the gastric mucosa.
5. One potentially important type of pharmacodynamic drug interactions involves the interruption of physiological control loops.
   - The use of β-blocking drugs in patients with insulin-dependent diabetics deprive them of insulin-induced hypoglycemia warning signs, which are mediated by sensations initiated by activation of β-receptors. They mask the signs and symptoms of hypoglycemia.
6. Combined use of diuretics with actions at different parts of the nephron (indapamide or metolazone with furosemide) is valuable in the treatment of resistant edema, but such combination readily cause excessive intravascular fluid depletion, electrolyte loss, and "pre-renal" renal failure.
   ↳ very strong inhibitor of sodium reabsorption in the loop of henle → excessive amount of sodium go to distal nephron ⇓ Hypertrophy of sodium absorping system in distal nephron ↩ increase sodium & water retention ← loop diuretic not as effective as it used to be
   - Thiazide and loop diuretics commonly cause hypokalaemia, which increase the binding of digoxin to plasma membrane Na+/K+-ATPase, and hence digoxin toxicity is increased.
   Cardiac Arrhythmias

* Salbutamol is selective β2-Agonist, but at higher concentrations it will stimulate β1 also (tachycardia)
→ selectivity is not apsolute, it is concentration dependent → reduced at higher concentrations

Total K^+ in the body is not reduced

→ increase the activity of Na^+-K^+ pump → increased intracellular K^+ → decrease in plasma

7. β2-Agonists (salbutamol) also may reduce the plasma potassium concentration.
8. Conversely, potassium-sparing diuretics may cause hyperkalemia if combined with potassium supplements and/or angiotensin converting enzyme inhibitors (which reduce circulating aldosterone), especially in patients with renal impairment.

↳ sodium & water retention with potassium excretion (with protons)

- Hyperkalaemia is one of the most common causes of fatal adverse drug reactions. ← cause cardiac arrest

9. Antagonistic interactions:

- The bronchodilator action of selective β2-agonists will be antagonized by β-blockers.
- The opioid antagonist naloxone blocks actions of opioids.
- Flumazenil blocks the action of benzodiazepines.
- Vitamin K blocks the action of oral anticoagulants (warfarin).
- levo-Dopa antagonizes the action of antipsychotics. → يقللوا dopamine ال

10. Neuroleptics and tricyclic antidepressants (TCAs) given with drugs producing electrolyte imbalance (diuretics) may cause ventricular arrhythmias. → prolongation of QTc interval

11. Drugs that prolong the QTc interval if used concurrently can cause fatal polymorphic ventricular tachycardia (torsade de pointes).

12. Serotonin syndrome occurs with combinations that increase serotonin. (Selective serotonin reuptake inhibitors and MAOIs).

→ similar to malignant hyperpyrexia & neurolyptic syndrome
↳ disterpance in intracellular Ca^{2+} stores → excessive muscle contraction → Fever

- Linezolid is an antibacterial with MAOI activity.

13. MAOIs can prevent metabolism of tyramine in the gut which is taken up by adrenergic nerve terminals, releasing catecholamine and causing hypertensive crisis, fatal intracranial hemorrhage and cardiac arrest.

- The same applies to amphetamines, phenylpropanolamine, and pseudoephedrine.
- Tyramine is found in cheese and red wine…/ banana
  ↳ fermented food

Pharmacokinetic Interactions

→ The drug should pass through membranes; being hydrophobic or unionized (non-polar)

Absorption:

1. Changes in gastric pH due to antacids, histamine H2-antagonists, or proton pump inhibitors may affect weak acidic drugs absorption.

* المفروض إذا أنت مضطر لل acid suppression إنه تعمل spacing of the doses

- Drugs affected include aspirin, itraconazole…

2. Some drugs within the GIT form chelates that are not absorbed:

- Tetracyclines and fluoroquinolones can complex with iron and antacids containing calcium, magnesium, and aluminium.
- Bisphosphonates are often co-prescribed with calcium supplements for treatment of osteoporosis and they reduce the bioavailability of each other, leading to therapeutic failure.

3. Adsorbents such as charcoal or kaolin, or anion-exchange resins (cholestyramine and colestipol) may reduce the absorption of many drugs (propranolol, digoxin, warfarin, TCAs, cyclosporine, l-thyroxine, ..).

- These effects can be avoided or reduced if an interval of 2-3 hours is allowed between administration of interacting drugs (spacing of drug administration). ← الدكتور كررها كثير

4. Drugs that affect the rate of gastric emptying can affect absorption of other drugs absorbed in the upper part of the small intestine.

