Drug Interactions

Drug Interactions

- Are considered adverse drug reactions.
- 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), non-prescription use of herbal and complementary medicines, and food- and drink – drug interactions.

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.**
- **The greater the number of drugs taken, the more likely there will be an interaction.**

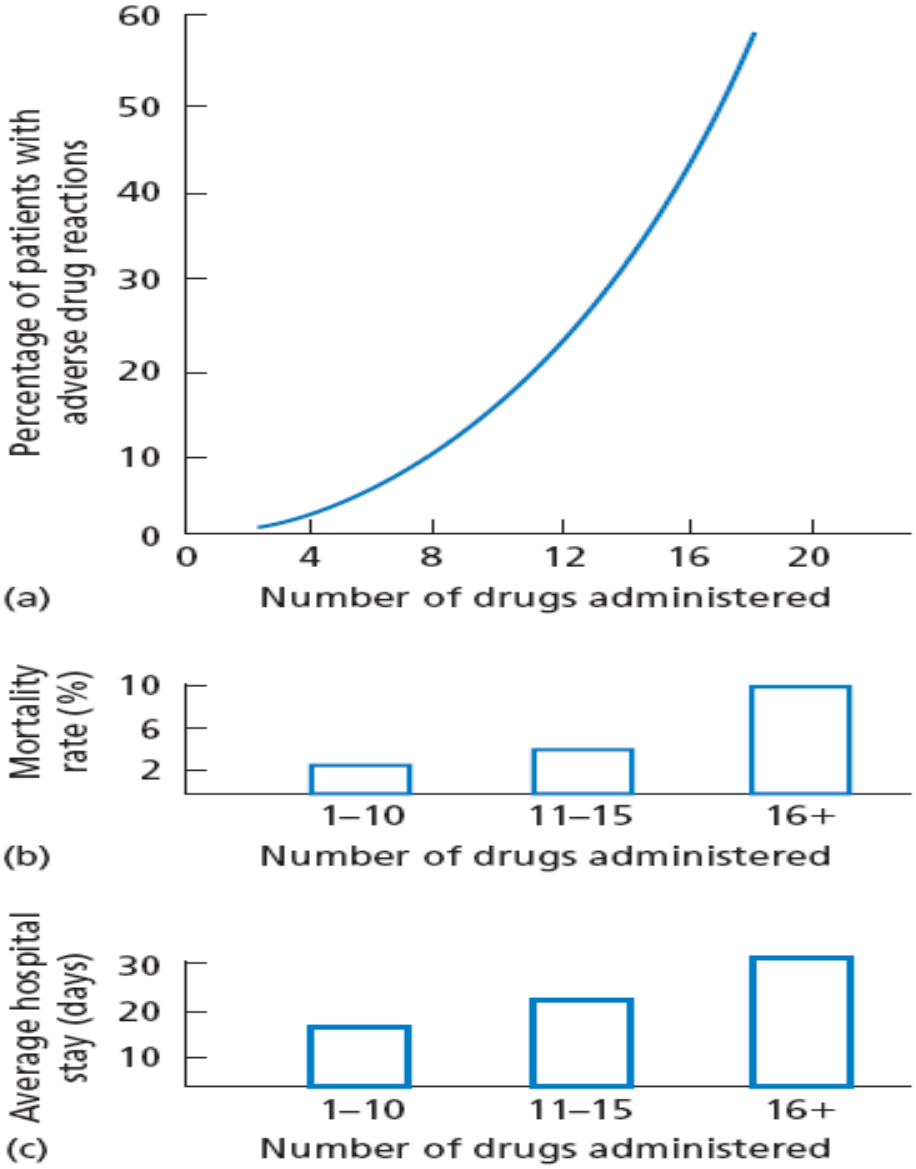


Figure 13.1: Relationship of number of drugs administered to (a) adverse drug reactions, (b) mortality rate and (c) average duration of hospital stay. (Redrawn by permission of the British Medical Journal from Smith JW et al. *Annals of Internal Medicine* 1966; 65: 631.)

Drug Interactions

Epidemiology:

- **It is difficult to obtain an accurate estimate of the incidence of drug interactions.**
- **In hospital in-patients, the incidence of drug interactions range from 1-2 %.**
- **In out-pateints, incidence of interactions ranged from 2-4 %.**
- **Other studies reported much higher incidence rates (7% and 22%, respectively).**

Drug Interactions

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

Drug Interactions

Susceptible patients:

1. **Those with poly-pharmacy.**
2. **Those with hepatic or renal disease.**
3. **Those with long-term therapy for chronic diseases (HIV infection, epilepsy, diabetes, patients with intensive care, transplant patients, patients undergoing complicated surgical procedures.**
4. **Those with more than one prescriber.**
5. **Critically ill and elderly patients (altered homeostatic mechanisms).**

Drug Interactions

- **Many elderly individuals not uncommonly have several co-morbid conditions, needing several drugs.**
- **When a drug results in an adverse effect, it may be treated by another drug, which may add to the problem.**
- **Drug interactions can be: useful, of no consequence, or harmful.**

Drug Interactions

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.

Drug Interactions

2. **The use of a β_2 agonist with a glucocorticoid in the treatment of asthma to cause bronchodilation and suppress inflammation, respectively.**
3. **Drug resistance via synthesis of a microbial enzyme that degrades antibiotic (penicillinase-producing staphylococci) can be countered by using a combination of the antibiotic (amoxicillin) with an inhibitor of the enzyme (clavulanic acid).**

Drug Interactions

4. **Combinations of antimicrobial drugs are used to prevent the selection of drug-resistant organisms in tuberculosis.**
5. **Imipenem is partly inactivated by a dipeptidase in the kidney. This inactivation can e overcome by administering imipenem in combination with cilastin, a specific renal dipeptidase inhibitor.**

Drug Interactions

6. **The use of the combination of ritonavir and saquinavir in antiretroviral therapy.**

- **Ritonavir increases the systemic bioavailability of saquinavir by:**

a. **inhibiting its first-pass gastrointestinal effect (CYP3A).**

b. **inhibiting its fecal elimination by blocking the P-glycoprotein that pumps it back into the intestinal lumen.**

Drug Interactions

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.**
2. **The combination of a peripheral dopa decarboxylase inhibitor (carbidopa) with levodopa permits reduction of dose of levodopa, while reducing the dose-related peripheral adverse effects (nausea and vomiting).**

Drug Interactions

C. Block acutely an adverse effect:

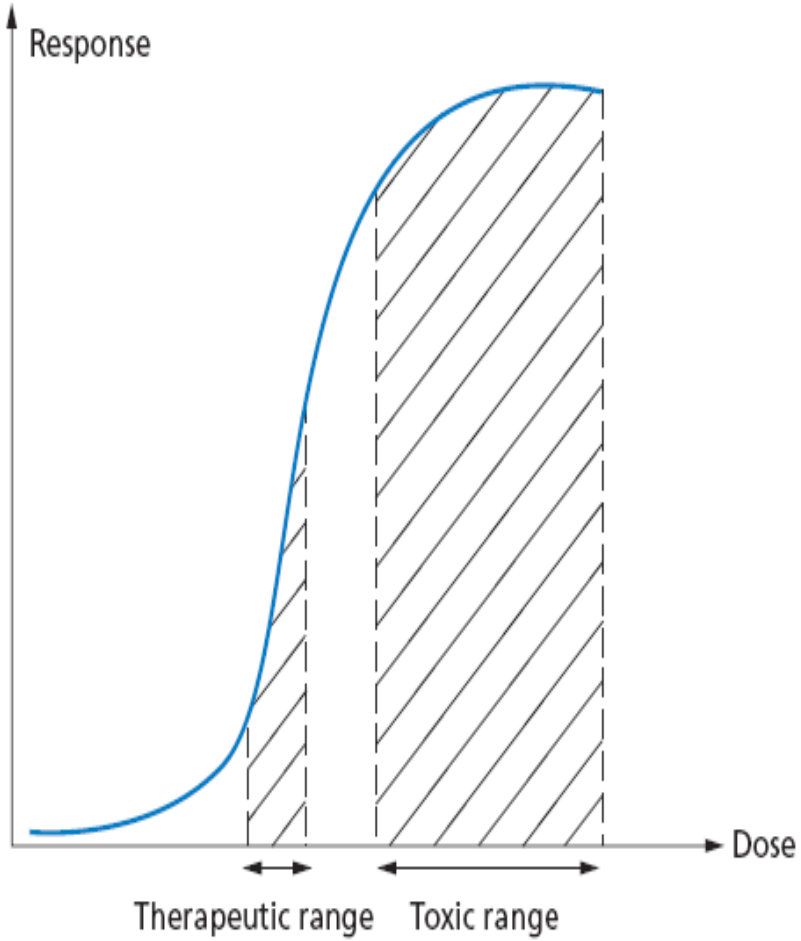
- **Drugs can be used to block an undesired or toxic effect:**

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.**

Drug Interactions

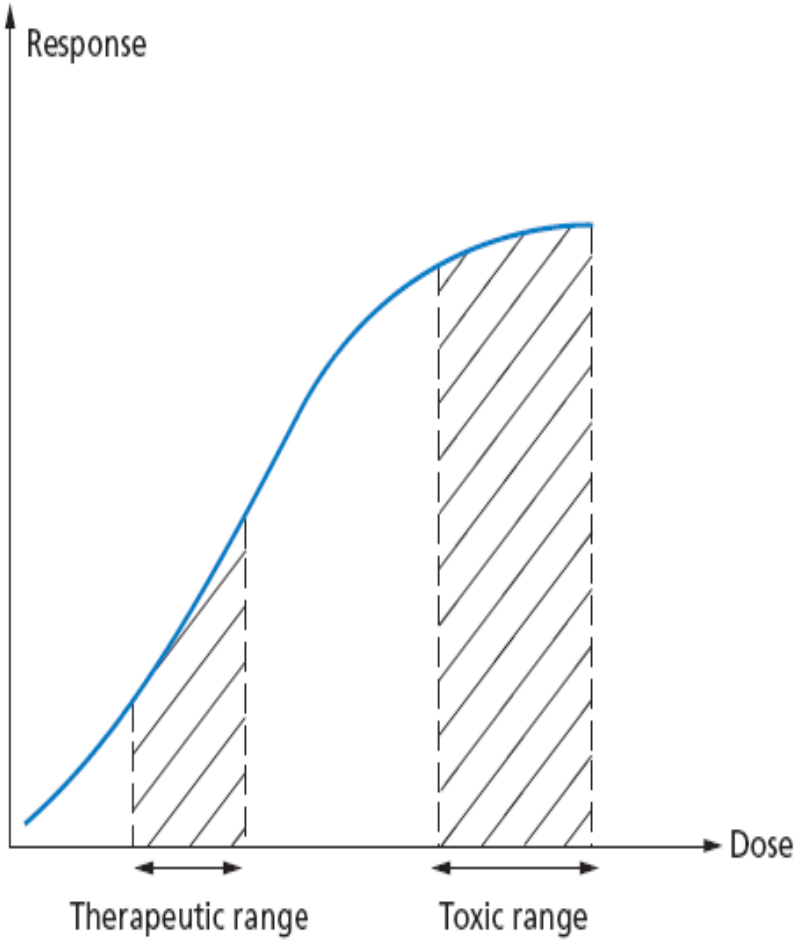
Harmful interactions:

- **It is impossible to memorize the many clinically important drug interactions, and prescribers should depend on suitable references to check for them.**
- **There are certain drugs with steep dose–response curves and serious dose-related toxicities for which drug interactions are especially liable to cause harm, and where special caution is required with concurrent therapy.**



Steep dose–response curve
Narrow therapeutic index

Adverse effect likely



Shallow dose–response curve
Wide therapeutic index

Adverse effect unlikely

Figure 13.2: Drug dose–response curves illustrating likelihood of adverse effect if an interaction increases its blood level.

Drug Interactions

Examples of drugs with high risk of interactions:

1. **Drugs with concentration-dependent toxicity: digoxin, lithium, aminoglycosides, cytotoxic agents, warfarin.**
2. **Drugs that the patient is dependent on their therapeutic effect: Immunosuppressants (cyclosporine, tacrolimus), glucocorticoids, oral contraceptives, antiepileptics, antiarrhythmics, antipsychotics, antiretrovirals…etc.**

Drug Interactions

3. **Drugs with steep dose-response curves: verapamil, sulfonyureas, levodopa.**
4. **Drugs with saturable hepatic metabolism: phenytoin. Why?**
5. **Monoamine oxidase inhibitors (antidepressants). Why?**

Drug Interactions

Severity of adverse drug interactions:

- **Adverse drug interactions are diverse:**
- **Unwanted pregnancy, from failure of the contraceptive pill due to concomitant medication, usually enzyme inducers.**
- **Hypertensive stroke, from hypertensive crisis in patients on monoamine oxidase inhibitors.**
- **Gastrointestinal or cerebral hemorrhage, in patients receiving anticoagulants (warfarin).**

Drug Interactions

- **Cardiac arrhythmias, secondary to interactions leading to electrolyte disturbances or prolongation of the QTc interval.**
- **Blood dyscrasias, from interactions between allopurinol and azathioprine.**

Drug Interactions

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. **Aminoglycosides and penicillins inactivate each other.**

- **Drugs may also interact in the lumen of the gut (tetracycline with iron, and colestyramine with digoxin and many other drugs).**

Table 13.1: Interactions outside the body

Mixture	Result
Thiopentone and suxamethonium	Precipitation
Diazepam and infusion fluids	Precipitation
Phenytoin and infusion fluids	Precipitation
Heparin and hydrocortisone	Inactivation of heparin
Gentamicin and hydrocortisone	Inactivation of gentamicin
Penicillin and hydrocortisone	Inactivation of penicillin

Pharmacodynamic Interactions

- **They are common.**
- **Most have a simple mechanism, consisting of summation or reduction of the effects of drugs with similar or opposing actions, respectively.**

Pharmacodynamic Interactions

1. **Drowsiness caused by an H_1-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 anti-epileptics leading to excessive drowsiness.**

Pharmacodynamic Interactions

2. **Antihypertensive drugs may be less effective by concurrent use of non-steroidal anti-inflammatory drugs, because of inhibition of biosynthesis of vasodilator prostaglandins in the kidney, and because of sodium and water retention.**
3. **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.**

Pharmacodynamic Interactions

4. **Warfarin inhibits the coagulation cascade, whereas aspirin influences haemostasis 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 E_2 biosynthesis in the gastric mucosa.**

Pharmacodynamic Interactions

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.**
- **β-blockers, therefore, will mask the signs and symptoms of hypoglycemia.**

Pharmacodynamic Interactions

6. **Alterations in fluid and electrolyte balance represent an important source of pharmacodynamic drug interactions.**

- **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.**

Pharmacodynamic Interactions

- **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.**

Pharmacodynamic Interactions

7. **β_2-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.**

- **Hyperkalaemia is one of the most common causes of fatal adverse drug reactions.**

Table 13.2: Interactions secondary to drug-induced alterations of fluid and electrolyte balance

Primary drug	Interacting drug effect	Result of interaction
Digoxin	Diuretic-induced hypokalaemia	Digoxin toxicity
Lidocaine	Diuretic-induced hypokalaemia	Antagonism of anti-dysrhythmic effects
Diuretics	NSAID-induced salt and water retention	Antagonism of diuretic effects
Lithium	Diuretic-induced reduction in lithium clearance	Raised plasma lithium
Angiotensin converting enzyme inhibitor	Potassium chloride and/ or potassium-retaining diuretic-induced hyperkalaemia	Hyperkalaemia

NSAID, non-steroidal anti-inflammatory drug.

