4. Mechanism

Drug enters host cells

Directly binds to (catalytic site of) reverse transcriptase

Inhibits cDNA formation (from ssRNA)

Inhibits viral replication

Killing of virus

5. Adverse effects:
   a) Hypersensitivities (rashes/urticaria/Steven-Johnson’s syndrome)
   b) Hepatotoxicity
   c) Headache, insomnia
   d) Nausea, vomiting, epigastric pain

*Host Pols are also inhibited
SUB-PART NA 03 (B): GnRH ANTAGONISTS

11. Uses:
   a) Advanced prostate cancer
   b) Uterine fibroid, endometriosis
   c) IVF (as adjuvant)

12. Advantages of GnRH antagonists over GnRH agonists:

1. **Shorter duration of administration** (due to immediate gonadotropin suppression by competitive antagonism)
2. ↓ risk of ovarian hyperstimulation syndrome & multiple pregnancy
3. More complete suppression of endogenous gonadotropin secretion

13. Rationale of combining GnRH agonists with androgen receptor antagonist in prostatic Ca:

1. In treatment of prostatic Ca, GnRH agonists can cause initial flare-up of tumor (due to ↑ gonadotropin secretion for the 1st 1 – 2 weeks)
2. This can be prevented by androgen receptor antagonists (flu-/ bicalu-tamide)
9. Mechanisms:
   a) Inhibits thyroperoxidase:
   b) Inhibits peripheral deiodination of $T_4 \rightarrow T_3$

10. Pharmacokinetics (of propylthiouracil):

<table>
<thead>
<tr>
<th>Stage</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Rapid oral absorption</td>
</tr>
<tr>
<td>D</td>
<td>*Widely distributed</td>
</tr>
<tr>
<td></td>
<td>*Crosses placenta &amp; enters milk</td>
</tr>
<tr>
<td></td>
<td>*Concentrated in thyroid gland</td>
</tr>
<tr>
<td>M</td>
<td>In liver</td>
</tr>
<tr>
<td>E</td>
<td>*Via urine</td>
</tr>
<tr>
<td></td>
<td>*$t_{1/2}$: 1.25 hrs</td>
</tr>
<tr>
<td></td>
<td>*$t_{1/2}$ (of methimazole): 4 – 6 hrs</td>
</tr>
</tbody>
</table>

11. Uses:

<table>
<thead>
<tr>
<th>Use</th>
<th>Description</th>
</tr>
</thead>
</table>
13. Severe allergic reactions not responding to antihistamines:
   a) Anaphylactic shock
   b) Angioneurotic edema
   c) Chronic urticaria
   d) Hay fever

14. Stimulation of fetal lung maturation:
   1. Accelerates surfactant formation
   2. Betamethasone is preferred due to...
      a) ↓ maternal protein binding → ↑ drug transfer via placenta to fetus
      b) ↓ placental metabolism

15. Malignancies:
   a) ALL (lympholytic; induces apoptosis)
   b) Hodgkin’s lymphoma

16. Cerebral edema (dexamethasone used; due to absence of MC activity)

17. Neurocysticercosis, rheumatic fever, septic shock, thyroid storm

SUB-PART ND 02 (D): ADVERSE EFFECTS

18. Adverse effects:

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Preview from Notesale.co.uk**

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1. Classification:

*Natural estrogens are rapidly inactivated in liver. Synthetic estrogens are metabolized less

**Conjugated estrogens are SO₄ esters of natural estrogens

2. Estrogen receptors:

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Predominant Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERα</td>
<td>Uterus, vagina, breast, hypothalamus, pituitary, vessels</td>
</tr>
<tr>
<td>ERβ</td>
<td>prostate, ovaries</td>
</tr>
</tbody>
</table>

*Most sites express both receptors

3. Post-menopausal symptoms (due to ↓ estrogen & progesterone):

<table>
<thead>
<tr>
<th>Change</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urogenital</td>
<td>Vaginal dryness/ itching, ↑ risk of UTI</td>
</tr>
<tr>
<td>CVS</td>
<td>Hot flushes, ↑ risk of MI &amp; stroke</td>
</tr>
<tr>
<td>Bone</td>
<td>↑ risk of osteoporosis</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Dryness &amp; thinning of skin</td>
</tr>
<tr>
<td>Psychological</td>
<td>Irritability, depression</td>
</tr>
</tbody>
</table>
4. Physiological actions:

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex organs</td>
<td>*Growth of uterus, Fallopian tubes &amp; vagina</td>
</tr>
<tr>
<td></td>
<td>*Endometrium proliferation (excess estrogens can cause hyperplasia → abnormal bleeding)</td>
</tr>
<tr>
<td></td>
<td>*Promotes rhythmic contractions of Fallopian tubes &amp; uterus</td>
</tr>
<tr>
<td></td>
<td>*Thin, watery &amp; alkaline secretions in cervix</td>
</tr>
<tr>
<td>2° sex characteristics</td>
<td>*Breast enlargement</td>
</tr>
<tr>
<td></td>
<td>*Axillary &amp; pubic hair growth</td>
</tr>
<tr>
<td></td>
<td>*Body fat distribution</td>
</tr>
<tr>
<td>Metabolic &amp; CVS</td>
<td>*↓ bone resorption</td>
</tr>
<tr>
<td></td>
<td>*Salt &amp; water retention → edema</td>
</tr>
<tr>
<td></td>
<td>*↑ HDL, ↓ LDL</td>
</tr>
<tr>
<td></td>
<td>*↑ circulating lvls of clotting factors (II, VII, IX, X) → ↑ coagulation</td>
</tr>
<tr>
<td></td>
<td>*(Weak) diabetogenic effects</td>
</tr>
</tbody>
</table>
16. Mechanism:

Binds to & blocks ERα & ERβ

Blocks –ve feedback of estrogens

Induces FSH & LH secretion

OVULATION

17. Uses:

a) Infertility due to anovulation [along with menotropins]

b) ♂ [surprise!!] infertility due to oligozoospermia (promotes testosterone secretion & spermatogenesis)

c) IVF [along with gonadotropins]

*In case of ovarian/pituitary failure, clomiphene citrate becomes useless

18. Adverse effects:

a) Hot flushes

b) Multiple ovulations ➔ multiple pregnancies

c) Hyperplastic/ polycystic ovaries

d) Weight gain, alopecia (reversible)
22. Adverse effects:
   a) Vomiting
   b) Hot flushes, menstrual abnormalities, endometrial Ca
   c) ↑ risk of thromboembolism

**SUB-SUB-PART NE 01 (B 4): RALOXIFENE**

23. Actions & uses: [same as #19 above, EXCEPT that it PREVENTS endometrial proliferation & hence, NO ↑ risk of endometrial Ca]

24. Adverse effects:
   a) Hot flushes
   b) Leg cramps
   c) ↑ risk of DVT & pulmonary embolism

*Tamoxifen is preferred in breast cancer while raloxifene post-menopausal osteoporosis

**SUB-PART NE 01 (C): AROMATASE @ ESTROGEN SYNTHESIS INHIBITORS**

25. E.g. drugs:

   1. Aminoglutethimide
   2. Let-/ anast-/ fad-rozole
   3. For-/ exe-mestane

26. Mechanism:
Amenorrhea

*If bleeding occurs, indicates active estrogen phase

8. Adverse effects:

1. **Breast engorgement** (↑ risk of breast Ca)

2. ↑ body **temperature**, headache

3. **Irregular menstrual bleeding**, ↓ libido

4. **Thromboembolism, atherosclerosis** (due to ↓ HDL & ↑ LDL; this does NOT apply to ○3)

5. Precipitates **diabetes** (by ↑ blood sugar)

6. **Maculinization** of ♀ fetus (in early stages of pregnancy)

---

**SUB-PART NE 02 (D): ANTI-PROGESTINS**

9. E.g. drugs: mifepristone/ onapristone/ gestin-one

10. **Competitively** bind to peripheral **progestin receptors**

11. Uses (of mifepristone):

<table>
<thead>
<tr>
<th>Use</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pregnancy (≤ 7 weeks) termination

*Single oral dose of 600 mg, followed by single dose misoprostol 400 mg after 48 hrs
*Blocks progesterone support to endometrium (→ menstruation)
*Releases PGs → uterine contractions → abortion
*Dislodges blastocyst → ↓ HCG (luteolysis)
*Softens cervix

Cervical ripening/softening

Given 48 hrs prior to induction of labor to soften/dilate cervix

Induction of labor in late pregnancy

*Causes uncontrolled PG release
*Stimulates uterine contractions (along with PGs & oxytocins)
*Expels dead/abnormal fetus