- Drugs with anticholinergic effects (TCAs, phenothiazines and antihistamines) decrease gut motility and reduce gastric emptying.
  ↳ Histamine H1 receptor blocker
- This can decrease or increase absorption of drugs. (How?) according to its major site of absorption

- Anticholinergics reduce the bioavailability of levodopa, as a result of increased metabolism in the intestinal mucosa.
- Opioids inhibit gastric emptying and reduce the absorption rate of paracetamol, without affecting the extent of absorption. / due to its effect on vagus nerve
- Metoclopramide increases gastric emptying and increases the absorption rate of paracetamol, propranolol, mefloquine, lithium and cyclosporine.

→ The rate of absorption is not important if the disease is not critical / بس في الحالات الحرجة مهم

5. Induction or inhibition of drug transport proteins: Drugs that inhibit P-glycoprotein (→ efflux transporter → foreign substances from entering the body) such as verapamil (Non-dihydropyridine calcium channel blocker) may increase bioavailability of digoxin, and thus its toxicity.

6. Malabsorption:

- Neomycin may cause a malabsorption syndrome causing reduced absorption of drugs.
- Orlistat, an inhibitor of pancreatic lipases, reduces absorption of co-administerd fatsoluble drugs and vitamins.

(+ Grape fruit juice do the same thing)

* Chloramphenicol should be used only for eye infections as eye drops not for nasal moistering ⇒ extensive absorption

Metabolism:

- Is the most important target of drug interactions.

A. Enzyme inhibition:

(→ doesn't need protein synthesis)

- The time-course is often more rapid than that for enzyme induction, since it depends on the presence of high-enough concentration of the inhibiting drug at the metabolic site.
- Enzyme inhibition is responsible for many clinically significant drug interactions.

- Concurrent administration of an enzyme inhibitor leads to reduced metabolism of the drug and an increase in its steady-state concentration. (after 4 half life of adminestration) → more action & adverse reaction
- Enzyme inhibition is dose-related.
- The inhibition effect will be seen faster when the inhibitor half-life is short, and will be delayed for drugs with long half-lives. (Why?) due to when we get the steady-state concentration = constant concentration in plasma
- Such interactions are most likely to affect drugs with narrow therapeutic ~~range~~ index = toxic dose for 50% / therapeutic dose for 50% such as: theophylline, phenytoin, cyclosporine, and oral anticoagulants.
- Erythromycin, an inhibitor of CYP3A4 (→ responsible for 50% of metabolism in therapeutically available drugs which eleminated by metabolism) may lead to carbamazepine toxicity due to inhibition of its metabolism leading to higher concentration.
- Grapefruit juice, an inhibitor of CYP3A4, can markedly increase the bioavailability of nifedipine and felodipine given orally.
- A single glass of grapefruit juice can cause inhibition of CYP3A for 1-2 days, while regular consumption may continuously inhibit enzyme activity. (simvastatin, tacrolimus, and cyclosporine).
- Enzyme inhibition usually results in increased pharmacological effect, but when the affected drug is a pro-drug, a reduced pharmacological effect may result.

(for MI & stents)

- Clopidogrel is metabolized to an active metabolite by CYP2C19 which is inhibited by the proton pump inhibitor (lansoprazole) leading to reduced effectiveness of clopidogrel. → could be fatal
- Xanthine oxidase is responsible for inactivation of 6-mercaptopurine, a metabolite of azathioprine. Allopurinol markedly potentiates these drugs by inhibiting xanthine oxidase.
- Hepatic CYP450 inhibition also accounts for clinically important interactions with phenytoin (isoniazid) and with warfarin (sulfonamides).
- Non-selective monoamine oxidase inhibitors (phenelzine) potentiate the action of indirectly acting amines such as tyramine, which is present in a wide variety of fermentation products (cheese, wine, ..).

- Clinically important impairment of drug metabolism may also result indirectly from hemodynamic effects rather than enzyme inhibition.
- Lidocaine is metabolized in the liver and the hepatic extraction ratio is high.
- Drugs that reduces hepatic blood flow (negative inotropes, β-blockers, H2-blockers) reduce hepatic clearance of lidocaine leading to its accumulation and toxicity.

(① → Non-dihydropyridine calcium channel blockers (Verapamil & Daltiasm) ② ③)