Pharmacodynamic Interactions

9. **Antagonistic interactions:**

- **The bronchodilator action of selective β_2-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.**

Pharmacodynamic Interactions

10. **Neuroleptics and tricyclic antidepressants (TCAs) given with drugs producing electrolyte imbalance (diuretics) may cause ventricular arrhythmias.**
11. **Drugs that prolong the QTc interval if used concurrently can cause fatal polymorphic ventricular tachycardia (*torsade de pointes*).**
12. **Serotonin syndrome occur with combinations that affect serotonin. Selective serotonin reuptake inhibitors and MAOIs.**

- **Linezolid is an antibacterial with MAOI activity.**

Pharmacodynamic Interactions

12. 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 effect is prolonged for several weeks until new MAO is synthesized (for irreversible inhibitors).**
- **The same applies to amphetamines [3,4-Methylenedioxymethamphetamine, MDMA (ecstasy)], phenylpropanolamine, and pseudoephedrine.**
- **Tyramine is found in cheese and red wine…**

Table 4.5 Examples of additive or synergistic interactions

Interacting drugs	Pharmacological effect
NSAID, warfarin, clopidogrel	Increased risk of bleeding
ACE inhibitors and K-sparing diuretic	Increased risk of hyperkalaemia
Verapamil and β-adrenergic antagonists	Bradycardia and asystole
Neuromuscular blockers and aminoglycosides	Increased neuromuscular blockade
Alcohol and benzodiazepines	Increased sedation
Pimozide and sotalol	Increased risk of QT interval prolongation
Clozapine and co-trimoxazole	Increased risk of bone marrow suppression

Pharmacokinetic Interactions

Absorption:

1. **Changes in gastric pH due to antacids, histamine H_2-antagonists, or proton pump inhibitors may affect weak acidic drugs absorption. The change affects the rate rather than the extent of absorption.**

- **Drugs affected include aspirin, ketoconazole, itraconazole.**

Pharmacokinetic Interactions

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.**

Pharmacokinetic Interactions

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).**

Pharmacokinetic Interactions

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.**
- **This can decrease or increase absorption of drugs. (How?)**

Pharmacokinetic Interactions

- ✓ **TCAs can increase dicoumarol absorption as a result of increasing the time available for its dissolution and absorption.**
- ✓ **Anticholinergics reduce the bioavailability of levodopa, as a result of increased metabolism in the intestinal mucosa.**

Pharmacokinetic Interactions

- ✓ **Opioids strongly inhibit gastric emptying and greatly reduce the absorption rate of paracetamol, without affecting the extent of absorption.**
- ✓ **Metoclopramide increases gastric emptying and increases the absorption rate of paracetamol, propranolol, mefloquine, lithium and cyclosporine.**

Pharmacokinetic Interactions

5. **Induction or inhibition of drug transport proteins: Drugs that inhibit P-glycoprotein such as verapamil 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 fat-soluble drugs and vitamins.**

Pharmacokinetic Interactions

Metabolism:

- **Is the most important target of drug interactions.**

A. Enzyme inhibition:

- **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.**

Pharmacokinetic Interactions

- ✓ **Concurrent administration of an enzyme inhibitor leads to reduced metabolism of the drug and an increase in its steady-state concentration.**
- ✓ **Enzyme inhibition appears to be 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?)**

Pharmacokinetic Interactions

- ✓ **Such interactions are most likely to affect drugs with narrow therapeutic range such as: theophylline, phenytoin, cyclosporine, and oral anticoagulants.**
- ✓ **Erythromycin, an inhibitor of CYP3A4, if taken by a patient on carbamazepine may lead to carbamazepine toxicity due to inhition of its metabolism leading to higher concentration.**

Pharmacokinetic Interactions

- ✓ **Ritonavir (an enzyme inhibitor) in patients receiving sildenafil could increase plasma concentrations of sildenafil markedly.**
- ✓ **Grapefruit juice, an inhibitor of CYP3A4, can markedly increase the bioavailability of nifedipine and felodipine given orally.**

Pharmacokinetic Interactions

- **A single glass of grapefruit juice can cause inhibition of CYP3A for 1-2 days, while regular consumption may continuously inhibit enzyme activity.**
- **Other drugs involved include 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.**

Pharmacokinetic Interactions

- **Clopidogrel is metabolized to an active metabolite by CYP2C19 which is inhibited by a proton pump inhibitor (lansoprazole) leading to reduced effectiveness of clopidogrel.**

✓ **Xanthine oxidase is responsible for inactivation of 6-mercaptopurine, a metabolite of azathioprine. Allopurinol markedly potentiates these drugs by inhibiting xanthine oxidase.**

Pharmacokinetic Interactions

- ✓ **Theophylline is not inactivated by xanthine oxidase, but rather by several CYPs (CYP1A2).**
- **Theophylline has serious dose-related toxicities, which are increased by Inhibitors of the CYP450 system, such as cimetidine, ciprofloxacin, erythromycin and clarithromycin.**
- **Severe exacerbations in asthmatic patients are often precipitated by chest infections, so an awareness of these interactions before commencing antibiotic treatment is essential.**

Pharmacokinetic Interactions

- ✓ **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 fermented products (cheese, wine, ..).**

Pharmacokinetic Interactions

- **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, H_2-blockers) will reduce hepatic clearance of lidocaine leading to its accumulation and toxicity.**

Table 13.4: Interactions due to CYP450 or other enzyme inhibition

Primary drug	Inhibiting drug	Effect of interaction
Phenytoin	Isoniazid	Phenytoin intoxication
	Cimetidine	
	Chloramphenicol	
Warfarin	Allopurinol	Haemorrhage
	Metronidazole	
	Phenylbutazone	
	Co-trimoxazole	
Azathioprine, 6-MP	Allopurinol	Bone-marrow suppression
Theophylline	Cimetidine	Theophylline toxicity
	Erythromycin	
Cisapride	Erythromycin	Ventricular tachycardia
	Ketoconazole	

6-MP, 6-mercaptopurine.

Box 4.2 Examples of enzyme inhibitors frequently implicated in interactions

Antibacterials
Ciprofloxacin
Clarithromycin
Erythromycin
Isoniazid
Metronidazole

Antidepressants
Duloxetine
Fluoxetine
Fluvoxamine
Nefazodone
Paroxetine
Sertraline

Antifungals
Fluconazole
Itraconazole
Ketoconazole
Miconazole
Voriconazole

Antivirals
Amprenavir
Indinavir
Nelfinavir
Ritonavir
Saquinavir

Cardiovascular drugs
Amiodarone
Diltiazem
Quinidine
Verapamil

Gastro-intestinal drugs
Cimetidine
Esomeprazole
Omeprazole

Antirheumatic drugs
Allopurinol
Azapropazone
Phenylbutazone

Other
Aprepitant
Bupropion
Disulfiram
Grapefruit juice
Imatinib
Propoxyphene
Sodium valproate

Table 4.3 Examples of interactions due to enzyme inhibition

Drug affected	Inhibiting agent	Clinical outcome
Anticoagulants (oral)	Ciprofloxacin Clarithromycin	Anticoagulant effect increased and risk of bleeding
Azathioprine	Allopurinol	Enhancement of effect with increased toxicity
Clopidogrel	Lansoprazole	Reduced anti-platelet effect
Carbamazepine Phenytoin Sodium valproate	Cimetidine	Antiepileptic levels increased with risk of toxicity
Sildenafil	Ritonavir	Enhancement of sildenafil effect with risk of hypotension

Pharmacokinetic Interactions

B. Enzyme induction:

- **The most powerful enzyme inducers are the antibiotic rifampicin and the antiepileptic drugs barbiturates, phenytoin and carbamazepine.**
- **Carbamazepine, and to a lessor extent barbiturates, can induce their own metabolism (autoinduction).**
- **Other inducers include cigarette smoking, chronic alcohol use, and the herb St John's wort.**

Pharmacokinetic Interactions

- **The 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.**

Table 13.3: Interactions due to enzyme induction

Primary drug	Inducing agent	Effect of interaction
Warfarin	Barbiturates Ethanol Rifampicin	Decreased anticoagulation
Oral contraceptives	Rifampicin	Pregnancy
Prednisolone/ ciclosporin	Anticonvulsants	Reduced immunosuppression (graft rejection)
Theophylline	Smoking	Decreased plasma theophylline

Pharmacokinetic Interactions

- **Enzyme induction is dose-dependent, but can occur at any dose for some drugs.**
- **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, pharmacological effect may increase.**

Pharmacokinetic Interactions

- **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 from the second drug. (The dose is NO longer appropriate).**

Pharmacokinetic Interactions

- **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.**

Table 4.2 Examples of interactions due to enzyme induction

Drug affected	Inducing agent	Clinical outcome
Oral contraceptives	Rifampicin	Therapeutic failure of contraceptives
	Rifabutin	Additional contraceptive precautions required
	Modafinil	Increased oestrogen dose required
Ciclosporin	Phenytoin Carbamazepine St John's wort	Decreased ciclosporin levels with possibility of transplant rejection
Paracetamol	Alcohol (chronic)	In overdose, hepatotoxicity may occur at lower doses
Corticosteroids	Phenytoin Rifampicin	Increased metabolism with possibility of therapeutic failure

Table 4.1 Examples of drug substrates, inducers and inhibitors of the major cytochrome P450 enzymes

P450 isoform	Substrate	Inducer	Inhibitor
CYP1A2	Caffeine Clozapine Imipramine Olanzapine Theophylline Tricyclic antide- pressants R-warfarin	Omeprazole Lansoprazole Phenytoin Tobacco smoke	Amiodarone Cimetidine Fluoroquinolones Fluvoxamine
CYP2C9	Diazepam Diclofenac Losartan Statins SSRIs S-warfarin	Barbiturates Rifampicin	Amiodarone Azole antifungals Isoniazid
CYP2C19	Cilostazol Diazepam Lansoprazole	Carbamazepine Rifampicin Omeprazole	Cimetidine Fluoxetine Tranylcypromine

	Substrate	Inducer	Inhibitor
CYP2D6	Amitriptyline Codeine Dihydrocodeine Flecainide Fluoxetine Haloperidol Imipramine Nortriptyline Olanzapine Ondansetron Opioids Paroxetine Propranolol Risperidone Thioridazine Tramadol Venlafaxine	Dexamethasone Rifampicin	Amiodarone Bupropion Celecoxib Duloxetine Fluoxetine Paroxetine Ritonavir Sertraline

	Substrate	Inducer	Inhibitor
CYP2E1	Enflurane Halothane	Alcohol (chronic) Isoniazid	Disulfiram
CYP3A4	Amiodarone Terfenadine Ciclosporin Corticosteroids Oral contra-ceptives Tacrolimus R-warfarin Calcium channel blockers Donepezil Benzodiazepines Cilostazol	Carbamazepine Phenytoin Barbiturates Dexamethasone Primidone Rifampicin St John's wort Bosentan Efavirenz Nevirapine	Cimetidine Clarithromycin Erythromycin Itraconazole Ketoconazole Grapefruit juice Aprepitant Diltiazem Protease inhibitors Imatinib Verapamil

Pharmacokinetic Interactions

Distribution:

- **Displacement from protein-binding sites results in increased free or unbound fraction temporarily, but it falls due to enhanced elimination or distribution (clearance).**
- **Therefore, there are only few clinically important interactions due to protein binding displacement, particularly for highly protein-bound drugs and those that are NON-restrictively eliminated especially when administered parenterally.**
- **Examples: Phenytoin, Lidocaine.**

Pharmacokinetic Interactions

- **Drugs whose hepatic extraction ratio exceeds their unbound fraction in plasma are non-restrictively eliminated.**
- **Drugs whose hepatic extraction ratio is smaller than their unbound fraction in plasma are restrictively eliminated.**

Pharmacokinetic Interactions

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, amphetamine, etc).**

Pharmacokinetic Interactions

2. **Changes in active renal tubule excretion: Probenecid increases plasma concentrations of penicillins by delaying their renal excretion.**
- **Salicylates and other NSAIDs can cause life-threatening 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.**

Table 13.5: Competitive interactions for renal tubular transport

Primary drug	Competing drug	Effect of interaction
Penicillin	Probenecid	Increased penicillin blood level
Methotrexate	Salicylates	Bone marrow suppression
	Sulphonamides	
Salicylate	Probenecid	Salicylate toxicity
Indometacin	Probenecid	Indometacin toxicity
Digoxin	Spironolactone	Increased plasma digoxin
	Amiodarone	
	Verapamil	

Pharmacokinetic Interactions

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.**

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

Pharmacokinetic Interactions

5. **Digoxin excretion is reduced by spironolactone, verapamil and amiodarone, all of which can precipitate digoxin toxicity as a consequence. Several of these interactions are complex in mechanism, involving displacement from tissue binding sites, in addition to reduced digoxin elimination.**

Pharmacokinetic Interactions

6. **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.**
- **Be careful, this interaction is NOT well recognized!!**

Pharmacokinetic Interactions

7. **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.**

Pharmacokinetic Interactions

- **P-glycoproteins can be induced or inhibited by some drugs.**
- **Verapamil increases digoxin level and toxicity at this level.**
- **There is also some overlap between P-glycoproten and CYP3A4 substrates, inducers and inhibitors.**