Once-a-month contraception

*Single dose of 200 mg given 2 days after mid-cycle
*Prevents progesterone-mediated secretory changes
*Not advisable (as it can disrupt next month’s cycle)
| Post-coital contraceptive | *Single dose of 600 mg given within 72 hrs of coitus  
*Blocks decidualization, interferes with implantation |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td><strong>Gestinone</strong> is more effective</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td></td>
</tr>
<tr>
<td>Breast Ca</td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td><strong>Mifepristone has anti-GC activity</strong></td>
</tr>
</tbody>
</table>

12. Adverse effects:
   a) Anorexia
   b) Vomiting, diarrhea
   c) Abdominal/uterine cramps (due to PG)
   d) Menstrual cycle alterations
   e) Prolonged bleeding
   f) Failed abortion

**SUB-PART NE 02 (E): SPRM (SELECTIVE PROGESTERONE RECEPTOR MODULATORS)**

13. Have **selective stimulation** in 1 organ & **selective inhibition** in another

14. E.g. drugs: ulipristal acetate, asoprisnil, proellex
15. Uses:
   a) Leiomyoma
   b) Endometriosis
   c) Breast Ca
23. Adverse effects
   a) Nausea, vomiting (amtiemetics shud be used), headache, dizziness
   b) Breast tenderness
   c) Leg/ abdominal cramps

SUB-SUB-SUB-PART NE 03 (B 2e): DRUG INTERACTIONS

24. Drug interactions (of OCPs):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on OCPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme inducers</td>
<td>↑ metabolism of OCPs → contraceptive failure</td>
</tr>
<tr>
<td>Tetracyclines/ ampicillin</td>
<td>Interferes with enterohepatic cycling of estrogens (these antibiotics kill the bacteria involved in deconjugation of OCPs) → ↓ absorption → ↓ bioavailability) → ↓ OCP efficacy</td>
</tr>
</tbody>
</table>

SUB-SUB-PART NE 03 (B 3): PARENTERAL CONTRACEPTIVES (INJECTABLES)

SUB-SUB-SUB-PART NE 03 (B 3a): LONG-ACTING PROGESTIN ALONE
**SUB-PART NE 04 (F): ED**

**SUB-SUB-PART NE 04 (F 1): GENERAL**

13. Treatment:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>E.g. Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE-5 inhibitors</td>
<td>Sildenafil, tadalafil, vardenafil</td>
</tr>
<tr>
<td>Intracavernosal injection therapy</td>
<td>Alprostadil</td>
</tr>
<tr>
<td>Transcutaneous application therapy</td>
<td>GTN, papaverine, minoxidil, alprostadil</td>
</tr>
<tr>
<td>Herbal agents</td>
<td>Ginseng, kava, Ginkgo biloba</td>
</tr>
<tr>
<td>Adjuvants</td>
<td>Dapoxetine</td>
</tr>
</tbody>
</table>

*PDE = phosphodiesterase

**SUB-SUB-PART NE 04 (F 2): PDE-5 INHIBITORS**

14. Mechanism:

*PDE-5 inhibitors are contraindicated in concurrent use of organic NO₃ as it is potentiates NO activity
3. Adverse effects:
   a) Constipation
   b) Bloating (esp with CaCO₃)

PART NF 02: PTH ET AL

4. Physiological actions (of PTH):

<table>
<thead>
<tr>
<th>Site</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>*↑ bone formation (in low/physiological doses)</td>
</tr>
<tr>
<td></td>
<td>*↑ activity &amp; # of osteoclasts (when in excess)</td>
</tr>
<tr>
<td></td>
<td>*↑ Ca²⁺ resorption (from bone)</td>
</tr>
<tr>
<td></td>
<td>*↑ renal tubular reabsorption of Ca²⁺ (direct action)</td>
</tr>
<tr>
<td></td>
<td>*↑ renal tubular excretion of PO₄³⁻</td>
</tr>
<tr>
<td></td>
<td>*(Results in ↑ Ca²⁺ &amp; ↓ PO₄³⁻ in serum)</td>
</tr>
<tr>
<td></td>
<td>*(Stimulates conversion of calcifediol → calcitriol (this amplifies effect of PTH))</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Intestines</td>
<td>↑ Ca²⁺ &amp; ↓ PO₄³⁻ absorption thru induction of calcitriol synthesis</td>
</tr>
</tbody>
</table>
8. Uses & adverse effects:

<table>
<thead>
<tr>
<th>Uses</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Paget’s disease</td>
<td>• Nausea</td>
</tr>
<tr>
<td>• Osteoporosis</td>
<td>• Flushings</td>
</tr>
<tr>
<td>• HyperCa(^{2+})emic states:</td>
<td>• Tingling sensation in fingers</td>
</tr>
<tr>
<td>a) Hyperparathyroidism</td>
<td>• Altered taste</td>
</tr>
<tr>
<td>b) Hypervitaminosis D</td>
<td>• Allergies</td>
</tr>
<tr>
<td>c) HyperCa(^{2+})emia of malignancy</td>
<td>• Interferes with action of digoxin</td>
</tr>
<tr>
<td>d) Osteolytic bone metastasis</td>
<td></td>
</tr>
</tbody>
</table>

**Paget’s disease**

PART NF 04: VIT D

9. Physiological actions:

<table>
<thead>
<tr>
<th>Site</th>
<th>Actions</th>
</tr>
</thead>
</table>
10. Uses:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Uses</th>
</tr>
</thead>
</table>
| Alfacalcidol/ dihydrotachysterol | *Renal rickets  
*Vitamin D-dependent/-resistant rickets  
*Hypoparathyroidism# |
Some bacteriostatic drugs can become bactericidal at higher conc (e.g. sulfonamides, erythromycin, nirofurantoin)

**Some bactericidal drugs may only be bacteriostatic under certain circumstances**

5. Susceptibility testing:
   a) Test measures the drug conc required to inhibit growth of the organism (MIC – minimal inhibitory conc) or to kill the organism (MBC – minimal bactericidal conc)
   b) PAE (post-antibiotic effect) = inhibition of bacterial growth which continues after antibiotic levels have ↓ to low lvls
   c) Conc-dependent killing = rate & extent of killing ↑ with ↑ drug conc
   d) Time-dependent killing = bactericidal activity continues as long as serum conc (of antimicrobial) > MBC

6. Empiric @ presumptive antimicrobial therapy:
   a) Therapy begun BEFORE a specific pathogen has begun
   b) Is based on presumption of an infection which requires immediate drug treatment

PART PA 02: PROBLEMS WITH ANTIMICROBIALS

7. Toxicity:

<table>
<thead>
<tr>
<th>Sub-problem</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local irritancy</td>
<td>*Gastric irritation</td>
</tr>
<tr>
<td></td>
<td>*Pain &amp; abscess formation (at site of IM infection)</td>
</tr>
<tr>
<td></td>
<td>*Thrombophlebitis (of injected vein)</td>
</tr>
<tr>
<td>Systemic toxicity</td>
<td>*Aminoglycosides: oto-, renal toxicity</td>
</tr>
<tr>
<td></td>
<td>*Tetracyclines: liver &amp; kidney damage, anti-anabolic effect</td>
</tr>
<tr>
<td></td>
<td>*Chloramphenicol: marrow depression</td>
</tr>
</tbody>
</table>

*The following drugs are used only when NO suitable alternative is available (reserve drugs):*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymixin B</td>
<td>Neurological/ renal toxicity</td>
</tr>
<tr>
<td>AMB</td>
<td>Kidney, marrow, neurological toxicity</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Hearing loss, kidney damage</td>
</tr>
</tbody>
</table>
CHAPTER PB: β-LACTAMS
PART PB 01: INTRODUCTION

1. General:
   a) Have β-lactam ring
   b) Are cell wall-active agents (prevent final step of bacterial cell wall synthesis)
   c) Range from very narrow spectrum to very broad spectrum

2. Major subdivisions (classification):
   a) Penicillins
   b) Cephalosporins
   c) Carbapenems
   d) Monobactams
   e) β-lactamase inhibitors (non-antibiotic; potentiate action of antibiotics)

PART PB 02: PENICILLINS
SUB-PART PB 02 (A): GENERAL

3. Classification:

*Natural penicillins are narrow spectrum & only effective against Gram (+) cocci

**Aminopenicillins are broad spectrum
38. Rationale of combining imipenem & cilastatin (NOT a statin):

- **Imipenem** is metabolized (in kidney) by a dehydro-peptidase (located at luminal surface of PCT cells)
- **Cilastatin** inhibits metabolism of imipenem by inhibiting the enzyme

- ↑ duration of action & ↓ nephrotoxic potential (of imipenem)