B. Enzyme induction: → increase the amount of the active enzyme in the liver ⇒ More Metabolism

- The most powerful enzyme inducers are the antibiotic rifampicin and the antiepileptic drugs barbiturates, phenytoin and carbamazepine.
- Carbamazepine can induce its own metabolism (autoinduction). induction يعمل حتى أسابيع ٢-٣ بده
- Other inducers include cigarette smoking, chronic alcohol use, and the herb St John's wort. + المشاوي
- The induction effect develops over several days or weeks because it requires new protein synthesis.
- Similarly, the effect generally persists for the same time period after withdrawal of the inducing agent.
- Inducers with short half-life (rifampicin) will induce metabolism more rapidly than those with long half-life (phenytoin) because they reach steady-state concentrations more rapidly.
- Enzyme induction is dose-dependent.
- Enzyme induction usually results in reduced pharmacological effect of the affected drug.
- There is a risk of therapeutic failure in patients taking cyclosporine, tacrolimus, HIV-protease inhibitors, irinotecan, and imatinib when patients take St John's wort (for depression).
- If the drug has active metabolites, induction increases its pharmacological effect.
- The dose of the drug may need to be increased in the presence of the inducer to attain the therapeutic effect.
- Withdrawal of an inducing agent during continued administration of a second drug can result in a slow decline in enzyme activity, leading to an increase in drug concentration and emergence of delayed toxicity. (The dose is NO longer appropriate).
- When a patient receiving warfarin receives treatment with an enzyme inducer for a new medical event, the dose of warfarin may need to be increased.
- When the inter-current problem is resolved and the inducing drug is discontinued and the patient is left with the larger dose of warfarin, bleeding may result from an excessive effect of warfarin days or weeks later, as the effect of the enzyme inducer gradually wears off.

Distribution:

- Displacement from protein-binding sites results in increased free or unbound fraction temporarily, but it falls due to enhanced elimination or distribution (clearance).
- It is clinically important for highly protein-bound drugs.
- Examples: phenytoin, lidocaine, warfarin…

Elimination Interactions:

Renal Excretion: at the following levels:

1. Changes in urinary pH: Weakly acidic drugs are ionized at alkaline pH, and thus, are unable to be reabsorbed. Therefore, making urine more alkaline enhances the excretion of acidic drugs. Conversely, the elimination of weak bases is enhanced in acidic urine.

- Change of urine pH can be used to enhance drug elimination in cases of poisoning (salicylates, -acidic- amphetamine, -alkaline-, etc).

→ You can alkalinize the urine to increase the elemination of weak acidic drugs

→ You can acidify the urine to get rid of weak alkaline drug

90% excreted in the urine by active transporter that inhibited by: probenecid

2. Changes in active renal tubule excretion: Probenecid increases plasma concentrations of penicillins by delaying their renal excretion.

- Salicylates and other NSAIDs can cause lifethreatening methotrexate toxicity by inhibiting this process.

3. Changes in renal blood flow: Inhibition of synthesis of vasodilator prostaglandins by NSAIDs increases serum lithium levels and thus toxicity.

4. Many diuretics reduce sodium reabsorption in the loop of Henle or the distal tubule. This leads indirectly to increased proximal tubular reabsorption of monovalent cations. (loop diuretics, thiazide diuretics)

- In patients treated with lithium salts, increased proximal tubular reabsorption of lithium can lead to lithium accumulation and toxicity.

5. Biliary excretion and the entero-hepatic circulation:

- Antibiotics which eliminate gut flora reduce the metabolism of drug conjugates back into the parent drug and thus it is quickly lost from the body reducing its plasma concentration and its pharmacological effect.
- This results in therapeutic failure as occurs in patients taking oral contraceptive concomitantly with broad-spectrum antibiotics. ⇝ very important drug interaction, women who are on OCP, may have contraception faliure & get pregnant if you give them broad-spectrum antibiotics
- Be careful, this interaction is NOT well recognized!!

6. Drug transporter proteins:

- P-glycoprotein acts as efflux pump in renal proximal tubules, hepatocytes, intestinal mucosa, pancreas and blood-brain-barrier.
- It exports drugs into urine, bile and intestinal lumen; and reduces drug accumulation in CNS, respectively.
- P-glycoproteins can be induced or inhibited by some drugs.
- There is also some overlap between Pglycoproten and CYP3A4 substrates, inducers and inhibitors.

Drug-food Interactions:

- Food can cause clinically important interactions via an effect on drug absorption and gastrointestinal motility:

a) Iron & antibiotics should NOT ideally be taken with food.
b) Tyramine and MAOIs.
c) Grapefruit juice and calcium-channel blockers (inhibit CYP3A4 and P-glycoprotein).
d) Cruciferous vegetables (Brussel sprouts, cabbage, broccoli) are inducers of CYP1A2. (produces carcinogens)

Drug-herb Interactions:

- Up to 24% of hospital patients report use of herbal remedies.

1. Extracts of Glycyrrihizin glabra (liquorice عرق السوس)
used for peptic ulcers can cause interactions in patients taking diuretics and digoxin.

- It may exacerbate hypokalemia induced by diuretics and cause digoxin toxicity.
- It also causes sodium and water retention like aldosterone and exacerbate heart failure and edema, and antagonize antihypertensive drugs action.

2. Chamomile (بابونج), and horse chestnut (كستناء) have anticoagulant properties that can increase the risk of bleeding when used with warfarin.

3. Herbal products with antiplatelet activity include Bromelain (أناناس), capsicum (الفليفلة), garlic (الثوم), and turmeric (الكركم), can increase the risk of bleeding when used with aspirin and other antiplatelet drugs.
4. Enhancement of hypotensive effect by hawthorn (الزعرور).

- Take history of herbal product intake because patients usually will NOT volunteer this information.