Table 4.4 Examples of inhibitors and inducers of P-glycoprotein

Inhibitors	Atorvastatin Ciclosporin Clarithromycin Dipyridamole Erythromycin Itraconazole Ketoconazole Propafenone Quinidine Ritonavir Valspodar Verapamil
Inducers	Rifampicin St John's wort

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.**

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.**

Drug-herb Interactions

- **Herbal products with antiplatelet activity include Borage (*Borago officinalis*), Bromelain (أناناس) (*Ananas comosus*), capsicum (الفليفلة), feverfew, garlic (الثوم), Ginkgo (*Ginkgo biloba*) and tumeric (الكركم) can increase the risk of bleeding when used with aspirin and other antiplatelet drugs.**
- **Enhancement of hypoglycemic effect by Asian ginseng.**
- **Enhancement of hypotensive effect by hawthorn (الزعرور).**

Drug-herb Interactions

- **Lowering of seizure threshold by evening primrose oil and *Shankapushpi*.**
- **St. John's wort (*Hypericum*) interactions – discussed.**
- **Take history of herbal product intake because patients usually will NOT volunteer this information.**

Therapy of Diabetes Mellitus

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Therapy of Diabetes Mellitus

- **Diabetes mellitus (DM) is a heterogeneous group of metabolic disorders characterized by hyperglycemia.**
- **It is associated with abnormalities in carbohydrate, fat, and protein metabolism.**
- **It may result in chronic complications including microvascular, macrovascular, and neuropathic disorders.**

Therapy of Diabetes Mellitus

- **DM is the leading cause of blindness and end-stage renal disease.**
- **It may result in lower extremity amputations, and cardiovascular events.**

TABLE 30-2 Type 1 and Type 2 Diabetes Mellitus

	TYPE 1	TYPE 2
Etiology	Autoimmune destruction of pancreatic β-cells	Insulin resistance, with inadequate β-cell function to compensate
Insulin levels	Absent or negligible	Typically higher than normal
Insulin action	Absent or negligible	Decreased
Insulin resistance	Not part of syndrome but may be present (e.g., in obese patients)	Yes
Age of onset	Typically <30 years	Typically >40 years
Acute complications	Ketoacidosis Wasting	Hyperglycemia (can lead to hyperosmotic seizures and coma)
Chronic complications	Neuropathy Retinopathy Nephropathy Peripheral vascular disease Coronary artery disease	Same as type 1
Pharmacologic interventions	Insulin	A number of drug classes are available, including insulin if other therapies fail

Type 1 and type 2 diabetes mellitus are both associated with increased blood glucose levels, but the two diseases result from distinct pathophysiologic pathways. In type 1 diabetes mellitus, there is an absolute lack of insulin secondary to autoimmune destruction of pancreatic β-cells. The etiology of type 2 diabetes is less well understood but seems to involve impaired insulin sensitivity and an inadequate level of compensatory insulin production by pancreatic β-cells. Although type 1 and type 2 diabetes have different acute complications (*see text*), they share similar chronic complications. Insulin is the primary pharmacologic intervention for type 1 diabetes, while type 2 diabetes can be treated with a number of different agents.

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Drug-induced Diabetes Mellitus

1. **Pyriminil (vacor) (rodenticide) – loss of pancreatic β-cells.**
2. **Pentamidine – cytotoxic effect on pancreatic β-cells (type 1).**
3. **Nicotinic acid – impairment of insulin action.**
4. **Glucocorticoids – Metabolic effects and insulin antagonism.**
5. **Thyroid hormones – increase hepatic glucose production.**
6. **Growth hormone - reduces insulin sensitivity resulting in mild hyperinsulinemia, and increased blood glucose levels**
7. **Diazoxide: inhibition of insulin secretion.**

Drug-induced Diabetes Mellitus

8. β-adrenergic agonists – glycogenolysis, and gluconeogenesis.
9. Thiazides – hypokalemia-induced inhibition of insulin release.
10. Phenytoin – induces insulin insensitivity.
11. Interferone – β-cell destruction (type 1)
12. Chronic alcoholism - insulin resistance and pancreatic β-cell dysfunction.
13. Cyclosporine – suppresses insulin production and release.

Drug-induced Diabetes Mellitus

14. **HIV protease inhibitors - insulin resistance with insulin deficiency relative to hyper-glucagonemia.**
15. **Atypical antipsychotics (clozapine and olanzapine) – weight gain and insulin resistance.**
16. **Megestrol acetate – insulin resistance.**
17. **Others …**

Therapy of Diabetes Mellitus

Desired Outcome:

The primary goals of DM management are:

1. **To reduce the risk of microvascular and macrovascular disease complications.**
2. **To ameliorate symptoms.**
3. **To reduce mortality.**
4. **To improve quality of life.**
5. **To minimize weight gain and hypoglycemia.**

Therapy of Diabetes Mellitus

- **Early diagnosis and treatment to near-normoglycemia reduces the risk of developing microvascular (retinopathy, nephropathy, and neuropathy) disease complications.**

Therapy of Diabetes Mellitus

- **Aggressive management of cardiovascular risk factors: smoking cessation, treatment of dyslipidemia, intensive blood pressure control, and antiplatelet therapy are needed to reduce the risk of developing macrovascular disease (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease).**

Therapy of Diabetes Mellitus

- **Hyperglycemia also contributes to poor wound healing by compromising white blood cell function and altering capillary function.**
- **Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are severe manifestations of poor diabetes control, always requiring hospitalization.**

Non-pharmacologic Management

1. **Screening (for the presence of DM).**
2. **Monitor for:**

- **blood glucose, HbA_{1c}, fasting lipid profile, urinary albumin (urine albumin-to-creatinine ratio [UACR]) and glomerular filtration rate (GFR), diabetic neuropathy, and dilated eye examination.**

Non-pharmacologic Management

3. **Glycemic goals:**

- **HbA_{1c} goal for non-pregnant adults of <7%, or of <6.5% without significant hypoglycemia.**
- **Critically ill (Hospital) glucose: 140-180 mg/dL, or more strict guidelines down to 110-140 mg/dL (without hypoglycemia).**
- **(*The above percentages may differ depending on the method of HbA_{1c} measurement*).**

Non-pharmacologic Management

5. **Medical nutrition therapy:**

- **Weight loss is recommended for all insulin-resistant/ overweight or obese individuals.**

a) **Either low-carbohydrate, low-fat, calorie-restricted diets, or Mediterranean diets.**

b) **Healthier eating behaviors leading to sustained weight loss over time is more important than a specific diet.**

Non-pharmacologic Management

- **In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations.**
- **Therefore, carbohydrate sources high in protein should NOT be used to treat or prevent hypoglycemia.**
- **Saturated fat should be <7% of total calories.**

Non-pharmacologic Management

- **A Mediterranean-style eating pattern, rich in monounsaturated fatty acids (olive oil), may benefit glycemic control and reduce CVD risk factors.**
- **Consider financial and cultural food issues.**
- **Discourage bedtime and between-meal snacks, and set realistic goals.**

Non-pharmacologic Management

- **A diet low in fat is recommended for patients with CVD.**
- **Avoid a high-protein diet in patients with nephropathy.**
- **Supplement with all of the essential vitamins and minerals.**

Non-pharmacologic Management

6. **Physical Activity:**

- **Aerobic exercise improves insulin sensitivity, modestly improves glycemic control, reduces cardiovascular risk, contributes to weight loss or maintenance, raises HDH-cholesterol and improves well-being.**
- **Physical activity goals include at least 150 min/wk of moderate intensity exercise spread over at least 3 days/week with no more than 2 days between activities.**

Non-pharmacologic Management

- **Resistance/Strength training is recommended at least 2 times a week in patients without proliferative diabetic retinopathy, and ischemic heart disease.**

Non-pharmacologic Management

7. **Patient Education:**

- **It is NOT appropriate to give patients with DM brief instructions and a few pamphlets.**
- **Diabetes education, at initial diagnosis and at ongoing intervals over a life-time, is critical.**
- **Healthy behaviors include healthy eating, being active, monitoring, taking medication, problem solving, reducing risk, and healthy coping.**

Non-pharmacologic Management

- **The patient must be involved in the decision-making process with knowledge of the disease and associated complications.**
- **Emphasize that complications can be prevented or minimized with good glycemic control and managing risk factors for CVD.**
- **Motivational interviewing techniques to encourage patients to identify barriers that hinder achieving health goals, and then work to solve them, are essential.**

Other Recommendations

A. **Blood pressure:**

- **Systolic/diastolic blood pressure should be treated to <140 mm / <90 mm Hg.**
- **Lower goals <130 mm Hg / <80 mm Hg may be appropriate for younger patients.**
- **Life-style intervention such as weight loss, and diet including reducing sodium and increasing potassium.**
- **Initial drug therapy should be with an ACEi or an angiotensin-receptor blocker (ARB); if intolerant to one, the other should be tried.**

Other Recommendations

B. **Dyslipidemia:**

- **Lifestyle modification focusing on the reduction of saturated fat, and cholesterol intake; increasing omega-3 fatty acids intake, use of viscous fiber, and plant sterols; weight loss, and increased physical activity should be recommended.**
- **Consider the use of statins according to risks.**

Other Recommendations

C. **Antiplatelet Therapy:**

- **Use aspirin (75-162 mg daily) for <u>secondary</u> cardioprotection.**

D. **Hospitalized Patients:**

- **Critically ill: IV insulin protocol.**
- **Non-critically ill: scheduled subcutaneous insulin with basal, nutritional, and correction coverage.**

E. **Psychosocial:**

- **Assess the patient's psychological and social situation as an ongoing part of the medical management of diabetes.**

Prevention of Diabetes Mellitus

A. Efforts to prevent type 1 diabetes focused on immunomodulators and low dose insulin, but the results are not yet conclusive.

B. Prevention of type 2 diabetes:

1. The "4 life-style pillars" for the prevention of type 2 diabetes are to:

a) decrease weight.

b) increase aerobic exercise.

c) increase fiber in diet.

d) decrease fat intake.

Prevention of Diabetes Mellitus

2. **Drugs:**

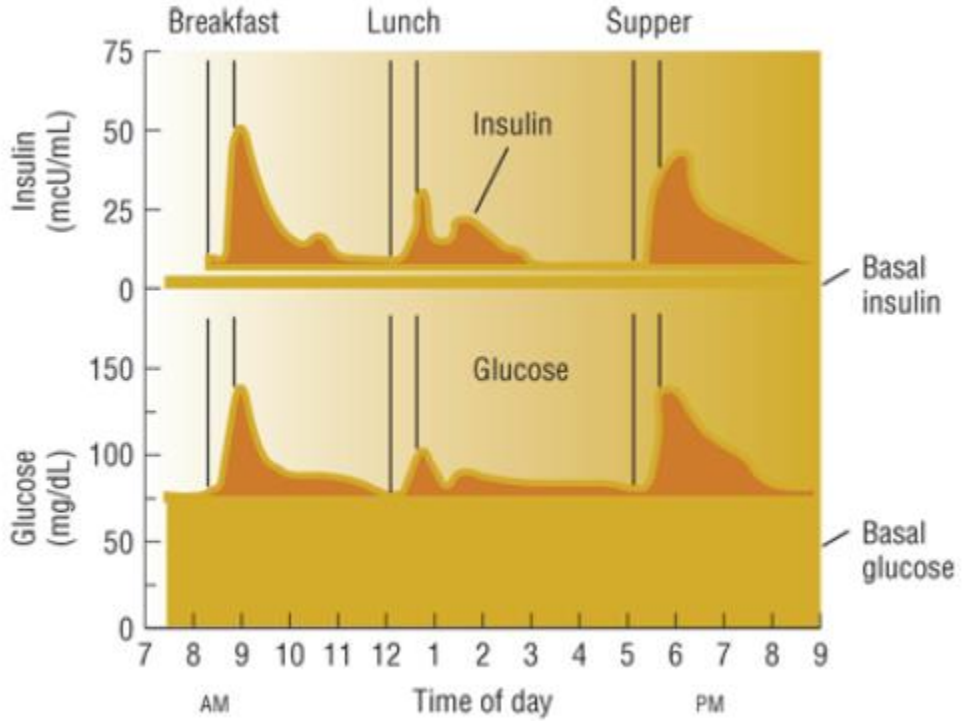
a. **Metformin therapy reduces the risk of developing type 2 DM, especially in obese, <60-year-old patients, and women with prior gestational diabetes mellitus (GDM).**

b. **Rosiglitazone reduces the incidence of type 2 diabetes.**

c. **Acarbose and liraglutide decrease progression to type 2 DM.**

Pharmacologic Therapy (Type 1 DM)

- **All patients with type 1 DM require insulin.**



Relationship between insulin and glucose over the course of a day.