---

**PART PB 05: MONOBACTEMS (AZTREONAM)**

39. No real β-lactam ring (therefore, is β-lactamase-stable)

40. Only binds to Gram (-) PBP’s

41. Narrow activity spectrum [only aerobic Gram (-) bacilli]

42. Alternative to aminoglycosides
Drug interactions: ↑ plasma theophylline, carbamazepine, warfarin, valproate levels
Interaction with theophylline, carbamazepine, warfarin, valproate unlikely

*Both drugs are excreted mainly via bile, & can cause abdominal pain

**PART PD 03: CLARITHROMYCIN & ROXITHROMYCIN**

9. Uses:

<table>
<thead>
<tr>
<th><strong>Clarithromycin</strong></th>
<th><strong>Roxithromycin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI/ LRTI, sinusitis, otitis media, whooping cough, atypical pneumonia</td>
<td></td>
</tr>
<tr>
<td>Skin &amp; skin structure infections (by <em>Staph. aureus</em> &amp; Strep)</td>
<td></td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td></td>
</tr>
<tr>
<td>Leprosy (2nd line drug)</td>
<td></td>
</tr>
<tr>
<td>RS, ENT, genital tract, skin &amp; soft tissue infections (alternative to erythromycin)</td>
<td></td>
</tr>
</tbody>
</table>
## Adverse effects:

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged QT interval</td>
<td>Levo-/ moxi-/ spar-floxacin</td>
</tr>
<tr>
<td>Phototoxicity</td>
<td>Moxi-/ spar-floxacin</td>
</tr>
</tbody>
</table>

| **Ofloxacin** | *Non-specific urethritis*  
|               | *Gonorrhea*  
|               | *Chronic bacterial prostatitis*  
|               | *RTI (bronchitis, sinusitis, TB)*  
|               | *Leprosy*  

| **Norfloxacin** | *UTI*  
|                | *Gonorrhea*  
|                | *GIT infections*  

| **Levofloxacin** | *(Bacterial exacerbation of) chronic bronchitis*  
|                 | *Acute sinusitis*  
|                 | *Community-acquired/ nosocomial pneumonia*  
|                 | *(Uncomplicated) skin & soft tissue infections*  
|                 | *(Uncomplicated) UTI*  
|                 | *(Bacterial) conjunctivitis, corneal ulcers*  

---

![Image of normal and prolonged QT intervals](image-url)
a) **Rashes, urticaria, abdominal pain**

b) **Diarrhea, pseudomembranous colitis** (due to *Cl. difficile*; potentially fatal)

c) **Thrombophlebitis** (during IV administration)

#When this happens, clindamycin shud be stopped IMMEDIATELY & oral metronidazole given

---

**PART PH 02: GLYCOPEPTIDES**

**SUB-PART PH 02 (A): VANCOMYCIN**

4. **Mechanism:**

   - Binds to **terminal dipeptide** (D-Ala, D-Ala) sequence of peptidoglycan
   - Prevents its release from bactoprenol lipid carrier
   - Inhibits assembly of these units at cell membrane & their cross-linking to form cell wall

5. **Uses:**
   a) **MRSA** infections (both treatment & prophylaxis)
   b) **Enterococcal endocarditis** (penicillin substitute, along with gentamicin)
   c) **Skin, soft tissue, bone** infections [by Gram (+)]
   d) **(Bacterial) meningitis** (along with ceftriaxone, cefotaxime)
   e) **Penicillin-resistant pneumococcal** infections
   f) **Diphtheroids** infection
   g) (Also used in **dialysis & cancer** chemotherapy)
   
   ```
   h) **Antibiotics-associated pseudomembranous colitis** (due to *Cl. difficile*)
   i) **Staph enterocolitis**
   ```

   **SYSTEMIC USES**

   **ORAL USES**
10. Uses:
   a) **Skin & soft tissue** infections
   b) Community & hospital-acquired pneumonias, bacteremias, drug-resistant Gram (+) infections
   c) Serious hospital-acquired **pneumonias, febrile neutropenia, wound infections**, etc. (caused by VRE, MRSA, etc)

*This is a valuable drug. So, to prevent resistance, its use shud be restricted to only (c) above

**This drug is given orally/ IV

11. **Adverse effects** (uncommon):
   a) Abdominal pain, nausea, dysgeusia, diarrhea
   b) Rashes, pruritus
   c) Headache
   d) Oral/ vaginal candidiasis
   e) **Anemia, neutropenia, thrombocytopenia** (due to prolonged use)
   f) **Optic neuropathy**