Pharmacologic Therapy (Type 1 DM)

- **Attempt to mimic normal secretion of insulin.**
- **One or two injections of insulin daily will in NO way mimic normal physiology, and therefore, is unacceptable.**
- **The timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve adequate blood glucose control throughout the day.**

Insulin

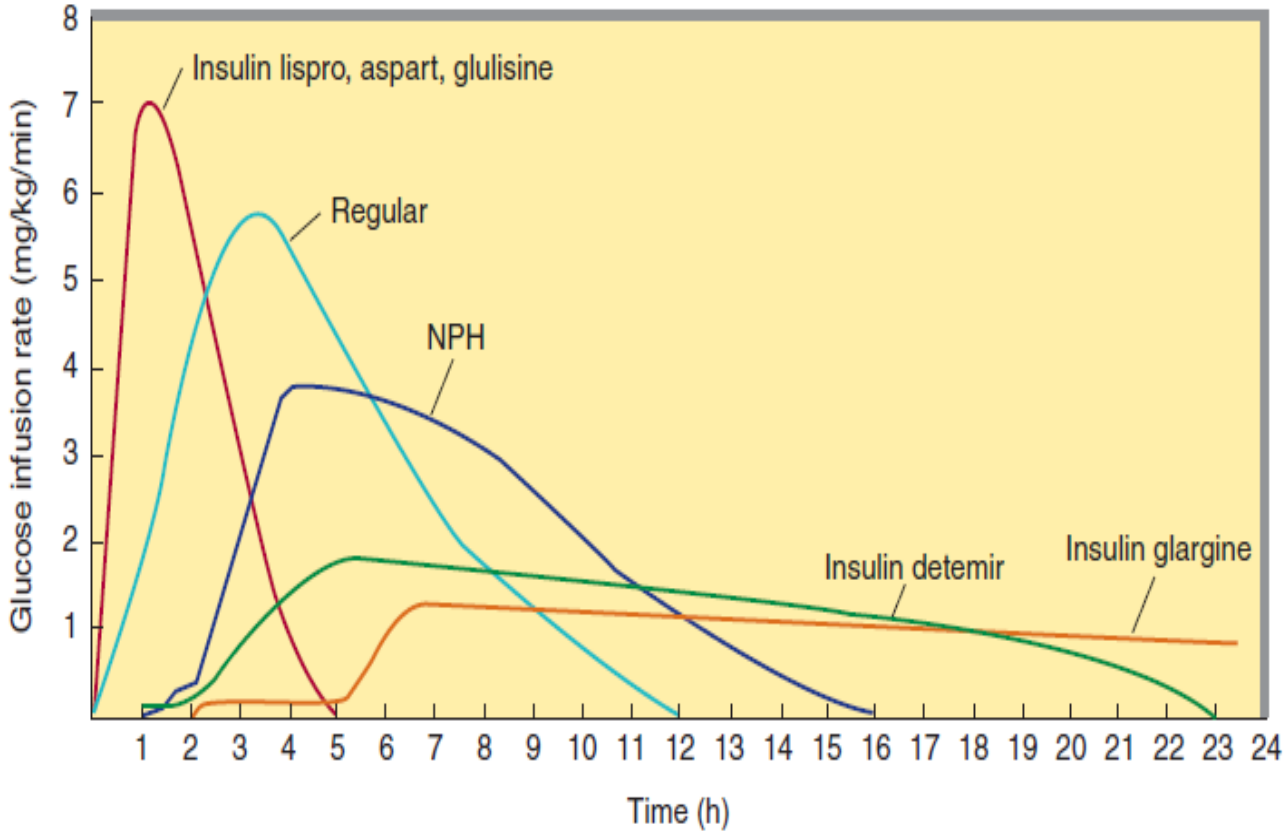


FIGURE 41–5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

Pharmacokinetics of Select Insulins Administered Subcutaneously

Type of Insulin	Onset (Hours)	Peak (Hours)	Duration (Hours)	Maximum Duration (Hours)	Appearance
Rapid acting					
Aspart	15-30 min	1-2	3-5	5-6	Clear
Lispro	15-30 min	1-2	3-4	4-6	Clear
Glulisine	15-30 min	1-2	3-4	5-6	Clear
Technosphere[a]	5-10 min	0.75-1	~3	~3	Powder
Short-acting					
Regular	0.5-1.0	2-3	4-6	6-8	Clear
Intermediate acting					
NPH	2-4	4-8	8-12	14-18	Cloudy
Long acting					
Detemir	~2 hours	__[b]	14-24	20-24	Clear
Glargine (U-100)	~2-3 hours	__[b]	22-24	24	Clear
Degludec	~2 hours	__[b]	30-36	36	Clear
Glargine (U-300)	~2 hours	__[b]	24-30	30	Clear

[a]Technosphere insulin is inhaled.

[b]Glargine is considered "flat" though there may be a slight peak in effect at 8-12 hours, and with detemir at ~8 hours, but both have exhibited peak effects during comparative testing, and these peak effects may necessitate changing therapy in a minority of type 1 DM patients. Degludec and U-300 insulin glargine appears to have less peak effect compared to U-100 insulin glargine.

Intensive Insulin Regimens

	7 am meal	11 am meal	5 pm meal	Bed time
2 doses (R or rapid acting) + N	R, L, A, Glu + N		R, L, A, Glu + N	
3 doses (R or rapid acting) + N	R, L, A, Glu + N	R, L, A, Glu	R, L, A, Glu + N	
4 doses (R or rapid acting) + N	R, L, A, Glu	R, L, A, Glu	R, L, A, Glu	N
4 doses (R or rapid acting) + N	R, L, A, Glu + N	R, L, A, Glu	R, L, A, Glu	N
4 doses (R or rapid acting) + long acting	R, L, A, Glu	R, L, A, Glu	R, L, A, Glu	G or D
CS-II pump	Adjusted basal + Bolus	Adjusted basal + Bolus	Adjusted basal + Bolus	
3 prandial doses	P added to previous regimens	P added to previous regimens	P added to previous regimens	

A, aspart; CS-II, continuous subcutaneous insulin infusion; D, detemir or degludec; G, glargine; GLU, glulisine; L, lispro; N, NPH; P, pramlintide; R, regular.

Pharmacologic Therapy (Type 1 DM)

- **The simplest regimens that can approximate physiologic insulin release use "split-mixed" injections consisting of a morning dose of an intermediate-acting insulin (NPH) and a "bolus" rapid-acting insulin or regular insulin prior to the morning and evening meals.**
- **The morning intermediate-acting insulin dose provides basal insulin during the day and provides "prandial" coverage for the midday meal.**

Pharmacologic Therapy (Type 1 DM)

- **The evening intermediate-acting insulin dose provides basal insulin throughout the evening and overnight.**
- **That is acceptable when patients have fixed timing of meals and carbohydrate intake.**
- **However, This regimen may NOT achieve good glycemic control overnight without causing nocturnal hypoglycemia.**
- **Moving the evening NPH dose to bedtime may improve glycemic control and reduce the risk of nocturnal hypoglycemia.**

Pharmacologic Therapy (Type 1 DM)

- **“Basal-bolus” regimens using multiple daily injections (MDIs) may mimic normal insulin physiology, with a combination of intermediate- or long-acting insulin to provide the basal insulin, and a rapid-acting insulin to provide prandial coverage.**
- **Long-acting insulins include insulin detemir, glargine, or degludec.**

Pharmacologic Therapy (Type 1 DM)

- **Bolus or prandial insulin can be provided by either regular insulin or rapid-acting insulin analogs: lispro, aspart, or glulisine.**
- **The rapid onset and short duration of action of the rapid-acting insulin analogs more closely replicate normal physiology than does regular insulin.**
- **(Remember that regular insulin is soluble or crystalline zink insulin).**

Pharmacologic Therapy (Type 1 DM)

- **Approximately 50% of total daily insulin replacement should be in the form of basal insulin and the other 50% in the form of bolus insulin, divided between meals.**
- **In new patients, the initial total daily dose is usually between 0.5 and 0.6 units/kg/day.**

Pharmacologic Therapy (Type 1 DM)

- **Continuous subcutaneous insulin infusion (CS-II) or insulin pumps using a rapid-acting insulin is the most sophisticated and precise method for insulin delivery. In highly motivated patients, it achieves excellent glycemic control more than MDI.**
- **Insulin pump therapy may also be paired to continuous glucose monitoring (CGM), which allows calculation of a correct insulin dose, as well as alert the patient to hypoglycemia and hyperglycemia.**

Pharmacologic Therapy (Type 1 DM)

- **Insulin pumps require greater attention to details and more frequent self-monitored blood glucose (SMBG) than does a basal-bolus MDI regimen.**
- **Patients need extensive training on how to use and maintain their pump.**

Pharmacologic Therapy (Type 1 DM)

- **All patients treated with insulin should be instructed how to recognize and treat hypoglycemia.**
- **At each visit, patients with type 1 DM should be evaluated for hypoglycemia including the frequency and severity of hypoglycemic episodes.**

Pharmacologic Therapy (Type 1 DM)

- Hypoglycemic unawareness may result from autonomic neuropathy or from frequent episodes of hypoglycemia.
- The loss of warning signs of hypoglycemia is a relative contraindication to continued intensive therapy.

Pharmacologic Therapy (Type 1 DM)

- **Patients who have erratic postprandial glycemic control despite proper insulin dose may benefit from addition of the amylinomimetic pramlintide.**
- **Amylin suppresses endogenous production of glucose in the liver.**
- **Pramlintide taken prior to each meal can improve postprandial blood glucose control.**
- **It is NOT a substitute for bolus insulin.**

Pharmacologic Therapy (Type 1 DM)

- **Pramlintide can NOT be mixed with insulin requiring the patient to take an additional injection at each meal.**
- **When pramlintide is initiated, the dose of prandial insulin should be reduced by 30 - 50%, to prevent hypoglycemia.**

Pharmacologic Therapy (Type 1 DM)

Pramlintide:

1. **Slows gastric emptying – mediated by the vagus nerve.**
2. **Reduces glucagon secretion.**
3. **Promotes satiety or reduce appetite - centrally.**
4. **Produces moderate weight loss.**

- **Main adverse effects include: Hypoglycemia and GIT disturbances (nausea & vomiting), and anorexia).**

Pharmacologic Therapy (Type 2 DM)

1. Symptomatic patients may initially require treatment with insulin or combination therapy.
2. All patients are treated with therapeutic life-style modification.
3. Patients with HbA_{1c} of 7.5% or less are usually treated with metformin (which is unlikely to cause hypoglycemia).
4. Those with HbA_{1c} > 7.5% but < 8.5% could be initially treated with a single agent, or combination therapy.

Pharmacologic Therapy (Type 2 DM)

5. **Patients with higher initial HbA_{1c} will require two agents OR insulin.**
6. **All therapeutic decisions should consider the needs and preferences of the patient, if medically possible.**
7. **Obese patients without contraindications are often started on metformin which is titrated up to 2,000 mg/day.**

Pharmacologic Therapy (Type 2 DM)

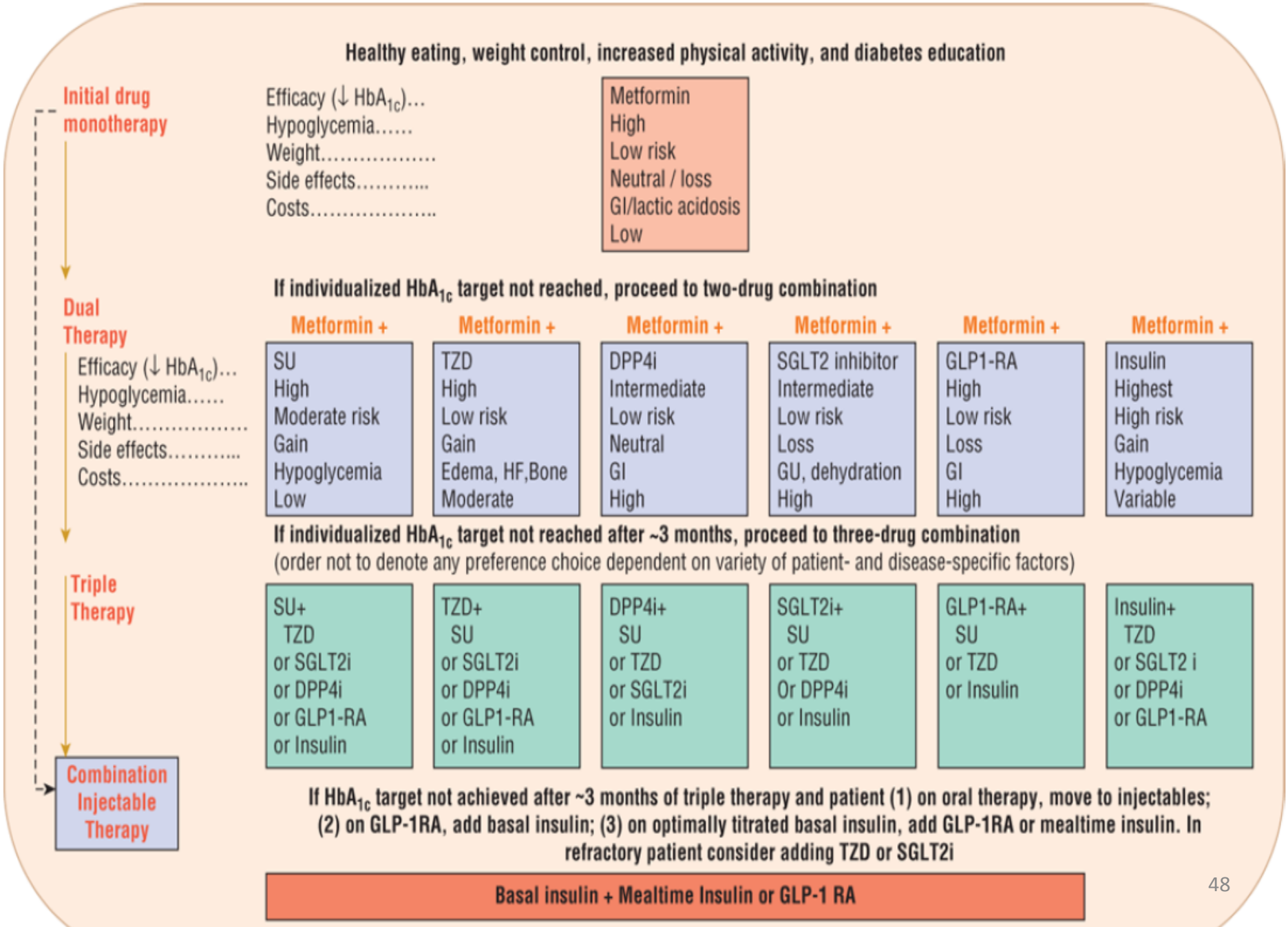
8. **Non-obese patients are more likely to be insulinopenic, necessitating medications that may increase insulin secretion.**
9. **An insulin secretagogue, such as a sulfonylurea, is often added second.**

- **Sulfonylureas have several potential drawbacks including weight gain and hypoglycemia.**
- **They do NOT produce a durable glycemic response.**

Pharmacologic Therapy (Type 2 DM)

10. Better choices include Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) and GLP-1 receptor agonist but they have therapeutic and safety limitations.
11. Thiazolidinediones (TZDs) produce a more durable glycemic response and are unlikely to cause hypoglycemia, but weight gain, fluid retention and the risk of new onset heart failure have limited their use.

Antihyperglycemic Therapy Recommendations in Type 2 Diabetes. General Recommendations. *(Data from reference 20.)*



Drug & class	Dose (mg)	Duration of action (hours)	Drug	Dose (mg)	Duration of action (hours)
Sulfonylureas					
Glimepiride	1-8	24	Glipizide	2.5-40	12-24
Glyburide	1.25-20	12-24	Glipizide extended release	5-20	24
Micronized glyburide	1-12	24			
Non-sulfonyureas secretagogues					
Rapaglinide	0.5-4	2-3	Nateglinide	60-120	2-4
Biguanides					
Metformin	500-2500	6-12	Metformin extended release	1500-2000	24
Thiazolidinediones					
Rosiglitazone	4-8	Poorly correlated with half-life. Max effect ~ 4 weeks	Poiglitazone	15-45	Poorly correlated with half-life. Max effect ~ 4 weeks
α-glucosidae inhibitors					
Acarbose	25-50	Affects absorption of carbohydrates in a single meal	Miglitol	25-100	Affects absorption of carbohydrates in a single meal
GLP-1 receptor agonists / Incretin mimetics					
Exenatide	5-10 mcg	10	Liraglutide	0.6-1.8	24
DPP-4 inhibitors					
Sitagliptin	100	24	Saxagliptin	2.5-5	24
Linagliptin	5	24			
Amylin mimetics					
Pramlintide	15-60 (type 1 DM) 60 or 120 (type 2 DM)	C_{max} 20 min			
Bile acid sequestrants					
Colesevelam	3750	N/A			

Pharmacologic Therapy (Type 2 DM)

Treatment selection should be based on multiple factors:

1. **A patient who has had diabetes for several years, due to progressive failure of β-cell function, is more likely to require insulin therapy.**
2. **If the patient has multiple co-morbidities (CVD, dementia, depression, osteoporosis, heart failure, recurrent genitourinary (GU) infections, some medications may be poor choices based on their potential adverse effects.**

Pharmacologic Therapy (Type 2 DM)

3. **If the patient's postprandial blood glucose readings are the primary reason for poor control, pick a medication that addresses postprandial blood glucose fluctuations.**
4. **If the patient's fasting blood glucose readings are consistently elevated, a medication that addresses fasting blood glucose would be a better choice.**

Pharmacologic Therapy (Type 2 DM)

5. **Adverse effect profile, contraindications, hypoglycemia potential, and tolerability by the patient, should be considered when selecting therapy.**
6. **Motivation, resources, and potential difficulties with adherence should also influence treatment selection.**

Pharmacologic Therapy (Type 2 DM)

7. If the patient is an older adult, the risk of hypoglycemia and other adverse effects increases and life expectancy diminishes. These factors should influence medication choices and HbA1c goals.
8. Non-glycemic effects (CVD reduction with medications, lipid effects, blood pressure effects, weight, and durability of HbA_{1c} reduction) may all influence the decision.

Pharmacologic Therapy (Type 2 DM)

9. **It is unlikely that any one drug class will arrest β-cell failure, necessitating combination therapy.**

- **The combination of a TZD and GLP-1 receptor agonist is a good one:**

a) **TZDs reduce apoptosis of β-cells.**

b) **GLP-1 receptor agonists augment pancreatic function.**

- **Metformin, pioglitazone, and exenatide are promising.**

Glucagon-like peptide-1 (GLP-1) from the GIT

1. It enhances insulin release in response to an ingested meal.
2. It suppresses glucagon secretion.
3. It delays gastric emptying.
4. It decreases appetite.
5. It is degraded by dipeptidyl peptidase-4 (DPP-4).

Pharmacologic Therapy (Type 2 DM)

Exenatide:

- **It is a long-acting analogue of GLP-1, Acts as agonist at GLP-1 receptors.**
- **Used as adjunctive therapy in patients with type 2 diabetes treated with metformin, or metformin plus sulfonylureas who still have suboptimal glycemic control.**
- **Delays gastric emptying.**
- **Suppresses postprandial glucagon release.**

Pharmacologic Therapy (Type 2 DM)

- It increases insulin secretion in a glucose-dependent manner. The increased insulin secretion is speculated to be due in part to:

a) an increase in beta-cell mass, from decreased beta-cell apoptosis.

b) increased beta-cell formation.

c) or both. (Noticed in culture)

- Suppresses appetite.
- Associated with weight loss.

Pharmacologic Therapy (Type 2 DM)

Adverse effects:

1. **Nausea, vomiting, diarrhea: major adverse effect is nausea (45%), which is dose-dependent and declines with time.**
2. **Acute pancreatitis.**
3. **Renal impairment and acute renal injury.**

- **Not associated with hypoglycemia unless used in combination.**

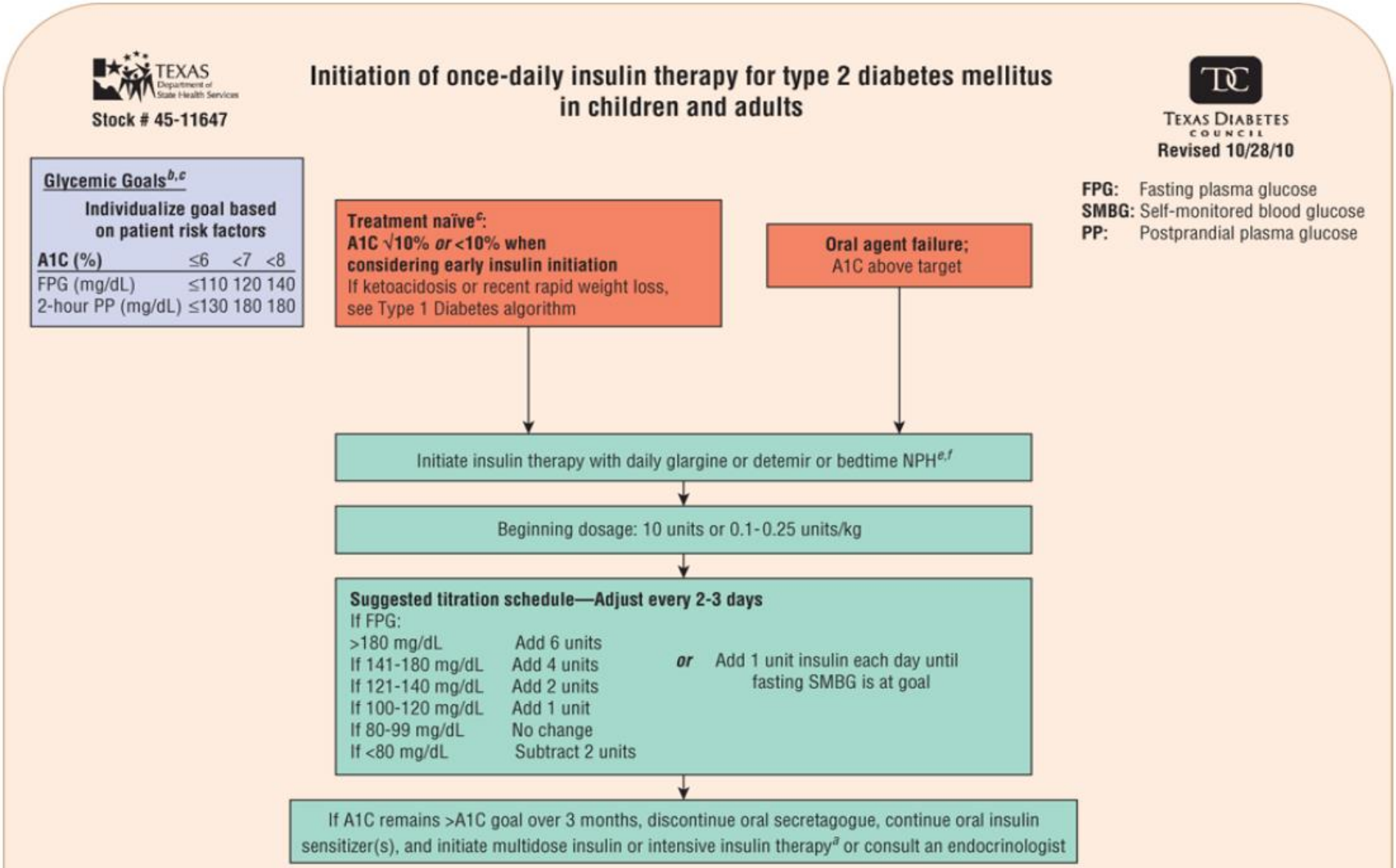
Pharmacologic Therapy (Type 2 DM)

- **With time some patients with type 2 DM become relatively insulinopenic necessitating insulin therapy.**
- **In these patients use insulin injections at bedtime (intermediate- or long-acting basal insulin) while continuing to use oral agents or GLP-1 receptor agonists for control during the day.**

Pharmacologic Therapy (Type 2 DM)

- **This strategy is associated with less weight gain, equal efficacy, and lower risk of hypoglycemia when compared to starting prandial insulin or split-mix twice daily insulin regimens.**
- ***Any modification of this strategy should depend on fasting and posprandial glucose monitoring, HbA_{1c} monitoring, and times of development of hypoglycemia.***

Simplified Insulin algorithm for type 2 DM in children and adults. See: www.texasdiabetescouncil.org for current algorithms. *(Reprinted from the Texas Diabetes Council.)*



The SI equivalents for A1C from the figure are: 4% (0.04; 20 mmol/mol Hb), 6% (0.06; 42 mmol/mol Hb), 7% (0.07; 53 mmol/mol Hb), 8% (0.08; 64 mmol/mol Hb), 10% (0.10; 86 mmol/mol Hb), and 1% change (0.01; 11 mmol/mol Hb).

The SI equivalents for glucose from the figure are: 80 mg/dL (4.4 mmol/L), 99 mg/dL (5.5 mmol/L), 100 mg/dL (5.6 mmol/L), 110 mg/dL (6.1 mmol/L), 120, and 121 mg/dL (6.7 mmol/L), 130 mg/dL (7.2 mmol/L), 140 and 141 mg/dL (7.8 mmol/L), 180 mg/dL (10 mmol/L).

Comparative Pharmacology of Antidiabetic Agents

Agent/Generic Name (Brand Name)/Mechanism	FDA Indications	A1C Efficacy[a]	Adverse Effects	Comments
Insulin Replaces or augments endogenous insulin	Monotherapy; combined with any oral agent	↓ A1C[b] ↓FPG[b] ↓ PPG[b] ↓ TG	Hypoglycemia, weight gain, lipodystrophy, local skin reactions	Offers flexible dosing to match lifestyle and glucose concentrations. Rapid onset. Safe in pregnancy, renal failure, and liver dysfunction. Drug of choice when patients do not respond to other antidiabetic agents.
Insulin-Augmenting Agents				
Nonsulfonylurea secretagogues (glinides) Repaglinide (Prandin) Nateglinide (Starlix) Stimulates insulin secretion	Monotherapy; combined with metformin or TZD	Monotherapy: ↓ A1C ~1% (repaglinide) ↓ A1C ~0.5% (nateglinide) Combination: additional 1% ↓ A1C	Hypoglycemia, weight gain	Take only with meals. If a meal is skipped, skip a dose. Flexible dosing with lifestyle. Safe in renal and liver failure. Rapid onset. Useful to lower PPG.
Sulfonylureas Various; see Table 53-28. Stimulates insulin secretion. May decrease hepatic glucose output and enhance peripheral glucose utilization.	Monotherapy; combined with metformin; combined with insulin (glimepiride)	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Hypoglycemia, especially long-acting agents; weight gain (5–10 pounds); rash, hepatotoxicity, alcohol intolerance, and hyponatremia rare	Very effective agents. Some can be dosed once daily. Rapid onset of effect (1 week).

Incretin-Based Therapies

Glucagonlike peptide-1 receptor agonists/incretin mimetic Exenatide (Byetta) Liraglutide (Victoza) Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Monotherapy (exenatide only) Combined with metformin, SFU, or TZD, combined with metformin + SFU; combined with metformin + TZD	Monotherapy: ↓ A1C 0.8%–0.9% Combination: additional 1% ↓ in A1C	GI: nausea, vomiting, diarrhea; hypoglycemia (with SFUs); weight loss; reports of acute pancreatitis	Weight loss. Exenatide: take within 60 minutes before morning and evening meals or before two main meals of the day (≥6 hours apart). Liraglutide: Do not use if personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Do not use in patients with gastroparesis or severe GI disease. Administered by SC injection; pen device in use does not need to be refrigerated. Rare cases of pancreatitis with both drugs.
DPP-4 inhibitors Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Stimulates insulin secretion and reduces postprandial glucagon levels	Monotherapy; combined with metformin, SFU, or TZD; insulin (sitagliptin only)	Monotherapy: ↓ A1C 0.5%–0.8% Combination: ↓ A1C 0.5%–0.9%	Headache, nasopharyngitis, hypoglycemia (with SFU), rash (rare)	Dosed once daily. Taken with or without food. No weight gain or nausea. Need to adjust sitagliptin and sazagliptin dose in renal dysfunction. Reduce dose of SFU when combined. Rare reports of pancreatitis.

Amylin Receptor Agonists

Amylin mimetic Pramlintide (Symlin)	Type 1: Adjunct to mealtime insulin	T1: ↓ A1C 0.33% T2: ↓ A1C 0.40%	GI: nausea, decreased appetite	Take only immediately before meals; administered by SC injection. Do not use in patients with gastroparesis.
Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Type 2: Adjunct to mealtime insulin; ± SFU and metformin		Headache; hypoglycemia; weight loss (mild)	

Insulin Sensitizers

Insulin Sensitizers

Biguanides Metformin (Glucophage) ↓ Hepatic glucose output; ↑ peripheral glucose uptake	Monotherapy; combined with SFU or TZD; or with insulin	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	GI: nausea, cramping, diarrhea; lactic acidosis (rare)	Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain; weight loss possible. Mild reduction in cholesterol. Do not use in patients with renal or severe hepatic dysfunction.
Thiazolidinediones Rosiglitazone (Avandia) Pioglitazone (Actos) Enhances insulin action in periphery; increases glucose utilization by muscle and fat tissue; decreases hepatic glucose output	Monotherapy; combined with SFU, TZD, or insulin; combined with SFU + TZD	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Mild anemia; fluid retention and edema, weight gain, macular edema, fractures (in women)	Can cause or exacerbate HF; do not use in patients with symptomatic HF or class III or IV HF. Rosiglitazone may increase risk of MI. Increased risk of distal fractures in older women. Pioglitazone may increase risk of bladder cancer when used for >1 year. Slight reduction in TG with pioglitazone; slight increase in LDL-C with rosiglitazone. LFTs must be measured at baseline and periodically thereafter. Slow onset (2–4 weeks).

Delayers of Carbohydrate Absorption

α-Glucosidase inhibitors Acarbose (Precose) Miglitol (Glyset) Slow absorption of complex carbohydrates	Monotherapy; combined with SFUs, metformin, or insulin	Monotherapy: ↓ A1C ~0.5% Combination: additional ~0.5% ↓ A1C	GI: flatulence, diarrhea. Elevations in LFTs seen in doses >50 mg TID of acarbose	Useful for PPG control (↓ PPG 25–50 mg/dL). LFTs should be monitored every 3 months during the first year of therapy and periodically thereafter. Because miglitol is not metabolized, monitoring of LFTs is not required. Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain. If used in combination with hypoglycemic agents, advise patients to treat hypoglycemia with glucose tablets because absorption is not inhibited as with sucrose.
Bile acid sequestrant Colesevelam (Welchol)	Combined with metformin, SFU, or insulin	↓ A1C 0.3%–0.4%	Constipation, dyspepsia, and nausea; ↑ TG	Added benefit of ↓ LDL-C (by 12%–16%). Administer certain drugs 4 hours before. Take with a meal and liquid.

[a]Comparative effectiveness data provided for SFUs, glinides, TZDs, and α-glucosidase inhibitors.[307]

[b]Theoretically, unlimited glucose lowering with insulin therapy.

A1C, glycosylated hemoglobin; DPP-4, dipeptidyl peptidase-4; FDA, Food and Drug Administration; FPG, fasting plasma glucose; GI, gastrointestinal; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; MI, myocardial infarction; PPG, postprandial glucose; SC, subcutaneously; SFU, sulfonylureas; TG, triglycerides; TID, three times a day; T1, type 1 diabetes; T2, type 2 diabetes; TZD, thiazolidinediones.

Effect of Some Antidiabetics on Body Weight

Drug	Effect on body weight
Insulin	Weight gain
Sulfonylureas	Weight gain
Meglitinides	Weight gain
Metformin	No change or reduce
Thiazolidinediones	Weight gain + fluid retention
Amylin Analogues -pramlintide	Moderate weight loss
GLP-1 analogues (exenatide)	Weight loss
DPP-4 inhibitors (sitagliptin)	Weight neutral

Special Populations (Children and Adolescents with Type 2 DM)

- **Type 2 DM is increasing in adolescence probably caused by obesity and physical inactivity.**
- **Need extraordinary efforts on life-style modification measures.**
- **If failed, use metformin, sulfonylureas (or TZDs) or any combination of these that may improve glycemic control.**

Special Populations (Children and Adolescents with Type 2 DM)

- **Insulin therapy is the standard of care when glycemic goals can NOT be achieved or maintained with metformin and sulfonylurea.**

Special Populations (Elderly patients with Type 2 DM)

- Consideration of the risks of hypoglycemia, the extent of co-morbidities, self-care, nutritional status, social support, falls risk, mental status, and life expectancy should all influence glycemic goals and treatment selection.
- Avoidance of both hypo- and hyperglycemia is extremely important.

Special Populations (Elderly patients with Type 2 DM)

- **Elderly patients may have an altered presentation of hypoglycemia because of loss of autonomic nerve function with age.**
- **DPP-4 inhibitors (Sitagliptin), shorter-acting insulin secretagogues (rapaglinide), low-dose sulfonylureas, or α-glucosidase inhibitors may be used.**

Special Populations (Elderly patients with Type 2 DM)

- DPP-4 inhibitors or α-glucosidase have low risk of hypoglycemia.
- Metformin may be used at low doses if Cl_{cr} is > 30 mL/min/1.73 m^2.
- Simple insulin regimens with daily basal insulin may be appropriate.

Dipeptidyl peptidase-4 (DPP-4) inhibitors (Sitagliptin)

- **Inhibit DPP-4, the enzyme that degrades incretin hormones.**
- **Prolong the half-life of endogenous GLP-1.**
- **Decrease postprandial glucose levels.**
- **Decrease glucagon concentration.**
- **Increase circulating GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) and thus, insulin concentrations in a glucose-dependent manner.**

Sitagliptin

- **Most commonly used in combination with a TZD or metformin, or sulfonylureas.**
- **May be used as monotherapy.**
- **Used for type 2 DM orally, peaks within 1–4 hours, and has a half-life of approximately 12 hours.**
- **Dosage should be reduced in patients with impaired renal function**
- **Weight neutral.**

Sitagliptin

Adverse effects:

1. **Nasopharyngitis, upper respiratory infections, headaches**
2. **Hypoglycemia when the drug is combined with insulin secretagogues or insulin. Not associated with hypoglycemia when used alone.**
3. **Acute pancreatitis which may be fatal.**
4. **Allergic reactions.**

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

- These are true emergencies.
- Insulin given by continuous IV infusion (regular insulin = soluble insulin = crystaline zinc insulin) to restore the patient's metabolic status is the cornerstone of therapy.
- Pay attention to volume deficits, electrolyte disturbances, and acidosis.
- Treat the precipitating problem.

Hospitalization for Intercurrent Medical Illness

- **Patients on oral agents may need transient therapy with insulin to achieve adequate glycemic control during hospitalization.**
- **It is important to stop metformin in all patients who arrive in acute care settings as contraindications to metformin are prevalent in hospitalized patients (renal dysfunction, hypoxia..).**

Perioperative Management

- **Patients who require surgery may experience worsening of glycemia similar to those admitted to hospital for a medical illness.**
- **Acute stress increases counter-regulatory hormones.**
- **Therapy should be individualized based on the type of DM, nature of the surgical procedure, previous therapy, and metabolic control prior to the procedure.**

Perioperative Management

- **Patients on oral agents may need to be transiently switched to insulin to control blood glucose, preferably as continuous insulin infusions.**
- **Metformin should be discontinued temporarily after any major surgery until it is clear that the patient is hemodynamically stable and normal renal function is documented.**

Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors

- **SGLT2 is the main transporter for glucose re-absorption in the proximal tubules (90%).**
- **Inhibitors include canagliflozin which increases urinary glucose loss.**
- **Not very effective in chronic renal dysfunction and are even contraindicated.**

(SGLT2) Inhibitors

Adverse effects:

1. **Increased incidence of genital and urinary tract infections.**
2. **Intravascular volume contraction and hypotension ← osmotic diuresis.**
3. **Increase LDL cholesterol.**
4. **Higher rates of breast cancer and bladder cancer.**

*** this class is a bad idea (in my opinion!).**

FDA Warnings & Information on SGLT2 Inhibitors

- Serious Infection Of The Genital Area
- Increased Risk Of Leg And Foot Amputations With Canagliflozin
- Strengthens Kidney Warnings
- Increased Risk Of Leg And Foot Amputations, Mostly Affecting The Toes.
- Acid In The Blood And Serious Urinary Tract Infections
- Bone Fracture Risk And New Information On Decreased Bone Mineral Density.

Reference: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sodium-glucose-cotransporter-2-sglt2-inhibitors

Therapy of Osteoporosis

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Therapy of Osteoporosis

- **Osteoporosis is a bone disorder characterized by: low bone density, impaired bone architecture, and compromised bone strength, that predispose to an increased fracture risk.**
- **Osteoporosis is a major public health threat, with 55% of the people 50 years of age and older are expected to have this disease.**

Risk Factors of Osteoporosis

1. Female gender.
2. Advanced age.
3. Low body weight.
4. Systemic oral glucocorticoid therapy.
5. Cigarette smoking.
6. Alcohol (3 or more drinks/day).
7. Low calcium intake.
8. Low physical activity.
9. Vitamin D insufficiency and deficiency.
10. Others.

Medical Conditions Associated with Osteoporosis

1. Ovarian failure.
2. Testosterone deficiency.
3. Hyperthyroidism.
4. Cushing's syndrome.
5. Diabetes Mellitus.
6. Primary hyperparathyroidism
7. Anorexia nervosa.
8. Malabsorption.
9. Chronic liver disease and primary biliary cirrhosis.
10. Hypercalciuria.
11. Chronic kidney disease
12. Malignancies
13. Others.

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Drug	Comments
Anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)	↓ BMD and ↑ fracture risk; increased vitamin D metabolism leading to low 25(OH) vitamin D concentrations
Canagliflozin (sodium-glucose co-transport (SGLT-2) inhibitors)	↓ BMD and ↑ fracture risk
Furosemide	↑ fracture risk; increased calcium elimination by the kidney
Glucocorticoids (long-term oral therapy)	↓ BMD and ↑ fracture risk; increased bone resorption and decreased bone formation; Dose- and duration-dependent

BMD = bone mineral density

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Drug	Comments
Heparin (unfractionated, UFH) or low molecular weight heparin (LMWH)	↓ BMD and ↑ fracture risk (UFH >>> LMWH) with long-term use (> 6 months); decreased osteoblast formation and increased osteoclast function
Proton pump inhibitor therapy (long-term therapy)	↓ BMD and ↑ fracture risk; possible calcium malabsorption secondary to acid Suppression. (calcium, vitamin B12, iron & magnesium absorption may be reduced)
Selective serotonin reuptake inhibitors	↓ BMD and ↑ fracture risk; decreased osteoblast activity
Thiazolidinediones (pioglitazone and rosiglitazone)	↓ BMD and ↑ fracture risk; inhibit osteoblast differentiation and activate osteoclast differentiation
BMD = bone mineral density	

Prevention and Treatment

Desired Outcomes:

1. **The primary goal of osteoporosis care should be prevention.**
2. **Optimizing skeletal development and peak bone mass gain in childhood, adolescence, and early adulthood will reduce the future incidence of osteoporosis.**
3. **Once low bone mass or osteoporosis develops, the objective is to stabilize bone, improve bone strength and bone mass and prevent fractures.**

Prevention and Treatment

4. In patients who have already suffered osteoporotic fractures, reducing pain and deformity, improving functional capacity, improving quality of life, and reducing future falls and fractures are the main goals.

Prevention and Treatment

General approach to prevention and treatment:

A. **A bone-healthy life-style should begin at birth and continue throughout life: weight reduction, proper nutrition, moderation of alcohol intake, smoking cessation, exercise, and fall prevention.**

- **If employed early in life, it will help to optimize peak bone mass, and if continued throughout life it minimizes bone loss over time.**

Prevention and Treatment

B. **Adequate intake of calcium and vitamin D is the first step in prevention and treatment.**

C. **Prescription therapy is advised in any postmenopausal woman, or man age 50 years and older, presenting with a hip or vertebral fracture or low bone mass.**

Nonpharmacologic Therapy

Diet:

- **A diet well balanced in nutrients and minerals (without excessive protein) and limited use of salt, alcohol, and caffeine are important for bone health.**
- **Adequate amounts of calcium, vitamin D, and protein have documented impacts on bone health.**
- **Strontium (Sr) ranelate may be used for prevention of osteoporosis. It both increases deposition of new bone by osteoblasts and reduces the resorption of bone by osteoclasts.**

Nonpharmacologic Therapy

- **Being thin or having anorexia nervosa decrease bone mass.**

Calcium:

- **Adequate calcium intake is necessary for calcium homeostasis throughout life, bone development during growth, and bone maintenance.**
- **Dairy products have the highest amount of calcium per serving and are available in low-fat options.**

Nonpharmacologic Therapy

- **Carbohydrates, fat, and lactose increase calcium absorption whereas fiber, wheat bran, phytates (beans), oxylates (spinach), high-protein diets, caffeine, and smoking decrease absorption.**
- **When diet is NOT associated with adequate intake of calcium, calcium supplements are required.**

Nonpharmacologic Therapy

Vitamin D:

- **The 3 main sources of vitamin D are sunlight (cholecalciferol and vitamin D_3), diet, and supplements.**
- **Vitamin D_3 and D_2 come from oily fish, eggs, fortified dairy products.**
- **Inadequate concentrations of 25(OH) vitamin D are common.**

Nonpharmacologic Therapy

- **Low vitamin D concentrations result from insufficient intake, dietary fat malabsorption, decreased sun exposure, decreased skin production, or decreased liver and renal metabolism of vitamin D (may be genetically determined).**
- **Endogenous synthesis of vitamin D can be decreased by Sunscreen use.**
- **Darkly pigmented skin can decrease vitamin D production.**

Nonpharmacologic Therapy

- **Seasonal variations in vitamin D concentrations are seen with troughs in late winter and peaks in late summer.**
- **Because few foods are naturally high or fortified with vitamin D, most people, especially older adults, require supplementation.**

Nonpharmacologic Therapy

Alcohol:

- **Excessive alcohol consumption increases the risk for osteoporosis and fractures.**
- **It increases bone resorption and decreases bone formation by inhibiting signaling pathways and increasing oxidative stress that results in osteoblast apoptosis.**
- **Alcoholics may have poor nutrition, decreased calcium absorption, altered vitamin D metabolism, and impaired balance resulting in falls and fractures.**

Nonpharmacologic Therapy

Caffeine (?):

- **Although results are conflicting, excessive caffeine consumption may be associated with increased calcium excretion, increased rates of bone loss, and a modestly increased risk for fracture.**

Nonpharmacologic Therapy

Smoking:

- **Smoking cessation helps to optimize peak bone mass, minimize bone loss, and reduce fracture risk.**
- **The effect is dose- and duration-dependent, but even passive smoking shows adverse effects on BMD.**
- **It reduces intestinal calcium absorption.**
- **It increases 25(OH) vitamin D catabolism.**

Nonpharmacologic Therapy

Exercise:

- **It decreases the risk of falls and fractures by stabilizing bone density and improving muscle strength, coordination, balance, and mobility.**
- **Lack of physical activity can lead to suboptimal loading/straining, decreased stimulation of bone deposition, and a subsequently reduced peak bone mass.**

Nonpharmacologic Therapy

- **All patients who are medically fit should be encouraged to perform:**

A. a moderate-intensity weight-bearing activity (walking, jogging, golf, and stair climbing) daily.

B. a resistance activity (weight machines, free weights, or elastic bands).

Pharmacologic Therapy

Drug Treatments of First Choice:

- **Biphosphonates (alendronate, risedronate, zoledronic acid), combined with adequate calcium and vitamin D intake, or denosumab are the prescription medications of choice.**
- **This is based on evidence of reduction of the risk of hip and vertebral fractures.**
- **Ibandronate, teriparatide or raloxifene are alternatives and calcitonin is last-line therapy.**

Pharmacologic Therapy

- **Prescription therapy should be considered in any postmenopausal woman or man age 50 years and older presenting with osteoporosis or low bone mass with a significant probability of hip or any other osteoporosis-related fracture.**

Antiresorptive Therapies

Antiresorptive therapies include:

1. **Calcium**
2. **Vitamin D**
3. **Bisphosphonates**
4. **Estrogen agonists/antagonists (known previously as selective estrogen receptor modulators or SERMs)**
5. **Tissue selective estrogen complexes**
6. **Calcitonin**
7. **Denosumab**
8. **Estrogen**
9. **Testosterone**

Antiresorptive Therapies

Calcium Supplementation:

- **Adequate calcium intake is part of osteoporosis prevention and treatment.**
- **It should be combined with vitamin D, especially when osteoporosis medications are taken.**
- **It produces a small increase in BMD.**
- **It prevents fractures when combined with vitamin D.**

Antiresorptive Therapies

Adverse Effects:

1. **Constipation: can be treated with increased water intake, dietary fiber, and exercise.**
2. **Calcium carbonate can create gas and cause stomach upset. Calcium citrate has fewer GI adverse effects.**
3. **May increase kidney stones (?).**

- **Calcium intake should be less than 1500 mg daily, and preferably achieved through diet.**

Antiresorptive Therapies

Drug Interactions:

- **Proton pump inhibitors can decrease absorption from the carbonate product, because it requires acid for disintegration.**
- **Fiber laxatives can decrease the absorption of calcium if given concomitantly.**
- **Calcium can decrease the oral absorption of some drugs including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.**

Antiresorptive Therapies

Vitamin D Supplementation:

- **Vitamin D intake is critical for intestinal calcium absorption and when combined with calcium can prevent bone loss and decrease osteoporotic fractures.**
- **Vitamin D maintenances doses (800-2,000 units daily).**
- **Serum 25(OH) vitamin D is the best indicator of total body vitamin D status.**

Antiresorptive Therapies

Vitamin D ranges:

1. **30 to 100 ng/mL (sufficient)**
2. **20 and 29 ng/mL (insufficient)**
3. **< 20 ng/mL (deficient).**

- **Depend on the assay method and (??).**

Antiresorptive Therapies

Drug Interactions:

- **Some drugs can induce vitamin D metabolism: rifampin, phenytoin, barbiturates, and carbamazepine.**
- **Vitamin D absorption can be decreased by cholestyramine, colestipol, orlistat, and mineral oil.**
- **Vitamin D can enhance the absorption of aluminum; therefore aluminum-containing products should be avoided to prevent aluminum toxicity.**

Antiresorptive Therapies

Bisphosphonates:

- **Alendronate, risedronate, and intravenous zoledronic acid are indicated for postmenopausal females, males, and glucocorticoid-induced osteoporosis.**
- **Intravenous and oral ibandronate is indicated only for postmenopausal osteoporosis.**

Bisphosphonates

Pharmacology:

- **Are analogs of pyrophosphate in which the P-O-P bond is replaced by a nonhydrolyzable P-C-P bond.**
- **Bisphosphonates mimic pyrophosphate, an endogenous bone resorption inhibitor.**
- **They block prenylation and inhibit GTP-signaling proteins, which lead to decreased osteoclast maturation, number, recruitment, bone adhesion, and life span.**

Bisphosphonates

- **They retard formation and dissolution of hydroxyapatite crystals within and outside the skeletal system.**
- **They localize to regions of bone resorption and so exert their greatest effects on osteoclasts.**

Bisphosphonates

Efficacy:

- **Reduce fracture risk and increases BMD.**
- **The effect is dose-dependent and greatest in the first 12 months of therapy.**
- **Weekly alendronate, weekly and monthly risedronate, and monthly oral and quarterly intravenous ibandronate therapy produce equivalent BMD changes to their respective daily regimens.**
- **After discontinuation, the increased BMD is sustained for a prolonged period of time.**

Bisphosphonates

Adverse Effects:

1. **GI complaints: heartburn and dyspepsia, esophageal erosion and ulceration, GI bleeding.**

- **GI complaints are the most common reasons for discontinuing therapy.**
- **Switching to a different bisphosphonate or less frequent administration might resolve GI problems.**
- **Intravenous ibandronate and zoledronic acid can be used for patients with GI contraindications or intolerances to oral bisphosphonates.**

Bisphosphonates

2. **Injection reactions and musculoskeletal pain.**
- **If severe musculoskeletal pain occurs, the medication can be discontinued temporarily or permanently.**
3. **Acute phase reactions (fever, flu-like symptoms, myalgias, and arthralgias) are typically associated with intravenous administration, but rarely with daily, weekly or monthly oral bisphosphonates. This reaction usually diminishes with subsequent administration.**

Bisphosphonates

4. **Rarely, osteonecrosis of the jaw and atypical subtrochanteric femoral fractures.**

- **More commonly in patients with cancer, receiving higher-dose intravenous bisphosphonates, and glucocorticoids; and in those having diabetes mellitus.**
- **Risk factors include maxillary or mandibular bone surgery and poor oral hygiene.**

Bisphosphonates

Contraindications:

1. **Patients with creatinine clearances less than 30-35 mL/min.**
2. **Patients who have serious GI upset, peptic ulcer disease or esophageal motility disorders.**
3. **Patients who are pregnant should not take bisphosphonates.**

Bisphosphonates

Administration:

- **Each oral tablet should be taken with at least (~180 mL) of plain water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for ibandronate) before consuming any food, supplements (calcium and vitamin D), or drugs.**
- **The patient should remain upright (either sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration.**

Bisphosphonates

- **A patient who misses a weekly dose can take it the next day.**
- **If more than 1 day has lapsed, that dose is skipped until the next scheduled ingestion.**
- **If a patient misses a monthly dose: if the next month's dose is > 7 days away, take the missed dose on the morning you remember. Then resume your normal schedule. If the next dose is < 6 days away, wait until the next scheduled dose.**
- **Before intravenous bisphosphonates are used, the patient's serum calcium concentration must be normalized.**

Bisphosphonates

- **Creatinine clearance should be monitored before each dose of zoledronic acid.**
- **The intravenous products need to be administered by a healthcare provider.**
- **The quarterly ibandronate injection is given intravenously over 15 to 30 seconds.**
- **The injection can also be diluted with dextrose 5% in water or normal saline and used with a syringe pump.**

Bisphosphonates

- **Once-yearly administration of zoledronic acid should be infused over at least 15 minutes with a pump.**
- **Acetaminophen can be given to decrease acute phase reactions.**
- **Although these medications are effective, adherence is poor and results in decreased effectiveness.**

Bisphosphonates

- **A drug holiday could be considered in postmenopausal women after 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates.**
- **In women with a high fracture risk or lower hip BMD, continuing oral bisphosphonates for 10 years or intravenous bisphosphonates for 6 years should be considered (evidence on duration??).**
- **Other therapeutic uses include hypercalcemia associated with malignancy.**

Antiresorptive Therapies

Denosumab:

It is indicated for treatment of osteoporosis:

1) **in women and men at high risk of fractures.**
2) **to increase bone mass in men receiving androgen deprivation therapy [antiandrogens (flutamide), LHRH agonists (Leuprolide) for non-metastatic prostate cancer.**
3) **in women receiving adjuvant aromatase inhibitor therapy (anastrozole) for breast cancer who are at high risk of fractures.**

Antiresorptive Therapies

Pharmacology:

- **Denosumab is a fully human monoclonal antibody that binds to RANKL, blocking its ability to bind to its RANK (receptor activator of nuclear factor-κb) receptor on the surface of osteoclast precursor cells and mature osteoclasts.**
- **RANKL/RANK signaling regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling.**
- **Thus, it inhibits osteoclastogenesis and increases osteoclast apoptosis.**

Antiresorptive Therapies

- **Following subcutaneous injection, rapid suppression of bone turnover occurs within 12 hours.**

Pharmacokinetics:

- **Peak concentration is ~ 10 days.**
- **The half-life is ~ 25 days and the concentration slowly declines over a period of 4 to 5 months.**
- **The drug does NOT accumulate with repeated dosing at 6-month intervals.**
- **No dosage adjustment is necessary in renal impairment.**

Antiresorptive Therapies

Efficacy:

- **Over 3 years, it significantly decreased vertebral fractures, non-vertebral fractures, and hip fractures in postmenopausal women with low bone density.**
- **The BMD effects are at least similar to weekly alendronate, and can increase BMD in patients with prior alendronate therapy.**
- **Activity dissipates with drug discontinuation .**

Antiresorptive Therapies

Adverse Effects:

1. **Dermatitis, eczema, and rashes.**
2. **Bone turnover suppression.**
3. **Serious infections including skin infections.**
4. **Muscle, bone, and joint pain and atypical fractures.**
5. **Hypocalcemia (more common in severe renal impairment).**

Antiresorptive Therapies

- **Any existing hypocalcemia should be corrected prior to use with adequate calcium and vitamin D supplements.**
- **Monitoring of serum calcium, magnesium, and phosphorus is recommended within 14 days of administration in patients having a Cl_{Cr} < 30 mL/min.**

Antiresorptive Therapies

Mixed Estrogen Agonists/Antagonists:

Raloxifene:

- **is a second-generation mixed estrogen agonist/antagonist used for:**

1. **prevention and treatment of postmenopausal osteoporosis**
2. **reducing the risk of invasive breast cancer in postmenopausal women with and without osteoporosis.**

- **No benefit on cardiovascular disease.**

Antiresorptive Therapies

Pharmacology:

- **Raloxifene is an agonist at bone estrogen receptors and antagonist at breast estrogen receptors; it has minimal effect on the uterus.**
- **Bazedoxifene is an agonist at bone, and antagonist at the uterus and breast, with no breast cancer prevention effects.**
- **After raloxifene discontinuation, the effect is lost, with bone loss returning to age- or disease-related rates.**

Antiresorptive Therapies

Adverse Events:

1. **Hot flushes are common with raloxifene but not with bazedoxifene.**
2. **Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these adverse events.**
3. **Leg cramps and muscle spasms are also common.**
4. **Thromboembolic events are uncommon, but can be fatal.**

Antiresorptive Therapies

Potential Drug Interactions:

1. **Raloxifene is highly protein bound (95%), and may have binding interactions with highly protein bound drugs (warfarin).**
2. **Cholestyramine can decrease raloxifene absorption.**
3. **Rifampin, phenytoin, carbamazepine, and phenobarbital can decrease bazedoxifene levels by inducing intestinal and liver uridine diphosphate glucuronosyltransferases.**
4. **Estrogen metabolism is decreased with CYP3A4 inhibitors.**

Antiresorptive Therapies

Contraindications:

1. **active or history of venous thromboembolic disease.**
2. **pregnancy, or childbearing potential.**
3. **known coronary artery disease.**
4. **peripheral vascular disease.**
5. **atrial fibrillation.**
6. **prior history of cerebrovascular accidents.**

Anabolic Therapies

Teriparatide:

- **It is a recombinant human product representing the first 34 amino acids in human PTH.**
- **It increases bone formation, bone remodeling rate, and osteoblast number and activity.**
- **It inhibits osteoblast apoptosis.**
- **Both bone mass and architecture are improved.**

Anabolic Therapies

Indications:

1. **Postmenopausal women at high risk of fractures.**
2. **Men with idiopathic or hypogonadal osteoporosis at high risk of fractures.**
3. **Men or women intolerant to other osteoporosis medications.**
4. **Patients with glucocorticoid-induced osteoporosis.**
5. **Patients who have a history of osteoporotic fracture, multiple risk factors for fracture, very low bone density, or have failed or are intolerant of previous bisphosphonate therapy.**

Anabolic Therapies

- **Discontinuation of teriparatide therapy results in a decrease in BMD.**

Administration:

- **Daily subcutaneous injection with site rotation.**
- **The administration of the first dose should take place with the patient either sitting or lying down to avoid orthostatic hypotension.**
- **Duration of therapy is 18 to 24 months.**

Anabolic Therapies

Adverse Effects:

- **Transient and rare hypercalcemia (avoid in patients having hypercalcemia).**
- **May predispose to osteosarcoma (seen in lab animals).**
- **Avoid in Paget's bone disease, unexplained elevations of alkaline phosphatase, patients with open epiphyses, or patients with prior radiation therapy involving the skeleton.**

Glucocorticoid-Induced Osteoporosis

- **Current and prior glucocorticoid use is the most common cause of drug-induced osteoporosis.**
- **Trabecular bone is affected more than cortical bone.**
- **The pathophysiology of glucocorticoid bone loss is multifactorial:**

1. **They decrease bone formation through decreased proliferation and differentiation and enhanced apoptosis of osteoblasts.**
2. **They increase apoptosis of osteocytes.**

Glucocorticoid-Induced Osteoporosis

3. They increase bone resorption by increasing RANKL.
4. They can reduce estrogen and testosterone concentrations.
5. Negative calcium balance: decreased calcium absorption and increased urinary calcium excretion via alterations in calcium transporters.
6. The underlying disease requiring this medication also can affect bone metabolism negatively.

Glucocorticoid-Induced Osteoporosis

- **All patients using glucocorticoids should practice a bone-healthy lifestyle.**
- **All patients starting or receiving glucocorticoid therapy (any dose or duration) should ingest 1,200 to 1,500 mg elemental calcium and 800 to 1,200 units of vitamin D daily or more to achieve therapeutic 25-(OH) VD concentration.**
- **Glucocorticoids should be used at the lowest dose and for the shortest duration possible.**
- **After discontinuation, fracture risk is still higher than never users.**

Glucocorticoid-Induced Osteoporosis

Treatment:

- **Alendronate, risedronate, zoledronic acid, and teriparatide can be used.**
- **Raloxifene and denosumab may decrease bone loss from glucocorticoids.**
- **Bisphosphonate drug holiday is generally NOT considered in this condition.**

Therapy of Gout and Hyperuricemia

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Introduction

Gout describes a heterogeneous clinical spectrum of diseases including:

1. **Elevated serum urate concentration (hyperuricemia).**
2. **Recurrent attacks of acute arthritis associated with:**

a. **monosodium urate (MSU) crystals in synovial fluid leukocytes.**

b. **deposits of monosodium urate crystals (tophi) in tissues in and around joints.**

c. **interstitial renal disease.**

d. **uric acid nephrolithiasis.**

Introduction

- **The underlying metabolic disorder of gout is hyperuricemia, defined as serum that is supersaturated with monosodium urate.**
- **At 37°C, serum urate concentrations around 7 mg/dL begin to exceed the limit of solubility for monosodium urate.**
- **Elevated serum urate level is the single most important risk factor for the development of gout.**

Introduction

- **Hyperuricemia does NOT always lead to gout, and many patients with hyperuricemia remain asymptomatic.**
- **Another major contributor to the increased prevalence of gout is obesity.**
- **Dietary and life-style factors linked to obesity (consumption of alcohol, sugary beverages, and red meat; along with a sedentary life-style) may be associated with gout.**

Introduction

- **Uric acid is produced from purines ← increased breakdown of tissue nucleic acids:**

1. **Starvation.**
2. **Chronic hemolytic anemias.**
3. **Toxemia of pregnancy.**
4. **Obesity.**
5. **Acute alcoholism.**
6. **Psoriasis.**

Introduction

7. **Myeloproliferative and lymphoproliferative disorders.**
8. **Polycythemia vera.**
9. **Cytotoxic drugs use can result in overproduction of uric acid secondary to lysis and breakdown of cells.**

Introduction

Acute Gouty Arthritis:

- **Acute inflammatory mono-arthritis.**
- **The first metatarsophalangeal joint is often involved.**
- **Any joint of the lower extremity, wrist or fingers can be affected.**
- **Gout may include: nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, etc.**

Introduction

- **Acute attacks of gout can be precipitated by a rapid change in serum uric acid levels, either rapid increase or rapid decrease.**
- **When serum uric acid level is rapidly decreased by uric acid lowering agent, dissolution of tophi takes place which will increase serum uric acid levels.**

Introduction

- **~ 90% of filtered uric acid is reabsorbed in the proximal tubule, by both passive and active transport mechanisms.**
- **Proximal tubular sodium reabsorption and uric acid reabsorption are linked, so that conditions that enhance sodium reabsorption (dehydration) lead to increased uric acid reabsorption. (Co-transport)**
- **Uric acid is also secreted in the tubules by an active transport process.**

Drug-Induced Hyperuricemia

Drugs capable of inducing hyperuricemia and gout:

1. **Diuretics.**
2. **Nicotinic acid.**
3. **Ethanol.**
4. **Pyrazinamide.**
5. **Levodopa.**
6. **Ethambutol.**

Drug-Induced Hyperuricemia

7. **Cytotoxic drugs.**
8. **Cyclosporine.**
9. **Salicylates:**

a) **At < 2g/day, salicylates block the active secreting system of uric acid leading to uric acid retention.**

b) **At > 2.5g/day, salicylates are uricosuric by blocking active uric acid reabsorption.**

- **Insulin resistance may be associated with gout, by enhancing renal urate reabsorption.**

Therapy of Gout and Hyperuricemia

The goals of treatment of gout:

1. **To terminate the acute attack.**
2. **To prevent recurrence of attacks.**
3. **To prevent complications associated with chronic deposition of urate crystals in tissues.**

- **These goals can be accomplished through a combination of pharmacologic and nonpharmacologic methods, including focused patient education.**

Acute Gouty Arthritis

Therapy:

- **For most patients, acute attacks of gouty arthritis may be treated successfully with:**

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs).**
2. **Corticosteroids.**
3. **Colchicine.**

- **All are considered first-line monotherapy for the treatment of acute gout.**

Acute Gouty Arthritis

- **Treatment should be started within 24 hours of the onset of an attack, and continued until complete resolution.**
- **Combination drug therapy is indicated in:**

1. **More severe cases.**
2. **Multiple joints involvement.**
3. **High intensity pain.**

Acute Gouty Arthritis

NSAIDs:

- **NSAIDs are a mainstay of therapy for acute attacks of gouty arthritis - excellent efficacy and minimal toxicity with short-term use.**
- **Following resolution of the attack, NSAID therapy may be tapered, especially in patients with hepatic or renal insufficiency. (to prevent rebound)**
- **Resolution of an acute attack takes 5-8 days after initiating therapy.**

Acute Gouty Arthritis

Adverse effects:

1. **GI: gastritis, bleeding, perforation.**
2. **Kidney: renal papillary necrosis, reduced creatinine clearance (renal dysfunction).**
3. **Cardiovascular system: sodium and water retention, increased blood pressure.**
4. **CNS: impaired cognitive function, headache, dizziness.**

- **etc**

Acute Gouty Arthritis

- **Should be use with caution in patients with a history of peptic ulcer disease, congestive heart failure, uncontrolled hypertension, renal insufficiency, coronary artery disease, or who are concurrently receiving anticoagulants or antiplatelet drugs.**
- **Some of the choices include but are NOT limited to indomethacin, naproxen, and sulindac.**
- **Selective cyclooxygenase-2 (COX-2) inhibitors are better tolerated in patients with GI problems, but have higher cardiovascular risk. (Celecoxib, etoricoxib and lumiracoxib are options).**

Acute Gouty Arthritis

Corticosteroids:

- **Corticosteroids are equivalent to NSAIDs in the treatment of acute gout flares.**
- **They can be used either systemically or by intra-articular injection, depending on the number of joints involved.**
- **Should be tapered gradually to avoid rebound.**
- **Prednisone, prednisolone, and methylprednisolone are some options for systemic use, and triamcinolone acetonide for intra-articular injections.**

Acute Gouty Arthritis

Adverse effects:

- **Are generally dose- and duration-dependent.**
- **Short-term use for treatment of acute attacks is generally well tolerated.**
- **Increase blood sugar.**
- **Monitor patients with a history of GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders.**
- **Long-term corticosteroid use should be avoided because of the risk for osteoporosis, hypothalamic–pituitary-adrenal axis suppression, and cataracts.**
- **etc…**

Acute Gouty Arthritis

Colchicine:

- **Colchicine is an antimitotic drug that is highly effective at relieving acute attacks of gout.**
- **When started within the first 24 hours of an acute attack, it produces a response within hours of administration.**
- **Should be started within 36 hours of attack.**
- **Delayed initiation of colchicine is associated with substantial reduction of response.**

Acute Gouty Arthritis

Adverse effects:

- **Dose-dependent GI adverse effects: nausea, vomiting, and diarrhea.**
- **Neutropenia and axonal neuromyopathy, worsened in patients taking statins, or in those with renal insufficiency.**
- **Concurrent administeration with P-glycoprotein or cytochrome P450 3A4 inhibitors (clarithromycin or cyclosporine), increases colchicine concentration.**
- **Use with caution inpatients with renal and hepatic dysfunction.**

Hyperuricemia in Gout

Nonpharmacologic Therapy:

- **Recurrent gout attacks can be prevented by maintaining low uric acid levels.**
- **Patient education is a critical first step in the management of hyperuricemia.**

Lifestyle/Dietary modification:

1. **Weight loss and exercise may enhance renal excretion of urate.**

Hyperuricemia in Gout

2. **Restriction of alcohol intake because alcohol reduces renal urate excretion.**
- **Long-term alcohol intake increases production of purines as a by-product of the conversion of acetate to acetyl coenzyme-A in the metabolism of alcohol.**
3. **Encourage the consumption of vegetables and low-fat dairy products, which lower urates.**

Hyperuricemia in Gout

4. Reduce consumption of high-fructose diet, and purine-rich foods (organ meats and some seafood), which cause uric acid elevation.
5. Avoid (if possible) drugs that may elevate uric acid levels:

a. Thiazide and loop diuretics.
b. Calcineurin inhibitors.
c. Niacin.
d. Low-dose aspirin.

Hyperuricemia in Gout

- **Thiazide diuretics and Low-dose aspirin are useful in treating hypertension and cardio-protection, respectively.**

Hyperuricemia in Gout

Pharmacologic Therapy:

- **After the first attack of acute gouty arthritis, consider prophylactic use of uric acid-lowering drugs.**
- **(Antiinflamatory drugs prevent attacks only).**

Other indications for lowering uric acid include:

1) **the presence of tophi.**
2) **chronic kidney disease (stage 2 or worse).**
3) **history of urolithiasis.**
4) **Cancer chemotherapy.**

Hyperuricemia in Gout

- **Uric acid-lowering therapy should be long-term.**
- **Reduction of serum uric acid concentrations can be accomplished pharmacologically by:**

a. **decreasing the synthesis of uric acid (xanthine oxidase inhibitors)**
b. **increasing the renal excretion of uric acid (uricosuric agents).**

Hyperuricemia in Gout

- **Xanthine oxidase inhibitors are first-line therapy.**
- **Probenecid, a potent uricosuric, is an alternative in patients with a contraindication or intolerance to xanthine oxidase inhibitors.**

Hyperuricemia in Gout

Xanthine Oxidase Inhibitors:

- **Impair the conversion of hypoxanthine to xanthine and xanthine to uric acid.**
- **Effective in over-producers of uric acid, as well as in those with low excretion.**

Allopurinol:

- **It is an effective uric acid-lowering agent, but long-term adherence is low.**

Hyperuricemia in Gout

Adverse effects:

- **Mild-moderate adverse effects: skin rash, leukopenia, GI disturbances, headache, and urticaria.**
- **More severe adverse reactions including severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), hepatitis, interstitial nephritis, and eosinophilia. These adverse effects are associated with a 20-25% mortality.**

Hyperuricemia in Gout

Febuxostat:

- **Similar to allopurinol, but newer drug.**

Adverse effects:

- **Nausea, arthralgias, and minor hepatic transaminases elevation.**
- **An advantage of febuxostat is that it does not require dose adjustment in patients with moderate hepatic and renal impairment.**

Hyperuricemia in Gout

Uricosuric Drugs:

- They increase the renal excretion of uric acid by inhibiting its proximal tubular reabsorption.
- The drug used most widely is probenecid.
- Uricosuric drugs cause marked uricosuria and may cause uric acid stone formation.
- The maintenance of adequate urine flow and alkalinization of the urine may reduce uric acid nephrolithiasis.

Hyperuricemia in Gout

- **Other major adverse effects include GI irritation and precipitation of acute gouty arthritis.**
- **Salicylates at low dose ranges may interfere with their mechanism and result in treatment failure.**
- **Probenecid can inhibit the tubular secretion of other organic acids and increase plasma concentrations of penicillins, cephalosporins, sulfonamides, and indomethacin.**

Hyperuricemia in Gout

Uricosuric drugs are contraindicated in patients:

1. **allergic to them.**
2. **with impaired renal function (a creatinine clearance less than 50 mL/min).**
3. **who are overproducers of uric acid. (for such patients, a xanthine oxidase inhibitor should be used).**

Hyperuricemia in Gout

Lesinurad:

- **It is a selective uric acid reabsorption inhibitor (SURI).**
- **It inhibits urate transporter 1 (URAT1), a transporter found in the proximal renal tubules, resulting in uric acid excretion.**

Adverse effects:

1. **Increased serum creatinine, elevated lipase, increased creatine kinase, and urticaria.**

Hyperuricemia in Gout

2. Acute renal failure.

- **It should not be used in patients with creatinine clearance less than 45 mL/min.**
- **May be used in a combination with a xanthine oxidase inhibitor for treatment of hyperuricemia in patients who have not achieved target serum uric acid levels with xanthine oxidase inhibitor monotherapy.**

Hyperuricemia in Gout

3. Headache, flu-like symptoms.
4. Gastroesophageal reflux disease (GERD).
5. Kidney stones.

Hyperuricemia in Gout

Pegloticase:

- **It is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, a water-soluble and easily excretable compound.**
- **It is effective in reducing serum uric acid and resolving tophi in patients with severe gout and hyperuricemia who failed or had a contraindication to allopurinol therapy.**

Hyperuricemia in Gout

- **Severe gout has at least one of the following criteria:**

1. **three or more gout flares within the last 18 months.**
2. **one or more tophi.**
3. **joint damage due to gout.**

- **Given as bi-weekly IV infusions over no less than 2 hours, which may NOT be convenient.**

Hyperuricemia in Gout

- May be associated with infusion-related allergic reactions, and patients must be pre-treated with antihistamines and corticosteroids before therapy.
- Duration of therapy is unknown.
- Immunogenic and leads to development of pegloticase antibodies.
- An agent of last resort that should be reserved for patients with refractory hyperuricemia with gout.

Anti-Inflammatory Gout Prophylaxis during Urate-Lowering Therapy (ULT)

- **Initiation of ULT can prompt an acute attack of gout due to remodeling of urate crystal deposits in joints as a result of rapid lowering of urate concentrations.**
- **Thus, prophylactic antiinflammatory therapy is recommended to prevent gout attacks.**
- **Low-dose oral colchicine and low-dose NSAIDs are first-line prophylactic therapies, with stronger evidence supporting use of colchicine.**

Anti-Inflammatory Gout Prophylaxis during Urate-Lowering Therapy (ULT)

- **Low-dose corticosteroid therapy is an alternative in patients with intolerance, contraindication, or lack of response to first-line therapy.**
- **Continue prophylaxis for at least 3 months after achieving target serum uric acid or 6 months total, whichever is longer.**
- **For patients with one or more tophi, prophylactic therapy should be continued for 6 months following achievement of serum urate target.**

Urate Nephrolithiasis

- **Treatment by life-style modification mentioned earlier.**
- **Hydration to maintain a urine volume of 2 to 3 L/day.**
- **Reduction of urinary uric acid excretion.**
- **Alkalinization of urine. Urine pH should be maintained at 6-6.5, by the administration of potassium bicarbonate or potassium citrate.**

  (At a urine pH of 6.75, > 90% of the total urinary uric acid will be as more soluble urate salt).

Urate Nephrolithiasis

- **Administration of alkali with sodium salts should be avoided for two reasons:**

1. **The sodium-induced volume expansion will increase sodium excretion, which can lead to proximal Na reabsorption.**
- **Such a mechanism may be associated with secondary calcium reabsorption with sodium, leading to hypercalcemia. This can lead to calcium oxalate stone formation.**

Urate Nephrolithiasis

2. **Older patients with uric acid kidney stones may also have hypertension, congestive heart failure, or renal insufficiency. Overload with alkalinizing sodium salts or unlimited fluid intake can worsen these conditions.**

- **Acetazolamide produces rapid and effective urinary alkalinization.**

Urate Nephrolithiasis

- **The mainstay of drug therapy for recurrent uric acid nephrolithiasis is xanthine oxidase inhibitors.**
- **They are also recommended as prophylactic treatment for patients who will receive cytotoxic agents for the treatment of lymphoma or leukemia.**